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RTO-MP-062

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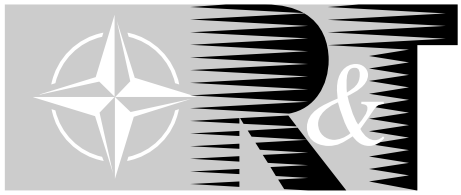


RESEARCH AND TECHNOLOGY ORGANIZATION

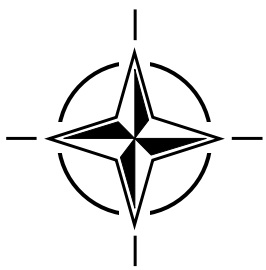
BP 25, 7 RUE ANCELLE, F-92201 NEUILLY-SUR-SEINE CEDEX, FRANCE

RTO MEETING PROCEEDINGS 62

Operational Medical Issues in Hypo- and Hyperbaric Conditions

(les Questions médicales à caractère opérationnel liées aux conditions hypobares ou hyperbares)

Papers presented at the RTO Human Factors and Medicine Panel (HFM) Symposium held in Toronto, Canada, 16-19 October 2000.



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14. Abstract

On 16-19 October 2000, NATO, Partnership for Peace (PfP) and Non-NATO nationals from 24 countries met in Toronto, Canada to attend a symposium on Operational Medical Issues in Hypo- and Hyperbaric Conditions relevant to the alliance, arranged by NATO/RTO/HFM. Exposures to the said conditions are experienced regularly in military operations, but this was the first time operational medical issues affecting air, sea and land forces were addressed in a NATO forum. Canada was chosen as venue site due to Canadian research establishments' expertise in special environmental issues. Themes addressed were decompression illness, breathing gas composition, hypoxia, hyperbaric oxygen treatment of combat injuries, selection, training and adaptation of personnel for special operations, Eustachian tube function, barotrauma, alternobaric vertigo, positive pressure breathing and long term health damage in divers. Relevant technical issues were also discussed.

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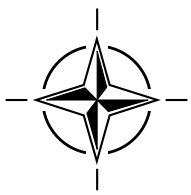

The Research and Technology Organization (RTO) of NATO

RTO is the single focus in NATO for Defence Research and Technology activities. Its mission is to conduct and promote cooperative research and information exchange. The objective is to support the development and effective use of national defence research and technology and to meet the military needs of the Alliance, to maintain a technological lead, and to provide advice to NATO and national decision makers. The RTO performs its mission with the support of an extensive network of national experts. It also ensures effective coordination with other NATO bodies involved in R&T activities.

RTO reports both to the Military Committee of NATO and to the Conference of National Armament Directors. It comprises a Research and Technology Board (RTB) as the highest level of national representation and the Research and Technology Agency (RTA), a dedicated staff with its headquarters in Neuilly, near Paris, France. In order to facilitate contacts with the military users and other NATO activities, a small part of the RTA staff is located in NATO Headquarters in Brussels. The Brussels staff also coordinates RTO's cooperation with nations in Middle and Eastern Europe, to which RTO attaches particular importance especially as working together in the field of research is one of the more promising areas of initial cooperation.

The total spectrum of R&T activities is covered by the following 7 bodies:

- AVT Applied Vehicle Technology Panel
- HFM Human Factors and Medicine Panel
- IST Information Systems Technology Panel
- NMSG NATO Modelling and Simulation Group
- SAS Studies, Analysis and Simulation Panel
- SCI Systems Concepts and Integration Panel
- SET Sensors and Electronics Technology Panel

These bodies are made up of national representatives as well as generally recognised 'world class' scientists. They also provide a communication link to military users and other NATO bodies. RTO's scientific and technological work is carried out by Technical Teams, created for specific activities and with a specific duration. Such Technical Teams can organise workshops, symposia, field trials, lecture series and training courses. An important function of these Technical Teams is to ensure the continuity of the expert networks.

RTO builds upon earlier cooperation in defence research and technology as set-up under the Advisory Group for Aerospace Research and Development (AGARD) and the Defence Research Group (DRG). AGARD and the DRG share common roots in that they were both established at the initiative of Dr Theodore von Kármán, a leading aerospace scientist, who early on recognised the importance of scientific support for the Allied Armed Forces. RTO is capitalising on these common roots in order to provide the Alliance and the NATO nations with a strong scientific and technological basis that will guarantee a solid base for the future.

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Operational Medical Issues in Hypo- and Hyperbaric Conditions

(RTO MP-062 / HFM-050)

Executive Summary

On 16-19 October 2000, NATO, Partnership for Peace, and Non-NATO nationals from 24 countries met in Toronto, Canada to discuss baromedical issues relevant to alliance operations. This was a symposium, not a consensus conference. Accordingly, the speeches and discussions presented the state-of-the-art, rather than arriving at definite conclusions or unanimous recommendations for all alliance nations.

Hypo- and hyperbaric exposures are encountered regularly in routine military operations, and require a high level of operational and medical expertise to avoid acute and long-term injury, or even mission failure.

In spite of more than 100 years of experience and research on decompression illness (DCI) in diving and aviation, this is still a major problem in alliance operations. Relevant research regarding improvement of operational and treatment procedures are in progress in several alliance nations. NATO/RTA/RTO/HFM should form a group of experts in baromedicine to follow closely research regarding DCI, breathing gas composition and possible long-term health damage from diving. The group should promote co-operation between relevant centres, and encourage exchange of research data. The group members should meet annually to discuss what should be recommended for implementation in technical and operational manuals, and which projects should be supported by the alliance.

Hyperbaric oxygen therapy (HBO) has proved valuable also on a number of indications other than dysbaric conditions, like typical battlefield injuries on sea and land. Accordingly, the alliance should see to that this treatment modality becomes available in or near theatres of operations, in order to save limbs and lives.

Alternobaric vertigo is encountered regularly, especially during diving. In aviation it may prove dangerous, especially in agile fighter aircraft. HFM should make sure that knowledge about how to tackle this type of dizziness becomes available in all alliance nations.

Selection, training and adaptation of personnel for special operations in hypo- and hyperbaric conditions are crucial for mission success. Several interesting and promising aspects on these issues were presented. HFM should follow up the ongoing research in this area, and recommend implication of relevant new knowledge into operational procedures. That could be done by arranging small consensus conferences on selected topics.

Eventually, in a few years another state-of-the-art symposium like the present one should be arranged.

les Questions médicales à caractère opérationnel liées aux conditions hypobares ou hyperbares

(RTO MP-062 / HFM-050)

Synthèse

Des représentants des pays membres de l'OTAN, des pays du Partenariat pour la Paix (PpP) et de 24 pays non-membres de l'OTAN se sont réunis du 16 au 19 octobre 2000 à Toronto au Canada pour aborder différentes questions baromédicales liées aux opérations de l'Alliance. Il s'agissait d'un symposium et non pas d'une conférence consensuelle. De ce fait, les présentations et les discussions n'ont présenté que l'état actuel des connaissances dans ce domaine et ne cherchaient donc pas à établir des conclusions ou des recommandations unanimes pour l'ensemble des pays de l'Alliance.

L'exposition aux conditions hypobares et hyperbares est fréquente lors des opérations militaires courantes et exige un haut niveau d'expertise médicale et opérationnelle pour empêcher toute lésion aigüe et de longue durée, voire même l'échec de la mission.

En dépit de plus de 100 ans d'expérience et de recherches sur les barotraumatismes (DCI) dans les domaines de la plongée et de l'aviation, ce type d'exposition pose toujours des problèmes considérables pour les opérations de l'Alliance. Des travaux de recherche sur l'amélioration des procédures de traitement et des procédures opérationnelles sont en cours dans plusieurs pays de l'Alliance. NATO/RTO/RTA/HFM devrait prochainement créer un groupe de spécialistes en baromédecine avec pour mandat de suivre de très près les travaux de recherche sur la DCI, la composition du mélange respiratoire et la dégradation possible de la santé à long terme liée à l'activité de plongée. Le groupe devra chercher à promouvoir la coopération entre les différents centres concernés et encourager l'échange de données résultant des recherches menées. Les membres du groupe devront se réunir une fois par an pour discuter d'éventuelles recommandations en ce qui concerne les manuels techniques et opérationnels et les projets qui devraient être soutenus par l'Alliance.

L'oxythérapie hyperbare (HBO) s'est avérée efficace dans un certain nombre de cas autres que dysbariques, comme les lésions de champ de bataille à terre ou en mer. Par conséquent, l'Alliance doit assurer la présence d'une telle capacité de traitement sur ou à proximité des théâtres d'opérations afin d'épargner des vies.

Le vertige alternobare est rencontré régulièrement, surtout lors des opérations de plongée sous-marine. En aviation il peut s'avérer dangereux, en particulier pour les pilotes d'avions de combat très manoeuvrants; HFM devra s'assurer que les informations concernant le traitement de ce type de vertige sont diffusées à l'ensemble des pays de l'Alliance.

La sélection, l'entraînement et l'adaptation des personnels devant exécuter des missions dans des conditions hypobares et hyperbares sont décisifs pour la réussite des missions. Différents aspects intéressants et prometteurs de ces questions ont été présentés. HFM devra suivre les travaux de recherche actuellement en cours dans ce domaine et faire des recommandations concernant l'intégration de ces nouvelles connaissances dans les procédures opérationnelles. Pour cela, il suffirait d'organiser des conférences consensuelles à petite échelle sur des sujets particuliers.

Ensuite, dans quelques années, un autre symposium résumant l'état des connaissances dans ce domaine pourrait être envisagé.

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Technical Evaluation Report

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Introduction

Hypo-and hyperbaric exposures are encountered in many routine and special military operations in most of the alliance member countries. Specific operational medical issues affecting air, sea and land forces have not previously been addressed in a NATO forum. The HFM Panel identified the need to discuss these issues in a wide forum. Symposia are held in conjunction with the bi-annual business meeting of the HFM panel, which is hosted in turn by the alliance nations. On this occasion it was Canada's turn, and since the present issues have been extensively studied in Canadian research establishments, it was natural to choose these topics this time.
Man is adapted to tolerate relatively small and slow pressure fluctuations, but can under certain circumstances manage earth-bound, self-propelled travel to any altitude on the planet. Likewise, human physiology functions normally only within narrow boundaries of oxygen partial pressure.
Differences in individual tolerance to stress of any kind, including the two mentioned, are great. Accordingly, appropriate selection of personnel for special operations is critical. Also, adequate training and time for adaptation and acclimatisation are important.
If something goes wrong during operations outside normal environmental conditions, causing disease or injury, effective treatment must be available.
In any hypo- or hyperbaric operation, technical solutions are critical.
The present symposium addressed all these aspects.

Decompression illness (DCI)

DCI has been a central problem since the technical development allowed man to exceed the narrow pressure limits defined by self-propelled surface travel. Early encounters were during flights in balloons and work in caissons. Much knowledge about how to avoid the problem, and how to treat it, has been gathered. Nevertheless, a final solution is yet not found. This reflected the fact that 19 (41%) of the 46 presentations in the symposium focussed on that problem.
Even routine operations of air and sea forces, and special operations of land forces, all the time expose personnel to environments where this is a threat.

Hyperbaric exposure

Eight (17%) of the 46 presentations focussed mainly on DCI during hyperbaric diving.
Although, according to paper 29, the risk of DCI is as low as 8.5 cases per 100,000 dives in shallow air diving, in deeper diving it increases to 14.8 on nitrox and 52 on heliox. In air dives exceeding 44 msw, the incidence was 166. Even though the incidence is relatively low, for those stricken, it may have serious consequences.
Traditionally, one has distinguished between type I and type II DCI, mainly depending on severity. When clinically obvious symptoms and signs from the nervous system are present, the condition is thought to be serious and is classified as DCI II. I am not convinced that this distinction is important. A short delay between symptom onset and treatment is generally accepted as important for the final outcome, based on theoretical considerations and practical experience. In paper 10 it is documented that when treatment started later than 6 hrs after

symptom debut, the rate of sequelae increased. Accordingly, stricken divers are rushed into the recompression chamber, usually without sophisticated neurological examinations. Often, the chamber attendant is not sufficiently trained to perform meticulous neurological examinations or evaluate the results. Further, after pressurisation, light neurological symptoms and signs may disappear, and avoid recognition during an examination at pressure. Consequently, reports about the incidence of DCI II may be inaccurate.
The recent tragedy with the Russian submarine Kursk, illustrates the importance of paper 21. Ideally, rescuees from a pressurised disabled submarine should be recompressed immediately before slow decompression. However, sufficient pressure chamber capacity to take care of the crew from a big submarine will most probably not be present at the scene. Accordingly, ample amounts of oxygen breathing apparatuses should be available on board rescue vessels.
Intestinal application of inert gas-metabolising microbes, or intravenous injection of perfluorocarbons, as presented in paper 22, is at present no operational issue, and will probably not be so in the foreseeable future.
Deep blow-up of divers using self-contained heliox breathing apparatuses is rare, but caries a high risk of fatality or serious permanent disability. Accordingly, adequate treatment procedures are crucial. Continuous evaluation, and possibly improvement of treatment tables, as discussed in papers 31-34, is thus an important operational issue for the alliance.

Hypobaric exposure

Eleven (24%) of the 46 presentations dealt with this issue, indicating the operational importance of hypobaric DCI.
An air operation has analogies to an upward saturation diving excursion, since the crew in both situations are saturated with inert gas. This may partly explain differences between DCI in aviation and surface oriented bounce diving, where the diver avoids saturation.
The overview and conclusions given on this subject in the first Key Note speech are important. Human physiology does not change fast, and safe cabin altitude is still thought to be a maximum of 18,000 feet for extended flight. This is in accordance with Haldane's postulate that a pressure drop not exceeding one half of the original ambient pressure, should be safe. However, altitude DCI has been observed below this altitude.
In paper 37 it is documented that venous gas emboli (VGE) formation occurs at cabin altitudes that will be encountered by aircrew of future agile aircraft. However, one hour of denitrogenation provided effective protection against DCI in resting subjects at 25,000 feet, while extended exposure at that level without preoxygenation incurred a substantial risk of developing DCI. Personnel at rest exposed to 30,000-35,000 feet were at risk even after prior denitrogenation.
VGE has been observed as low as 15,000 feet, and exposure to 25,000 feet without preoxygenation gave a DCI incidence of 88%, according to paper 40. Of operational importance is also the observation that DCI risk is less with multiple short flights than with a single continuous flight of equal duration. It is also interesting to note that the seriousness of DCI symptoms is related to the prebreathing time, rather than to altitude. The alliance should follow closely research regarding DCI risk in future combat aircraft while the crew perform different workloads and breathe different gas mixtures.
Cabin pressurisation may effectively protect against altitude DCI. However, some Special Operations Forces (SOF) missions, like high altitude airdrop, do not allow for the use of this countermeasure. Further, restriction on post-flight physical activity, as practised after chamber flights, is not applicable to SOF missions. The preliminary observation presented in paper 40, that DCI was not observed in an exercise group after high altitude exposure, while one case of DCI was observed in a resting group, is interesting. The final results of this investigation will have operational implications for alliance operations, and should be followed closely.

In addition to cabin pressurisation, preoxygenation is an important DCI countermeasure. Optimising the denitrogenation by exercise during prebreathing has proved effective in reducing preoxygenation time and DCI incidence significantly, as reported in paper 46. This, combined with in-flight denitrogenation, has important operational implications for alliance missions. Accordingly, further development along these lines should be followed closely and supported.

To keep track of DCI incidence, severity and treatment results, as presented in paper 1, is important in order to continually evaluate and possibly improve treatment algorithms and procedures. Annual multicenter studies in collaboration between several alliance countries should be encouraged. Continually updated knowledge will allow monitoring of the impact of improvements in operational procedures.

Patent foramen ovale (PFO) is commonly occurring in the general population, with an autopsy prevalence of about 25%. The significance of PFO as an ethiological factor in hyperbaric DCI has been debated for many years. In paper 3 the relevance of PFO during hypobaric exposure is discussed, particularly related to extra-vehicular activity (EVA) during space operations. Since the pressure inside the space suit corresponds to an altitude of 30 000 feet, special precautions have to be taken in order to avoid DCI during extended EVA. DCI in relation to EVA is also given some considerations in paper 45. Space operations will probably not be of operational relevance for the alliance as such in the foreseeable future. However, the problem is relevant also for modern combat aircraft.

Since the probability of finding a PFO in a DCI occurrence without a casual relationship is one in four, its significance may be difficult to evaluate in any single case. The investigation reported upon in paper 3, could not confirm an excess risk for altitude DCI in their limited cohort. Observations like this have a bearing on whether or not examination for PFO should be included in the screening of candidates for extended hypobaric exposure, and is thus of interest for the alliance.

Paper 4 gives an overview of the literature regarding the relevance of PFO to type II DCI, as well as an evaluation of examination, screening and treatment methods for PFO. Most investigations have been in connection with hyperbaric exposures, where the weight of evidence favours an association between diving DCI and PFO, although the absolute risk seems small. In my opinion, screening for PFO in candidates for altitude exposure is at present unneccessary. However, future research on this topic should be followed by the alliance.

Other altitude DCI susceptibility factors are discussed in paper 5. The Altitude DCI Risk Assessment Computer model (ADRAC) is an interesting concept, and the finding that exercise during preoxygenation can reduce DCI incidence, is of operational significance to the alliance. This also applies to the extra risk associated with exercise during exposure. Further, altitude DCI usually occurs during the mission, like DCI from upward excursions during saturation diving. This is in contrast to DCI from surface oriented bounce diving, where DCI most often occurs after the mission. Accordingly, altitude DCI may force the aircrew to abort the mission. Consequently, an altitude DCI risk prediction model (on which the above mentioned ADRAC is based), as described in paper 36, may prove a valuable tool for planning alliance operations.

Since most recorded DCI incidents from altitude exposure have occurred in hypobaric chamber operations, designing efficient and effective, operationally relevant high altitude training profiles is important. This issue is addressed in paper 14, and continued efforts to develop safe procedures should be supported by the alliance.

In altitude DCI, the distinction between type I and II may have important operational implications, which may apply somewhat differently to the regulations issued by different

authorities. Type I may ground an aircraft pilot for three to seven days, and type II for one month. Headache after exposure has traditionally been classified as type II. However, in paper 2, scull sutures are viewed as joints, where bubbles may cause pain. This opens up for the possibility that headache may be classified as type I DCI. It is also possible that the pain may stem from other scull structures than the sutures, and still be classified as type I. I do not think the classification of DCI in type I and II is very helpful, because this distinction implies that any neurological symptom is regarded as more serious than any symptom from other structures. Besides, for any bubble effect to be detected by the subject, nerve endings must be affected. Thus, any DCI symptom could theoretically be classified as type II. I would regard massive joint pain as more serious than a small hypesthetic skin patch caused by a bubble compressing a small, peripheral nerve branch, or compromising the blood supply to the same. However, with respect to rules and regulations, the issue discussed in paper 2 may have important operational implications for special alliance missions. Further, the neurologic damage markers demonstrated in recent stroke studies, may prove helpful in the distinction between DCI I and II. The development in this field should thus be followed.

Breathing gas composition

Most military sea and land surface operations can be conducted safely and effectively without paying attention to the ambient atmosphere, except for pollution. However, in hyperbaric diving and altitude exposure the breathing gas composition becomes a prime concern.

Hyperoxia

This may be a problem only during hyperbaric diving and the operation of high altitude flying in agile combat aircraft.

Aviation

Oxygen is a very reactive and aggressive element, but essential to most life forms. Man is adapted to function optimally in an atmosphere with an oxygen partial pressure (pO_2) of approximately 21 kPa.

Toxic effects of pure oxygen breathing are not a problem at reduced ambient pressure during high altitude flying. However, when oxygen replaces also the nitrogen in the breathing gas, +Gz accelerations exceeding 4G rapidly induce absorption collapse of the basal parts of the lungs, associated with large right to left shunting and bouts of uncontrollable coughing. This may have an unfavourable influence on pilot efficiency in fight.

The high rate of gas absorption from non-ventilated middle ears, may cause delayed middle ear barotrauma, with ear discomfort and deafness. As stated in the first Key Note presentation, these problems can be avoided by preventing the nitrogen concentration from dropping below 40%. Accordingly, the oxygen concentration in the breathing mixture should not exceed 60% at high altitude if sustained high +Gz accelerations may be encountered, like in the new generation of agile combat aircraft. However, this requirement may be in conflict with the oxygen concentration required to prevent hypoxia at high cabin altitude, as well as to prevent alveolar pO_2 from dropping below 30 mmHg after rapid cabin decompression. This conflict will increase with increasing cabin differential pressure, and is obviously an important operational problem in alliance aviation missions. Accordingly, these aspects must be given priority regarding the construction and operation of this type of aircraft.

Diving

As stated in paper 23, central nervous system (CNS) and pulmonary oxygen toxicity are central problems in hyperbaric diving. Thus, regulation of pO_2 in the breathing mixture is

critical. The so-called technical diving has become reasonably safe in the 100 msw range, using open circuit scuba for bottom times up to 30 min, and in water decompression up to 3 hr. In this area there is room for both technical and procedure improvements. The alliance should follow and support the development and refinement of these techniques, since it may have important implications for special operations.

Hypoxia

Although serious accidents have happened in diving operations due to the use of inappropriate breathing mixture with too low pO_2, hypoxia is mainly an altitude problem at high mountains and in aviation.

It is possible to maintain the alveolar oxygen tension at the value associated with breathing air at sea level by progressively enriching the inspired gas with oxygen up to 33,000 feet. However, at that altitude there will not be adequate time for recognition and correction of hypoxia in the case of a malfunctioning oxygen delivery system, or due to leak of air into an ill-fitting oronasal mask. The incidence and severity of hypoxia will increase above 15,000 feet, and is six times greater at 25,000 than at 20,000 feet, according to Key Note speech 1.

Efforts have been made to find prognostic factors for resistance to hypoxia in military pilots by studying cardiovascular and respiratory responses, as presented in paper 7. Appropriate personnel selection and training, as described in papers 12-15, 17, 19 and 20, will play a role in avoiding hypoxic aircraft accidents, since most trainees do not recognise hypoxia symptoms up to 18,000 feet (paper 48).

Positive pressure breathing (PPB) provides short term emergency protection against hypoxia in the event of cabin depressurisation in military aircraft operating at altitudes exceeding 40,000 feet. However, PPB causes significant disturbance to the normal function of the respiratory and circulatory system. According to paper 44, near normal cardiovascular function can be maintained during PPB while wearing full coverage anti-G trousers inflated to 1.5 – 2.5 times PPB pressure. This is important information applicable to alliance operations, especially regarding future agile aircraft.

In paper 35, an excellent correlation is demonstrated between physiologic and thermographic answer to hypobaric stress. However, the main focus must be on technical improvement of cabin pressurisation systems as well as the oxygen delivery systems and operational procedures. This is an area of great importance for allied air operations, and should be supported.

Paper 49 describes a mask protecting against high altitude hypoxia and inhalation of smoke and fumes in case of fire. Protective equipment like this may play an important role in emergency situations also during military flight operations, and should be considered in connection with the operation of highflying aircraft.

Hypoxia is probably the most serious problem in mountain medicine, constituting a central ethiological factor in mountain sickness. Acetazolamide has been used by mountaineers for many years to prevent or ameliorate mountain sickness. Beside adaptation, a new pharmacological approach to increase hypoxia tolerance is presented in paper 6. Great emphasis was placed in military medicine in the former Soviet Union on ensuring the fighting ability of soldiers at high altitude. It is documented that a substance called Bemithylum (2-benzylidazol-thioethyl) increases hypoxic resistance, and thus significantly improves high altitude acclimatisation, improves mental work capacity during hypoxia and increases physical work capability at altitude. The main effect of the substance is said to be antioxidative. It has been developed at the Laboratory of Actoprotectors, Institute of Pharmacology, Russian Academy of Medical Sciences, it is patented and the structural formula is an industrial secrecy. Results of basic research on hypobaric hypoxia, like that presented in papers 38 and 41, are also not yet ready for operational considerations.

In principle, I think that natural, slow adaptation to altitude without the use of pharmacological intervention is preferable in young, healthy soldiers. An interesting approach to altitude adaptation with operational implications, by means of stepwise ascent, is presented in paper 47. However, under special circumstances where quick adaptation is crucial, the availability of a substance like Bemithylum, could be helpful. Obviously, NATO cannot yet rely on the supply of a substance from Russia in order to prepare soldiers for fast high altitude operations. However, the approach is interesting, and the HFM Panel should encourage a competent group within the alliance to take a closer look at the described substance and evaluate its effects and possible side effects.
A special, but relevant operational problem is to choose the right ventilators and procedures for air evacuation of battlefield casualties in order to avoid hypoxic complications. Valuable information on this important issue is given in paper 42.

Hyperbaric oxygen treatment

Hyperbaric oxygenation (HBO) has proven useful on many indications, although the mechanisms of the observed HBO effects sometimes are not well understood, and may even seem paradoxical. Most alliance nations pay attention to the guidelines given by Undersea and Hyperbaric Medical Society (UHMS). The second Key Note speaker picked indications from the UHMS approved list, relevant for combat situations, and unveiled important subcellular mechanisms which explain several of the observed beneficial effects of HBO. The operational importance of HBO is obvious, regarding the treatment of DCI in diving and aviation. This is highlighted in papers referred to under the heading *"Decompression illness (DCI)"* above. However, the benefit of mobile HBO units in the theatre of surface operations to treat injuries not related to pressure variations, has so far not been sufficiently exploited in any of the alliance nations. As underlined in paper 25, HBO is an important adjuvant in the treatment of typical combat injuries, like high velocity missile wounds with a zone of ischemia, which may progress to tissue necrosis. The relevant operational use of HBO also on indications other than those related to pressure changes, is described in paper 28. Evacuation under increased pressure is another aspect focussed on in paper 24. Although the indication described in paper 26 is not relevant for military operations, it describes a prognostic marker, which may be useful also in other HBO indications.
The bottom line is that the alliance should make HBO available also for surface combat theatres. Although it may sometimes complicate medical contingency planning, the benefit of saved limbs and lives will probably far outweigh the inconveniences. Traditionally, HBO units are carried on board ships related to diving operations. Very often battlefields are located within reach of helicopters from a shoreline. Accordingly, HBO units on board ships could be used also for treating surface combat injuries. Future hospital ships should definitely have the capability of HBO. Plans are underway in Norway for a fast moving hospital ship also carrying a HBO unit. This could prove a valuable asset for allied operations under or outside article 5, like peace keeping and peace enforcing operations.

Eustachian tube function

The "bottleneck" of hyperbaric diving and some aviation operations is the Eustachian tube. At its narrowest, isthmus, the opening is only 1 x 2 mm. It is lined by a ciliated epithelium covering lymphatic tissue and a rich blood and lymph vasculature, which can easily become congested from upper respiratory infections or allergic reactions, and from increased thoracic pressure, unfavourable body positions relative to the force of gravity, or G-forces. At rest the pharyngeal end of the tube is closed. Contracting pharyngeal muscles, mainly mm. tensor and

levator veli palatini, like when swallowing or yawning, will normally open the tube and supply the middle ear cavity with air, to replace the oxygen which is steadily being absorbed through the middle ear mucosa. In an alternobaric environment, tubal patency is critical to avoid barotrauma of the ear, the most common medical problem in diving.
Paper 39 discusses the use of tympanogrammes for the evaluation of Eustachian tube function in aviation and altitude chamber operations, in order to avoid barotrauma of the ears, and also used in the selection of personnel for relevant military careers. This tool may give some useful information, even in the hands of non-specialists. However, the Eustachian tube function varies over time, so testing should be repeated in unclear cases, and always be combined with a complete ENT examination; especially so in the selection of candidates for a career in military aviation or diving.

Alternobaric vertigo
Asymmetric Eustachian tube function may cause pressure induced vertigo if the pressure differential between the two middle ears exceeds a value equivalent to 60 cm of water. This is an often-encountered problem in diving, but may also occur in aviation, as described in paper 8, which also gives recommendations on how to deal with it. This important information should be included in the education of alliance aircraft pilots.

Long-term neurological damage in divers
There is no dispute about the fact that some divers suffer permanent damage of the nervous system after acute incidents, like DCI. However, within the diving community there has in recent years been a growing concern that divers may suffer long-term damage also without having experienced any acute injury. Two international workshops on the issue have been arranged in Norway, in 1983 and 1993. The consensus statement from the last was:
"There is evidence that changes in bone, the CNS and the lung can be demonstrated in some divers who have not experienced a diving accident or other established environmental hazard. The changes are in most cases minor and do not influence the diver's quality of life. However, the changes are of a nature that may influence the diver's future health. The scientific evidence is limited, and future research is required to obtain adequate answers to the questions of long term health effects of diving."
Paper 9 documents that a group of Navy mine-clearance divers showed no abnormal neuropsychometric test results, compared to Navy controls. This is reassuring regarding that type of military divers. However, the cohort of divers where most cases of long-term health effects have been demonstrated, is deep-sea saturation divers. On the other hand, one has to consider "the healthy worker effect". In the first place, Navy divers are highly selected healthwise, much more than the controls. Further, divers with health problems will disappear from the cohort. Accordingly, I think prospective, rather than retrospective, investigations also in Navy divers should be performed also in the future.
Regarding physical fitness testing of diver candidates, a method is presented in paper 18.
However, for individual evaluation a standard maximum oxygen uptake test should be performed.

Conclusions

The subject of the symposium was very well chosen. It covers several aspects important to routine as well as special alliance operations.

Decompression illness is still a central problem in diving and high altitude operations relevant for the alliance. In spite of more than a hundred years of research, there is still room for

improvements regarding operational procedures, equipment, diagnosis and treatment. Co-operation in future research and development between alliance nations and close contact with other relevant nations is strongly recommended. Research funding has become increasingly scarce in this area in most countries. Accordingly, international co-operation at project level and sharing of data is mandatory for optimal use of dwindling resources.

Correct breathing gas composition is crucial in both diving and aviation, i.e. routine alliance operations. Besides optimal oxygen content, the choice of inert gas component is decisive in many dive operations. This part should probably also be looked at more closely in aviation, especially pertinent to Eustachian tube function. Maybe heliox could reduce the risk of alternobaric vertigo. Co-operation and exchange of research data at project report level within the alliance is recommended. It takes a long time to wait for new knowledge to be published in international professional journals.

Hyperbaric oxygen therapy is well established within the alliance for the treatment of pressure related illnesses. Time is now overdue to make this modality available also for combat injuries. Limbs and lives may be saved by early and correct use HBO as an adjunct in the treatment of battlefield injuries at sea and on land. Development in this field should be followed closely, encouraged and supported.

Work regarding follow up of possible long-term health damage in divers is in progress in Norway, and is planned in the UK. The alliance should pay attention to, and possibly support these efforts.

Recommendations

NATO/RTO/HFM should form a group with special interest in baromedicine. They should meet annually and keep the alliance updated on progress with operational relevance in this field.

On the said group’s recommendation, HFM should stage broad meetings like the present one.

NATO should encourage and support research and development of operational medical issues in hypo- and hyperbaric conditions.

Present and Future Compromises in Altitude Protection in Combat Aircraft

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Summary

The crews of high performance combat aircraft operating at high altitude are protected against the effects of exposure to high altitude by two methods viz pressurisation of the cabin and raising the concentration of oxygen in the gas delivered by the oxygen system to the respiratory tract. The historical development of the current compromises between cabin pressurisation and increasing the concentration of oxygen in the inspired gas is reviewed. The physiological requirements with respect to the prevention of hypoxia, decompression sickness, and otitic and sinus barotrauma are considered. The criteria for avoiding lung damage and hypoxia on rapid decompression are discussed.

The changes required to the present specification for the cabin pressurisation schedule of high altitude fighter aircraft associated with the increase in the operational ceiling above 50,000 feet and the agility of future fighter aircraft are considered. It is proposed that the maximum cabin pressure differential should be increased at altitudes above 40,000-45,000 feet to 6.0-6.7 Lb in^{-2}. The relative simple fixed cabin pressurisation control systems currently employed should be replaced by variable differential pressure control, so that the optimum compromise can be made depending upon the nature and duration of the sortie.

Introduction

A fundamental consideration in the design of a combat aircraft is the provision of protection to the crew against the effects of the low environmental pressure of altitude. This protection should prevent hypoxia, decompression sickness, and minimise the incidence of otitic and sinus barotrauma during routine flight and in emergency situations. It should allow the crew to perform efficiently throughout the flight envelope of the aircraft and minimise the effects on the crew and the aircraft of a malfunction or failure of any components of the protective systems.

Two methods are employed, usually together, to provide altitude protection to the crews of combat aircraft flying at altitude. These are supplemental oxygen to raise the partial pressure of oxygen in the inspired gas and pressurisation of the cabin to increase the absolute pressure to which the crew are exposed. The extent to which each of these methods is employed depends upon physiological, engineering and operational considerations. The physiological requirements relate to hypoxia, decompression sickness, otitic and sinus barotrauma and the effects of failure of the pressure cabin. The engineering requirements are concerned principally with the mass of the aircraft, the reliability and life of the pressure cabin and the reduction of the risk of losing the aircraft and its crew in the event of a failure of the pressure cabin due to enemy action. Operational considerations which influence the way in which altitude protection is provided include the role of the aircraft and hence the other protective and aircrew performance enhancing systems with which the altitude protection has to be integrated.

The manner in which altitude protection is provided in modern fighter aircraft represents a series of compromises between the physiological, engineering and operational requirements. The current compromises have developed over the last sixty years or so. An understanding of how these compromises have developed is of value in considering the compromises that should be made in future combat aircraft. This paper therefore commences with a historical overview of the development of altitude protection. The basis of the way in which altitude protection is provided in present high performance combat aircraft is then considered. Finally proposals are made as to how altitude protection should be affected in future combat aircraft.

Historical Overview

Whilst the effect of the lowered partial pressure of oxygen in producing hypoxia at altitude was well recognised by the third quarter of the 19th century, the syndrome of decompression sickness at altitude, in spite of J S Haldane's

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prediction in 1917, was not described until the early 1930s. Indeed altitude decompression sickness was not widely recognised until the last two years of the third decade of the last century (Armstrong, 1939). Paul Bert (1878) not only proved that the hypoxia induced by breathing air at altitude was due to the fall of the partial pressure of oxygen in the inspired gas, but also conducted the first demonstrations using human subjects that the altitude hypoxia can be prevented by raising the concentration of oxygen in the gas breathed. Furthermore Paul Bert must also be recognised as the first to propose that pressurisation of the crew compartment of an aerial vehicle would protect the occupants against the effects of exposure to high altitude. Thus the methods by which the occupants of aircraft flying at altitude could be protected against the effects of exposure to low environmental pressure had been proposed before the end of the 19th century and indeed before the first flight of a heavier than air machine.

The first two decades of the last century spurred by the increasing performance of aircraft saw the firm establishment both in the laboratory (in hypobaric chambers) and in flight of the basic requirements for supplemental oxygen (Haldane 1920). By the 1930s the requirements for full pressure suits to prevent hypoxia at altitudes above 40,000 feet had been recognised and during the third decade full pressure suits were worn by aviators attempting high altitude records in open cockpit aircraft. The earliest exposure to very high altitude (84,000 feet) whilst wearing a full pressure suit inflated with oxygen was conducted in a hypobaric chamber by Haldane in 1933 (Haldane and Priestly 1935). Whilst positive pressure breathing had been employed to treat a variety of clinical conditions its use to prevent significant hypoxia breathing oxygen at altitudes between 40,000 and 50,000 feet was exploited by Gagge (Gagge et al 1945) in the United States and by Bazett initially in Canada and later in the United Kingdom (Bazett and Macdougall, 1942). The development of partial pressure suits employing pressure helmets or pressure demand masks to provide protection at altitudes between 40,000 and 100,000 feet occurred principally in the twenty years or so following World War II (Jacobs & Karstens, 1948; Ernsting, 1966). The last twenty years has seen the further development of improved partial pressure suit assemblies in the United States and Canada (Shaffstall et al, 1995; Holness et al, 1980; Goodman et al, 1993) and in the United Kingdom (Gradwell, 1991) for the new generation of agile combat aircraft.

Whilst the concept of pressurising the cabin of an aircraft so that the occupants are not exposed to the environmental pressure at altitude is older than powered flight itself, the first attempt to do so did not occur until 1921 when the US Army Air Corps conducted a test flight in which the pilot was enclosed in a tank which was pressurised with air. The flow capacity of the discharge valve fitted to the tank was, however, totally inadequate so that during flight at 3,000 feet, the pressure within the tank increased to the equivalent of 7,000 *below* sea level. The pilot suffered severe otitic barotrauma and the temperature within the cabin rose to 66ºC. This failure of engineering design delayed further attempts in the United States at cabin pressurisation. Aircraft fitted with experimental pressure cabins were, however, developed and flown during the early 1930s by several European nations, including Germany and France. The parallel concept of the sealed cabin pressurised with oxygen carried with the vehicle was, however, developed and exploited by high-altitude balloonists such as the Belgian Piccard who ascended to an altitude of 51,000 feet in 1931, and Stevens and Anderson in the United States who ascended to an altitude of 72,395 feet in 1935.

The early attempts to pressurise the crew compartment of an aircraft revealed the major factors that had to be taken into account in producing an acceptable pressure environment for the occupants. It was recognised that the absolute pressure to be maintained within the cabin during flight was a function of the physiological effects of altitude, specifically hypoxia, and whether the occupants would be using supplemental oxygen. The earliest studies had shown the importance of adequate control of the differential pressure of the cabin. It was also recognised that the strength of the pressure-holding structure was a vital consideration, both with regard to the integrity of, and the increased weight penalty imposed by, the pressure cabin. The possibility of a sudden failure of the pressure cabin in flight was considered and led to the extensive studies of rapid decompression performed in the late 1930s and the 1940s. The importance of adequate control of the ventilation of the pressure cabin and the temperature within it was established. The fundamental aeromedical requirements for the pressure cabin were specified in the classic report by Armstrong in 1935. These requirements were embodied in the design of the XC-35 sub-stratosphere airplane built by Lockheed for the US Army Air Corps. This aircraft completed a very successful flight test programme in 1937 which provided a firm basis for the pressurisation of the crew and passenger compartments of future aircraft.

World War II saw the development and introduction into service in the United States and the United Kingdom of fighter and bomber aircraft equipped with pressure cabins. The requirement for minimum aircraft mass and the likelihood of rapid decompression of the cabin due to enemy action led to the adoption of a low pressure differential for fighter aircraft – typically of the order of 2.0 to 2.75 Lb in^{-2}, whilst the advantages of being unencumbered with oxygen equipment throughout flight led to the selection of a pressure differential of 6.5 to 7.5 Lb in^{-2} for bomber aircraft. The aeromedical requirements which determined the pressurisation schedules of the military aircraft constructed during World War II were well summarised by Lovelace and Gagge (1946). These set the maximum cabin altitude without supplemental oxygen at 10,000 feet [5,000 feet for night vision] and the maximum allowable cabin altitude to avoid decompression sickness (aeroembolism) at 25,000 to 30,000 feet. The use of a limit to the Relative Gas Expansion

(RGE) as the safety criterion for a sudden decompression of the cabin was widespread. Thus Lovelace and Gagge (1946) advocated a maximum RGE of 2.3 for a fighter cockpit with a volume of 50 cubic feet.

The late 1940s saw the adoption of cabin pressurisation for virtually all high-altitude aircraft. The maximum cabin altitude allowed in the high-differential pressure cabins of bomber aircraft in which cabin air was breathed throughout flight was set at 8,000 feet. In fighter aircraft the high mass and hence aircraft performance penalties of a high-differential pressure cabin such that the crew could breathe air throughout flight were unacceptable. Furthermore it was considered that the threat to the integrity of the pressure cabin by enemy action and the possible ensuing decompression should be taken into account in this type of aircraft. Thus, it was generally accepted that the crew of fighter aircraft would wear oxygen equipment throughout flight so that the magnitude of the cabin pressure differential in this type of aircraft could be considerably less than if the maximum cabin altitude was limited to the 8,000 feet required when breathing air. The maximum cabin altitude for this type of aircraft was set at 25,000 feet (Roxburgh, 1941; Lovelace and Gagge, 1946). The relationship between cabin altitude and aircraft altitude, the pressurisation schedule, in fighter aircraft was set in construction of the aircraft and could not be varied by the aircrew. There was a divergence in the pressurisation schedules subsequently developed for fighter aircraft between the United States and the United Kingdom (Figure 1). The concept of the isobaric pressurisation schedule in which with ascent of the aircraft the cabin altitude is held constant at the value at which pressurisation commences until the maximum cabin differential pressure is attained was adopted in the United States. The United Kingdom, in contrast, employed in all its indigenous fighter aircraft a pressurisation schedule in which the cabin altitude increased progressively with ascent of the aircraft with the maximum cabin pressure differential not being attained until the aircraft was at an altitude of 35,000 – 40,000 feet [the cabin differential pressure with an isobaric pressure schedule is constant at all aircraft altitudes above about 23,000 feet].

Physiological Requirements for the Pressurisation of Combat Aircraft

Avoidance of Hypoxia

It is possible to maintain the alveolar oxygen tension at the value associated with breathing air at sea level by progressively enriching the inspired air with oxygen at altitudes up to 33,000 feet. However, the rate at which the function of the central nervous system is impaired by an interruption of the oxygen supply, so that the aircrew member reverts to breathing air increases progressively as the altitude is raised above about 15,000 feet. The time available at an altitude of 20,000 feet for an individual to recognise that his oxygen supply has ceased and for him to carry out the appropriate corrective action is approximately three times greater than the time available at an altitude of 25,000 feet. Furthermore, the reduction of the partial pressure of oxygen in the inspired gas produced by a given fractional inboard leak of air due to an ill-fitting oronasal mask increases with increase of altitude. Thus, although it is theoretically possible to maintain a normal sea level alveolar oxygen tension at altitudes of up to 33,000 feet by increasing the concentration of oxygen in the inspired gas, these considerations suggest that both the incidence of hypoxia and its severity will increase with increase of altitude above 15,000 feet. The incidence of hypoxia accidents in unpressurised aircraft in World War II was six times greater for flights at 25,000 feet as for those at 20,000 feet (Swann, 1946). The experience of the Royal Air Force over the last forty years has amply confirmed these wartime observations, with the incidence and severity of hypoxia accidents rising significantly with increase of cabin altitude between 20,000 feet and 25,000 feet. It is concluded that in order to minimise the risks of hypoxia arising from an ill-fitting mask or a malfunction of the oxygen delivery system, and to provide adequate time for the recognition and correction of a malfunction of the oxygen system, the cabin altitude should not exceed 20,000 feet.

Avoidance of Decompression Sickness

Pressurisation of the cabin of a combat aircraft plays an essential role in preventing the occurrence of decompression sickness when the aircraft is at high altitude, especially when the length of time at altitude extends to several hours. The experience of the incidence of decompression sickness during World War II led to the decision that the maximum cabin altitude in fighter aircraft should not exceed 25,000 feet (Roxburgh, 1941; Lovelace and Gagge, 1946). Subsequent experience in several air forces, including the United States Air Force (Lewis, 1972) and the Royal Air Force (Fryer, 1962), showed that there are occurrences of decompression sickness at cabin altitudes below 22,000 feet and that a few cases, occasionally severe, have occurred at cabin altitudes as low as 18,000 feet. A review of the cabin pressurisation schedules for combat aircraft conducted in the UK in the late 1960s concluded that whilst the maximum safe altitude for the avoidance of decompression sickness was 18,000 feet, very few cases of serious decompression sickness were likely to occur below a cabin altitude of 22,000 feet. With the general adoption of a cabin differential pressure of 5.0 Lb in^{-2} in USAF aircraft since the early 1960s and in the RAF since the late 1960s [which provides a cabin altitude of 18,500 feet at an aircraft altitude of 45,000 feet], and the relatively rare occasions on which fighter aircraft operated at altitudes above 45,000 feet for any significant length of time, the incidence of decompression sickness in fighter aircraft

became negligible [the incidence remained high however in lower cabin differential pressure reconnaissance aircraft in which the crew were exposed for several hours to cabin altitudes as high as 26,000 to 28,000 feet].

The extensive studies conducted by the Armstrong Laboratory using Doppler ultrasound to detect and semi-quantify the occurrence of venous gas emboli in the right side of the heart have demonstrated that significant quantities of venous gas emboli occur in subjects exposed for several hours to altitudes as low as 15,000 feet when the inspired gas contains nitrogen (Webb and Pilmanis, 1993). This group of investigators has advocated that the cabin altitudes of combat aircraft, which may fly at very high altitudes for several hours, should not exceed 16,000 feet (Webb et al, 1993). Although serious symptoms of decompression sickness are extremely rare at cabin altitudes below 20,000 feet, serious decompression sickness could well develop rapidly after the rapid decompression to high altitude of a pilot with severe venous gas embolism. Further experimental evidence is urgently required with respect to the possibility and the incidence of *symptoms* of decompression sickness at altitudes between 16,000 and 20,000 feet under the conditions to be expected in modern and future combat aircraft, viz. the crew performing light work and breathing gas containing 30-40% nitrogen. At present it is considered that decompression sickness should be avoided by not allowing the cabin altitude to exceed 18,000 feet. Short duration exposures to cabin altitudes as high as 20,000 feet are very unlikely to produce a significant incidence of decompression sickness.

Ventilation of the Middle Ears and Sinuses

Failure to ventilate the middle ear during descent gives rise to increasing discomfort in the ear and deafness, and eventually to otitic barotrauma. The discomfort produced in the ear by descent and the need to occlude the nostrils to perform the Frenzel manoeuvre can distract the aircrew member from his primary task. It is vital to avoid otitic and sinus barotrauma, which often prevent the individual flying for several days. It is highly desirable that in war aircrew with an upper respiratory tract infection can continue to fly operationally. All these considerations argue for the minimum rate of increase and decrease of cabin altitude during flight. Other factors which have been discussed in the introduction to this paper do not allow this solution in high-performance combat aircraft, although the isobaric cabin pressurisation schedule of the United States Military Specification for low pressure differential cabins provides the ideal of no change of cabin altitude during aircraft manoeuvres between altitudes of 8,000 and 23,000 feet (Figure 1). The rate of increase of pressure within the cabin on descent of a combat aircraft should be as low as possible to avoid ear discomfort and the minimise the frequency with which the nose must be occluded to perform the Frenzel manoeuvre and the incidence of otitic barotrauma. Aeromedical advice in the United Kingdom has recommended (Roxburgh, 1964) that on descent, the rate of increase of absolute pressure in the cabin should not exceed 2.0 Lb in^{-2}/min over a change of pressure of 1.0 Lb in^{-2}. This advice was based on the incidence of otitic barotrauma in flight and hypobaric chamber studies.

Integrated Physiological Requirements

It is considered that in respect of the avoidance of hypoxia due to failure of the oxygen supply and decompression sickness, the cabin altitude of a combat aircraft should not exceed 20,000 feet when the aircraft is at its service ceiling. Furthermore, it is highly desirable that the cabin altitude does not exceed 18,000 feet on the vast majority of operational sorties. Avoidance of ear discomfort and the minimisation of the frequency with which the nostrils have to be occluded to introduce gas into the middle ear, and of the risk of otitic barotrauma, requires that the rate of increase of cabin pressure during descent of the aircraft should be as low as possible, and ideally should not exceed 2.0 Lb^{-2}/min for an increase of pressure of 1.0 Lb in^{-2}.

Physiological Aspects of Rapid Decompression of the Cabin

The pressurisation of the cabin of a combat aircraft may fail due to cessation of the flow of air into the cabin (due to engine failure of malfunction of the environmental control system), opening of the cabin outlet valve (due to a failure of the control system or selection by the pilot) or a defect in the pressure cabin structure (due to enemy action, human error, mechanical failure or as a prelude to ejection). The cabin altitude-time profile on decompression is determined by the ratio of the effective area of the defect in the structure to the volume of the cabin, the magnitude of the air flow into the cabin, the magnitude of the aerodynamic suction and the altitude-time profile of the aircraft, including the initial aircraft altitude, the time taken to initiate descent and the rate of descent of the aircraft.

The hazards of a rapid decompression of the cabin include physical injury due to the structural failure and very high air flow velocities in the cockpit, lung barotrauma, hypoxia, decompression sickness, cold injury and hypothermia. Of particular concern in relation to the cabin differential pressure at the instant at which the decompression occurs are pulmonary barotrauma and hypoxia.

Pulmonary Barotrauma

Free venting of the gas in the lungs on a sudden reduction of the environmental pressure is hindered by the resistance to the flow of gas from the alveoli through the airways to the mouth and nose and by the resistance imposed by the breathing equipment (Luft and Bancroft, 1956; Ernsting et al, 1960). If the rate and range of the decompression are large, then the expanding lung gas will be unable to escape and the consequent increase in the pressure difference between the alveolar gas and the surface of the chest and abdomen (the trans-thoracic pressure) will expand the lungs and chest wall and force descent of the diaphragm. Excessive distension of the lungs will tear the lung parenchyma and gas will enter the pulmonary tissues and, more seriously, enter torn pulmonary vessels so that gas passes into the left side of the heart and hence into the systemic circulation (Violette, 1954). Surgical emphysema in the mediastinum and neck and pneumothorax can also occur. A trans-thoracic pressure difference of the order of 80-100 mm Hg is required with the respiratory muscles relaxed to distend the lungs to the extent that the lung parenchyma is torn (Henry 1945).

The worst case with respect to lung damage on a rapid decompression is when the glottis is closed so that gas cannot escape from the respiratory tract. Thus a decompression from 16,000 feet to 38,000 feet with the lungs at functional residual capacity and the glottis closed will produce a transthoracic pressure of 50 mm Hg (Luft and Bancroft, 1954; Ernsting et al, 1960). The chance of the glottis being closed at the instant that a rapid decompression occurs is usually considered to be so remote that this risk is not considered in determining cabin pressurisation schedules.

Experiments using a variety of animal models (Violette, 1954) and man (Sweeney, 1944; Hitchcock et al, 1948; Luft and Bancroft, 1956; Ernsting et al, 1960) have provided information on the conditions of rapid decompression (pressure range and rate of decompression) which are safe and those which may give rise to lung damage when the expanding lung gas can flow freely from the mouth and nose. A valuable approach to describing these conditions, relates the probability of lung damage on rapid decompression to the ratio of the initial to the final pressures in the cabin and the time characteristic of the decompression as described by the ratio of the volume of the cabin to the area of the orifice through which it is decompressed. Violette defined, using a variety of animals, a curve (Figure 2) which separated decompressions which caused lung damage from those which did not. There is a paucity of experimental data with respect to rapid decompressions which can cause lung damage in man. The conditions of rapid decompression to which human subjects, wearing either no breathing equipment or equipment which allowed free venting of gas from the respiratory tract, have been exposed without any evidence of injury to the lungs are indicated in Figure 2. It may be seen that the decompression of the cabin of an aircraft with a cabin pressure differential of 5.0 Lb in^{-2} flying at 40,000 feet in 0.05 sec is very unlikely to produce lung damage provided that gas can escape freely from the respiratory tract. Avoidance of the possibility of lung damage on a very rapid decompression such as occurs with the sudden loss of the canopy of the cockpit when there is no hindrance to the flow of gas from the respiratory tract requires ideally that the differential pressure of the cabin should not exceed 5.0 Lb in^{-2}. Taking into account, however, the uncertainties of the conditions of safe decompression as presented in Figure 2 and mindful that human subjects have not been exposed under controlled conditions to decompressions in the “zone of uncertainty”, it is believed that the increased risk of pulmonary barotrauma associated with a cabin pressure differential of 6.0 to 7.0 Lb in^{-2} is probably very low.

The oxygen equipment worn by the crew, especially when the oronasal mask has good dynamic sealing properties, may well hinder the venting of gas from the respiratory tract on a rapid decompression. Indeed the compensated outlet valve of the mask in a conventional pressure demand system will be held shut during a rapid decompression by the pressure of the gas trapped in the hose between the demand regulator and the inlet valve of the mask (Ernsting, 1996). This behaviour will greatly increase the likelihood of damage to the lungs during the decompression. Opening of the compensated valve of the mask on a rapid decompression can be ensured by fitting a compensated dump valve to the outlet of the pressure demand regulator. Even with this facility the outlet valve often provides some hindrance to the free venting of lung gas on a very rapid decompression. Current standards for the maximum mask cavity pressure in these circumstances (41 mm Hg) are probably conservative and further experimental work is required to define better allowable resistances to the venting of gas from the lungs on a rapid decompression (Ernsting, 1995a). The use of pressure breathing to enhance tolerance of high sustained accelerations (PBG) has brought with it the possibility that a rapid decompression could occur when the pressure in the respiratory tract is already raised by 50-60 mm Hg. Very high pressures occur in the mask, respiratory tract and the bladder of the chest counterpressure garment on rapid decompression with PBG operative unless an additional dump valve is fitted to the garment connector (Ernsting, 1995a). Although the rise of pressure in the bladder over the chest may limit the distension of the lungs during a rapid decompression there is no experimental information on the effects of rapid decompression on the lungs when exposed to +Gz acceleration either with or without PBG. There is an urgent need for studies of the behaviour of the lungs in these circumstances and to define acceptable pressures in the mask and chest bladder and acceptable pressure differences between them.

Composition of the Inspired Gas

Hypoxia is prevented when the cabin is pressurised in fighter type aircraft by increasing the concentration of oxygen in the inspired gas as the aircrew are breathing gas from the breathing gas delivery system throughout flight. Ideally the concentration of oxygen in the gas breathed at altitude should always be such as that the partial pressure of oxygen (Po_2) in the alveolar gas is equal to or greater than the normal value associated with breathing air at ground level i.e. 103 mm Hg (*figure 3*). This is the standard employed in virtually all military oxygen delivery systems. Should economy in the use of oxygen demand it then it may be acceptable for the inspired oxygen concentration to be reduced to the level required to maintain a minimum alveolar PO_2 of 75 mm Hg – equivalent to breathing air at an altitude of 5,000 feet (Ernsting, 1966).

Whilst the toxic effects of breathing high concentrations of oxygen do not arise in the low pressure differential cabins of fighter aircraft, breathing high concentrations of oxygen has two important disadvantages due to the concomitant reduction of the concentration of nitrogen in the inspired gas. It produces acceleration-induced atelectasis and delayed otitic barotrauma (Ernsting, 1995b). Thus exposure to +Gz accelerations greater than 3-4 G, whilst breathing 100% oxygen rapidly induces marked absorption collapse of the basal parts of the lungs which is associated with a large right to left shunt due to venous blood flowing through collapsed lung without undergoing oxygenation. The conditions also gives rise to bouts of uncontrollable coughing. The high rate of absorption of gases from non-ventilated cavities when 100% oxygen is breathed also gives rise to delayed otitic barotrauma with ear discomfort and deafness. These effects of breathing high concentrations of oxygen on the lungs and middle ear cavity are prevented by maintaining the concentration of nitrogen in the inspired gas at or above 40% (Green, 1963; Haswell et al, 1986). Inflight experience and limited laboratory studies (Ernsting, 1965) support the theoretical conclusion that at altitude this effect of nitrogen is a function of the concentration of this gas. Thus in order to avoid acceleration induced lung collapse and delayed otitic barotrauma the concentration of oxygen at altitude should not exceed 60% (Ernsting, 1995b). This requirement for the limit of the concentration of oxygen in the inspired gas at altitude eventually conflicts at the higher cabin altitudes with the concentration of oxygen required to prevent hypoxia (*figure 3*). The degree of this conflict depends essentially upon the sustained G capability of the aircraft at high altitude. Thus most current fighter aircraft are incapable of sustaining +Gz accelerations greater than 2-3G at aircraft altitudes above 35,000-40,000 feet. The +Gz acceleration performance of the new generation of agile combat aircraft is, however, well maintained at aircraft altitudes considerably above 50,000 feet. The intersection of the two oxygen concentrations altitude curves at 60% oxygen at a cabin altitude of 24,500 feet requires close control of the concentration of oxygen delivered by the oxygen system at cabin altitudes above 18,000 – 20,000 feet if both requirements are to be fully met.

The hypoxia which can follow decompression of the pressure cabin to altitudes above 30,000 feet in spite of 100% oxygen being delivered to the mask cavity immediately after the decompression is a further factor which determines the concentration of oxygen in the gas breathed *prior* to the decompression (Ernsting, 1963; and 1995b). The alveolar PO_2 prior to the decompression must be high enough to ensure that the fall of alveolar PO_2 induced by the reduction of the pressure in the respiratory tract does not reduce the alveolar PO_2 to below 30 mm Hg. The concentration of oxygen required in the gas breathed prior to the decompression to prevent the alveolar PO_2 falling below 30 mm Hg is a function of the pressurisation schedule of the pressure cabin and the final cabin altitude (Ernsting, 1995b). This relationship for a typical fighter aircraft with a maximum aircraft altitude of 50,000 feet is presented in *figure 3.* Increasing the differential pressure of the cabin will increase the concentration of oxygen which must be breathed at a given cabin altitude to prevent hypoxia on rapid decompression (*figure 4)*. Similarly the lower the intrapulmonary pressure after the decompression, which is determined at high altitude by the pressure breathing-altitude schedule employed in the partial pressure assembly system, the higher the concentration of oxygen which must be breathed to prevent hypoxia on rapid decompression (*figure 4)*. Thus the conflict between the minimum concentration of oxygen required to prevent hypoxia after a rapid decompression and the maximum permitted concentration to avoid acceleration atelectasis will be increased by an increase in the cabin differential pressure.

Compromises in Future Aircraft

It has been seen that the compromise between pressurisation of the pressure cabin and the concentration of oxygen in the breathing gas delivered to the aircrew employed over the last forty years has been to employ a maximum cabin differential pressure of 5.0 (US) to 5.25 (UK) Lb in^{-2}. The manner in which this cabin altitude has varied with aircraft altitude has, however, differed – the US military specification has employed an isobaric schedule, whilst in the UK and FR the maximum pressure differential has only been operative at aircraft altitudes above 35,000-40,000 feet (*figure 1)*. The latter pressurisation schedule has the advantage in avoiding very high rates of increase of the absolute pressure in the cabin during descent of the aircraft from high altitude (Ernsting, 1995a).

Future fighter aircraft may well operate for considerable periods of time at altitudes significantly above 50,000 feet (Neubeck, 1995). Current cabin pressurisation schedules which employ a maximum cabin differential pressure of 5.0 – 5.25 Lb in^{-2} will not maintain an acceptable cabin aircraft at those aircraft altitudes. Thus the cabin altitude will rise to 22,500 feet at 60,000 feet and to 24,000 feet at an aircraft altitude of 70,000 feet. These cabin altitudes are significantly above the level at which decompression sickness will occur and they almost certainly increase the risk of serious decompression sickness arising rapidly following loss of cabin pressurisation. Aeromedically, it is extremely desirable that the cabin altitude in these aircraft does not exceed 18,000 feet at the aircraft ceiling and indeed Webb et al (1993) have argued that it should not exceed 16,000 feet, in order to reduce the risk of venous gas emboli. It is suggested therefore that the maximum cabin differential pressure in new high-altitude fighter aircraft should be increased above 5 Lb in^{-2} so that the cabin altitude at the aircraft's operational ceiling does not exceed 18,000 feet. Thus a cabin pressure of 6.3 Lb in^{-2} gauge will be required at 60,000 feet, whilst at 70,000 feet a cabin pressure of 6.7 Lb in^{-2} gauge would be required to provide a cabin altitude of 18,000 feet. The maximum differential pressures would only be required at aircraft altitudes above 40,000-50,000 feet, and there may well be structural, and hence aircraft mass, advantages in employing a UK type of pressurisation schedule which, whilst minimising the rate of increase of cabin pressure on rapid descent, also reduces the magnitude of the cabin differential pressure at aircraft altitudes up to 40,000 feet. A further possibility, the operating and engineering advantages of which should be explored is to replace the fixed relationship between cabin and aircraft altitudes provided by the aircraft pressurisation systems fitted to present combat aircraft by one in which this relationship can be varied between and within sorties to provide the optimum cabin altitude. Such a control system would take account of the aircraft altitude-time profile of the sortie, the likelihood of a rapid decompression occurring during the sortie and, for high altitude flights, the partial pressure assembly worn by the crew.

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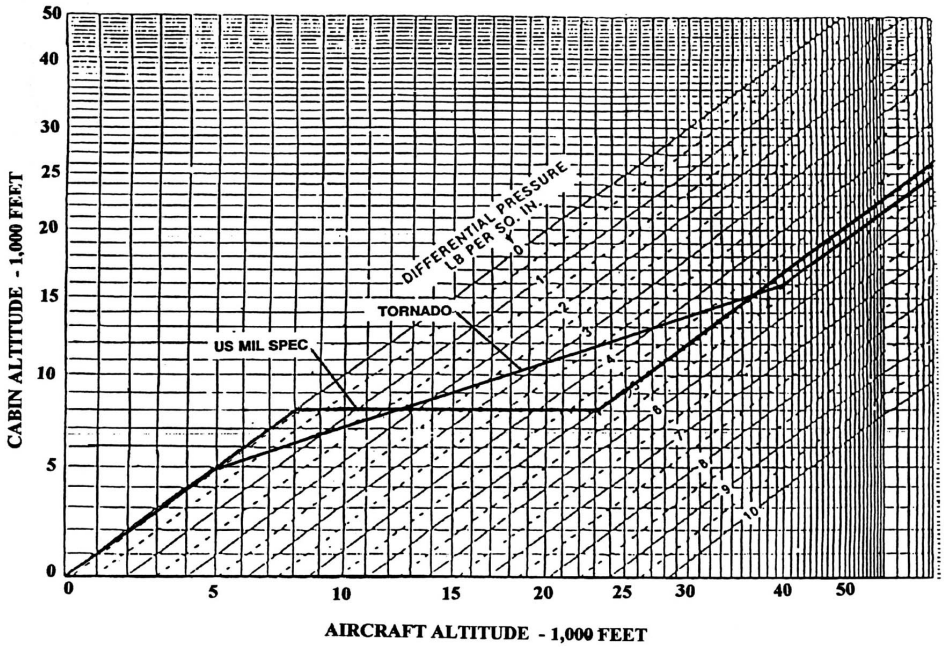

Figure 1 Cabin Pressurisation schedules commonly employed in low differential pressure cabin combat aircraft designed to United States Military Specification [US MIL SPEC] and to United Kingdom Military Specification [Tornado].

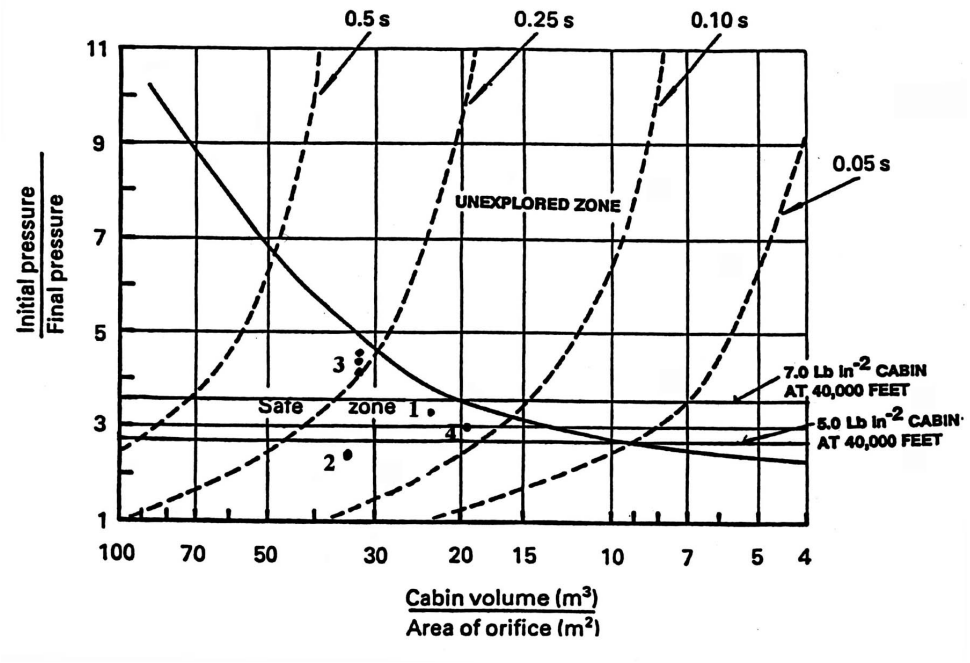

Figure 2 Lung damage on rapid decompression, related to the ratio of the initial pressure to the final pressure of the decompression and the ratio of cabin volume (m^3) to the effective area (m^2) of the orifice through which the cabin was decompressed. The broken lines indicate the duration of the decompression calculated using the equations developed by Haber and Clamann (1953). The solid curve labelled Violette was the relationship found by Violette (1954) using animal models which separates decompressions which caused lung damage and gas embolism (conditions above and to the right of the curve) from decompressions which did not cause any detectable damage to the animals (conditions below and to the left of the curve). The solid points indicate conditions to which human subjects have been decompressed [with no obstruction to the flow of gas from the respiratory tract] with no untoward effect. 1- Sweeney (1944); 2- Hitchcock et al (1948); 3- Luft and Bancroft (1954); 4- Ernsting et al (1960). The two solid horizontal lines indicate the ratios of initial to final pressures for decompression of an aircraft at 40,000 feet with cabin differential pressures of 5.0 and 7.0 Lb in^{-2} respectively.

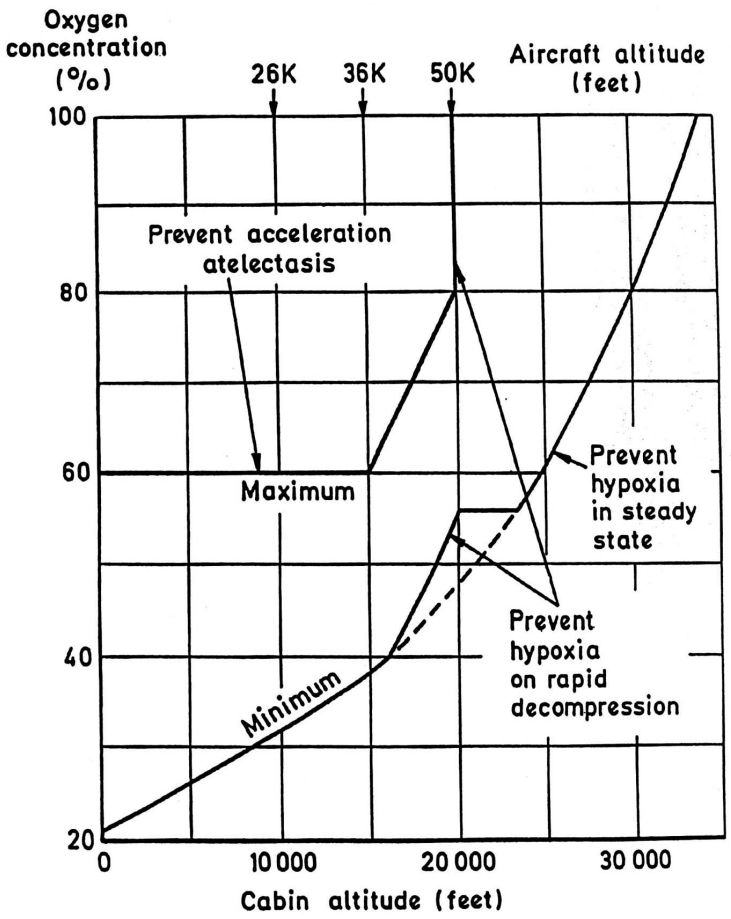

Figure 3 The relationships between the minimum and maximum concentrations of oxygen in the inspired gas and cabin altitude with the cabin pressurised for a typical combat aircraft with a ceiling of 50,000 feet, a maximum cabin differential pressure of 5.0 Lb in^{-2} and a "3G ceiling" of 35,000 feet. The lowermost curve (minimum) defines the oxygen concentration required to maintain an alveolar oxygen tension of 103 mm Hg. The notch in the latter curve defines the higher oxygen concentration required in the inspired gas to prevent hypoxia on rapid decompression of the cabin [assuming that 100% oxygen is delivered immediately after the decompression]. The uppermost curve (maximum) defines the maximum concentration of oxygen to avoid acceleration induced lung collapse.

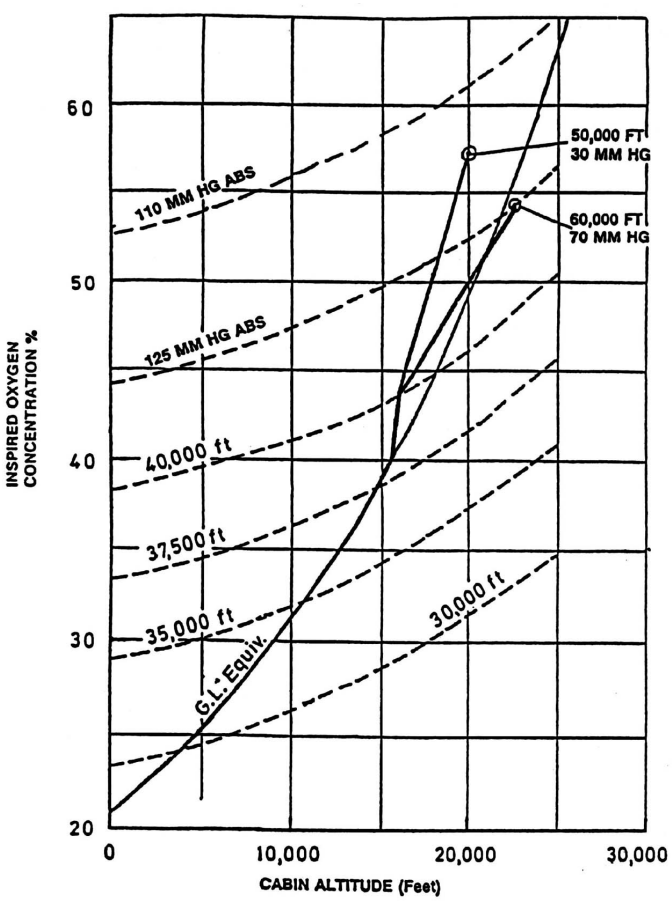

Figure 4 The relationships between the concentration of oxygen in the inspired gas and the pressure-altitude within the pressurised cabin [cabin altitude] required

i. to maintain an alveolar PO_2 of 103 mm Hg i.e. equivalent to breathing air at ground level [GL Equiv],

ii. to produce an alveolar PO_2 of 30 mm Hg on an instantaneous decompression from the cabin altitude indicated on the X axis of the figure to the cabin altitude/absolute intrapulmonary pressure indicated by the broken horizontal curves [final cabin altitudes of 30,000, 35,000, 37,500 and 40,000 feet and final intrapulmonary absolute pressures of 141 mm Hg (40,000 feet curve) 125 and 110 mm Hg],

iii. to ensure, with a cabin pressure differential of 5 Lb in^{-2}, that an instantaneous decompression from the cabin altitude indicated on the X axis, the alveolar PO_2 immediately after the decompression will be 30 mm Hg when

a. using a pressure breathing system which provides a breathing pressure of 30 mm Hg gauge at 50,000 feet [50,000 FT; 30 mm Hg]

and

b. using a pressure breathing system which provides a breathing pressure of 70 mm Hg gauge at 60,000 feet [60,000 FT; 70 mm Hg].

Hyperbaric Oxygen: A Scientific Update

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Introduction

There are presently 13 indications for hyperbaric oxygen therapy (HBO), which are recognized by the Undersea and Hyperbaric Medical Society and supported by a significant body of scientific evidence[1]. Eleven of these indications are relevant to combat casualty management *. (Table 1) From the military perspective, decompression sickness and cerebral gas embolism have received the greatest attention. Recent investigations have established the medical benefits of the remaining nine indications for selected combat injuries. These indications can be broadly grouped into one of three categories: crush injuries and their sequelae, shock, and thermal burns.

Table 1 Accepted Indications:
1. Decompression Sickness *
2. Gas Embolism *
3. Crush Injury *
4. Gas Gangrene *
5. Necrotizing Infections *
6. Refractory Osteomyelitis *
7. Problem Wounds *
8. Compromised Grafts and Flaps *
9. Exceptional Blood Loss Anemia *
10. Thermal Burns *
11. Carbon Monoxide Poisoning *
12. Intracranial Abcess
13. Delayed Radiation Injury

Mechanisms of Action

The effects of high-pressure oxygen are considerable. Initially the benefits of oxygen were ascribed to improved cellular respiration. Over the past 20 years researchers have come to understand that oxygen under pressure exerts a number of "pharmacologic" effects that transcend the simple notion that HBO works by eliminating tissue hypoxia. Each of the currently accepted indications for HBO therapy is physiologically based on one or more of the following mechanisms.

- **DIRECT PRESSURE –** Perhaps the earliest perceived mechanism of action was simply the mechanical effects of pressure on gas bubbles as described by Boyle's Law. This effect is only beneficial for the acute "gas phase" treatment of decompression sickness and arterial gas embolism. Current evidence suggests that a substantial portion of HBO's benefit for these diseases is mediated through containment of reperfusion-mediated phenomenon (see below).

- **HYPEROXYGENATION** – At a pressure of 3 atmospheres absolute (ATA) the partial pressure of oxygen in plasma is over 2,000 mm Hg (6.6 volume %) which is sufficient to support life in the absence of red cells. This was dramatically demonstrated using pigs whose blood supply was rapidly exchanged with Ringers solution to reduce their hemoglobin level to less than 0.6 gm while being supported with HBO.2 In addition to the high oxygen content, the high partial pressure extends the diffusion gradient of oxygen from a typical distance of 64 microns to more than 250 microns.[3] The clinical relevance of high oxygen content and partial pressure for the salvage or support of marginally perfused or edematous tissues is clear.

- **VASOCONSTRICTION** - As a drug oxygen is unique because it is the only agent capable of inducing mild vasoconstriction while simultaneously elevating tissue pO2 levels.[4] This phenomenon occurs because hyperoxia-induced reductions in blood flow are more than offset, more than compensated by the large increase in oxygen content. The clinical benefit of this mechanism is an alteration of the

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Starling forces in favor of interstitial fluid absorption. The clinical implications are important when dealing with injured tissue where interstitial edema produces a diffusion barrier and compresses the microcirculation. HBO has the capacity to support injured edematous tissue while simultaneously reducing excess interstitial fluid. In more acute situations HBO may prevent the evolution of edema altogether.

- **NEOVASCULARIZATION** - Nonhealing or "problem" wounds are usually due to a multiplicity of factors. For most patients local hypoxia is a significant part of the problem. The use of transcutaneous oximetry allows for a more accurate identification of those wounds in which the cells are too hypoxic to respond to the reparative call of local growth factors. Under the influence of HBO, new blood vessels bud into these pathologically hypoxic wounds. In time, the pO2 levels within the wound may reach a level where the healing process becomes self-sustaining without the support HBO. Until recently little was known about the physiology of oxygen induced angiogenesis.[5,6] At the cellular level there is evidence that oxygen behaves as a cell signal to trigger wound healing as manifest by the sustained effect messenger ribonucleic acid (mRNA) production following a single dose of HBO. Work from several different investigators describe the effects of HBO more as a growth factor than a metabolite demonstrating that a single dose of oxygen stimulates mRNA transcription for 24-72 hrs.[7,8] Cells in a wound may sense oxygen pressure as a trigger which signals that appropriate conditions exist to proceed with healing.[9] Regular subsequent exposure to the threshold level reinforces the signal and supplies an important factor for repair.

- **ANTIBACTERIAL EFFECTS** - Despite the very high arterial pO2 achieved with HBO, the tissue levels in the heart of necrotic wounds may only achieve one to two hundred mm Hg. Although such levels are not bactericidal to anaerobes, it is bacteriostatic. As such, oxygen behaves like many bacteriostatic antibiotics by containing the infection and allowing normal host defense mechanisms to eradicate the infection. In addition, HBO has been shown to produce a direct synergistic effect with numerous antibiotics, such as aminoglycosides, cephalosporins, penicillin, and amphotericin B.[10,11,12] HBO also exerts an indirect synergism by converting anaerobic wounds w[it]h a low pH to aerobic wounds characterized by a normal pH. This pH shift is important, as many antibiotics do not work well at an acid pH.

- **LEUKOCYTE OXIDATIVE KILLING** - Although phagocytosis is relatively unhindered by an anaerobic environment, the killing capacity of neutrophils is markedly reduced. It is important to understand that phagocytosis per se does not kill bacteria.[13] The actual destruction of bacteria is a complex interdependence of neutrophil enzymes with neutrophil generated oxygen radicals.[14,15] By providing supplemental oxygen, HBO "turbocharges" the destructive capacity of the neutrophil.[16]

- **ATTENUATION OF REPERFUSION INJURY** - Much of the damage associated with reperfusion is mediated by the inappropriate activation of leukocytes. Following an ischemic interval the total injury pattern is the result of two components: a direct and irreversible injury component from hypoxia, and an indirect injury, which results from leukocyte activation. Hyperbaric oxygen diminishes the indirect component of injury by reducing the inappropriate activation of leukocytes.[17] The net effect is the preservation of marginal tissue that would otherwise be lost to reperfusion injury. The clinical ramifications of this mechanism are self evident for those scenarios involving significant interruptions of blood flow e.g. plastic surgery, vascular surgery, and fluid resuscitation of the microcirculation.

Selected Indications

CATEGORY I - CRUSH INJURIES AND THEIR SEQUELAE

Crush injuries are often associated with both immediate and delayed problems. Immediately following a crush or blast type injury, tissue can be categorized as viable, nonviable, or transitional. Viable tissue

recovers spontaneously without intervention. On the other hand, nonviable tissue is destined for necrosis, regardless of therapy. Transitional tissue occupies the watershed zone between nonviable and viable tissues. Clinical intervention alone will determine its fate. Edema control, tissue oxygen levels and attenuation of reperfusion phenomenon are critical determinants of outcome. Hyperbaric oxygen therapy is advocated for the treatment of severe limb trauma in association with surgery because of its effects on peripheral oxygen transport, ischemic muscle necrosis, compartment syndrome, and infection prevention. Using a variety of animal models, multiple investigators have demonstrated the benefits of HBO in the setting of ischemic muscle injury or compartment syndrome. [18,19,20,21,22,23,24,25,26,27,28]

The best human evidence for this complex injury pattern comes from Bouachour et al who performed a randomized, double-blind, placebo-controlled, clinical trial of hyperbaric oxygen therapy.[29] Thirty-six patients with crush injuries were assigned in a blinded randomized fashion, within 24 hours after surgery, to treatment with HBO (session of 100% O2 at 2.5 ATA for 90 minutes, twice daily, over 6 days) or placebo (session of 21% O2 at 1.1ATA for 90 minutes, twice daily, over 6 days). All the patients received the same standard therapies (anticoagulant, antibiotics, wound dressings). Transcutaneous oxygen pressure (TCOM) measurements were done before (patient breathing normal air) and during treatment (HBO or placebo) at the first, fourth, eighth, and twelfth sessions. The two groups (HBO group, n = 18; placebo group, n = 18) were similar in terms of age; risk factors; number, type or location of vascular injuries, neurologic injuries, or fractures; and type, location, or timing of surgical procedures. Complete healing was obtained for 17 patients in the HBO group vs. 10 patients in the placebo group ($p < 0.01$). New surgical procedures (such as skin flaps and grafts, vascular surgery, or amputation) were performed on one patient in the HBO group vs. six patients in the placebo group ($p < 0.05$). Analysis of groups of patients matched for age and severity of injury showed that in the subgroup of patients older than 40 with grade III soft-tissue injury, wound healing was obtained for seven patients (87.5%) in the HBO group vs. three patients (30%) in the placebo group ($p < 0.05$). No significant differences were found in the length of hospital stay and number of wound dressings between groups. For the patients with complete healing, the TCOM values of the traumatized limb, measured in normal air, rose significantly between the first and the twelfth sessions ($p < 0.001$). No significant change in TCOM values were found for those patients who failed to heal. The Bilateral Perfusion Index (BPI = TCOM of the injured limb / TCOM of the uninjured limb) at the first session increased significantly from 1 ATA air to 2.5ATA O2 ($p < 0.05$). In conclusion, this study demonstrates an HBO mediated improvement in healing and reduction in repetitive surgery. Extremity studies like Bouachour's are especially relevant to combat casualty management. Given the torso protection afforded by lightweight body armor, a redistribution of injury patterns to the extremities can be expected in the future.

Following the initial crush injury or blast injury, a second wave of clinical complications may ensue which are also amenable to HBO therapy. These include the necrotizing infections, which stem from the low redox potential of injured tissues, refractory osteomyelitis, and problem wounds. Each of these problems is fundamentally related to the microcirculatory damage and scar tissue generated by severe crush or blast injuries.

Necrotizing infections – The low redox potential of traumatized tissue sets the stage for both clostridial and synergistic infections. Multiple studies have confirmed the efficacy of a three-pronged approach to these diseases utilizing surgery, antibiotics, and HBO. Where HBO is available, the surgical debridements are fewer, as there is a clearer demarcation of viable and non-viable tissue and a more rapid arrest of the infection. Multiple mechanisms of action come into play to provide this tissue sparing effect and reduce mortality. The literature regarding gas gangrene and synergistic necrotizing infections has been is well established. Although there is some variability in survival between authors, the pooled survival for gas gangrene managed with HBO is 19.3% in contrast to 45.2% when only surgery and antibiotics are used. For necrotizing fasciitis, the pooled survival with HBO is 20.1% versus 47.4% when HBO is not available.

Table 2 - Necrotizing Fasciitis

Managed with HBO

Author	Number	Died	Mortality
Aasen (1989)	9	1	11.1
Bakker (1984)	27	5	18.5
Chevallier (1987)	13	4	30.8
Gozal (1986)	16	2	12.5
Him (1988)	11	1	9.1
Krasova (1992)	11	3	27.3
Ledingham (1975)	9	8	88.9
Mader (1988)	10	2	20.0
Riseman (1990)	17	4	23.5
Duke University(1991)	54	11	20.3
TOTAL	141	28	20.1%

Managed without HBO

Author	Number	Died	Mortality
Farrell (1988)	11	5	45.5
Ledingham (1975)	3	0	0.0
Mader (1988)	12	6	50.0
Majeski (1984)	20	10	50.0
Oh (1982)	28	10	35.7
Pessa (1988)	33	13	39.4
Reigels-Nielsen(1984)	5	1	20.0
Riseman (1990)	12	8	66.7
Rouse (1982)	27	20	74.7
Spirnak (1984)	20	9	45.0
Wang (1992)	18	6	33.3
Woodburn (1992)	19	7	36.8
TOTAL	208	95	47.4%

Gas Gangrene

Managed with HBO

Author	Number	Died	Mortality
Bakker (1988)	409	48	11.7
Caplan (1976)	34	11	32.4
Gibson (1986)	29	9	31.0
Gurtner (1983)	73	23	31.5
Hart (1983)	139	27	19.4
Heimbach (1980)	58	3	5.2
Him (1988)	32	9	28.1
Holland (1975)	49	13	26.5
Nier (1984)	78	30	38.5
Shupak (1984)	4	1	25.0
Unsworth (1984)	73	15	20.5
Duke University(1991)	35	7	20.0
TOTAL	141	28	20.1%

Managed without HBO

Author	Number	Died	Mortality
DeLalande (1981)	22	9	40.9
Freischlag (1985)	21	11	52.0
Gibson (1986)	17	12	70.6
Hichcock (1976)	33	14	42.4
Kaiser (1981)	20	8	42.4
Katlic (1981)	7	5	71.4
Paillier (1986)	20	8	41.0
Vo (1986)	77	31	40.0
TOTAL	217	98	45.2%

Refractory osteomyelitis - The use of HBO for the treatment of osteomyelitis is reserved for those patients who have refractory osteomyelitis characterized as a failure to respond to respond to antibiotics, debridement and correction of any soft-tissue defects. For selected “refractory” patients the use of the Ilizarov technique may permit “en block” resection of infected bone from the appendicular skeleton. However in those instances involving refractory osteomyelitis of the spine, sternum, skull, or other settings, which do not permit such aggressive resection, HBO therapy becomes an treatment option. Controlled animal studies have demonstrated the hypoxic nature of chronically infected bone and verified the benefits of HBO.[30,31,32,33,34,35] Specifically, HBO enhanced collagen production, capillary angiogenesis, improved osteoclast and neutrophil function.

Problem wounds - Problem or chronic wounds are characterized as those defects that fail to respond to 4-6 weeks of established medical and surgical management. The associated pathology is usually an interplay between hypoxia and infection. Tissue oxygen tension in or near such wounds is usually 20 mm

Hg or less. The attendant hypoxia blunts fibroblast proliferation, collagen production and capillary angiogenesis. As previously noted, the oxidative killing capacity of the leukocyte is markedly diminished as well as bacterial phagocytosis.[36] Experimentally the elevation of oxygen tension may be as effective as antibiotic administration.[37] More recent investigations have pursued the concept of oxygen as a cell regulator. The discovery of nitric oxide as a cell signal has opened the possibility that other gases, such as oxygen, may also regulate cell function at the nuclear level. Experimental findings have associated oxygen with upregulation of platelet derived growth factor receptor gene expression, nitric oxide synthase gene upregulation, production of epidermal growth factor receptors, production of vascular endothelial growth factor and sustained fibroblast proliferation for periods of 24-72 hrs following a single dose of HBO. [6-8,38,39,40,41]

Patient selection – Although tissue hypoxia may be inferred on clinical grounds, it has been difficult to reliably confirm its presence until recently. The development of transcutaneous oxygen measurements (TCOM's) now permits an evidenced based use of hyperbaric oxygen therapy.[42] Padberg demonstrated that there is no single threshold value that is associated with healing but rather a probability continuum. When the periwound pO2 is 20 mm Hg the probability of spontaneous healing is less than 50%.[43] Typical TCOM studies are a two-stage process. The first phase involves calibration and measurements on room air to determine the distribution and magnitude of hypoxia. The second phase utilizes an "oxygen challenge" wherein the patient is placed on 100% oxygen for 10 minutes. When these 2 elements are combined, they answer two important questions: is hypoxia a limiting factor in healing and is it correctable by oxygen supplementation. Transcutaneous oxygen values are increasingly recognized as the most reliable noninvasive measure of perfusion, oxygen tensions and predictor of clinical outcome. In addition TCOM's help to select the most distal amputation level that is associated with spontaneous healing and has been demonstrated to be superior to clinical judgment.[44] Choosing the most distal amputation level that will heal is difficult. Mars et al compared clinical site selection versus clinical opinion augmented with TCOM data and found that the amputation revision rate was reduced from 51% to 8.2% when TCOM's were used to supplement clinical opinion.

Following the primary crush injury, the secondary complications of infections and problem wounds there may be a third wave of complications, which occur if flaps or grafts become compromised during the reconstructive phase. Here too, HBO therapy is beneficial when provided in a timely manner. A number of studies have demonstrated enhanced survival of flaps and graft with HBO therapy.[45,46,47,48,49]

In the early work of Champion et al, using a rabbit pedicle flaps, 100% survival was achieved using HBO.[50] In contrast, the non HBO group experienced 40% necrosis. Perrins demonstrated improved outcome of skin grafts in a prospective randomized trial of HBO. In terms of the "reconstructive ladder" the free flap is the most complex option.[51] Stevens et al designed a model to simulate a free flap procedure with a period of secondary ischemia. In this model, an axial skin flap is subject to six hours of ischemia, which would simulate the initial interruption of perfusion that occurs with the creation of a free flap followed by 2 hours of reperfusion. This was than followed by a secondary ischemia time of 6, 10, or 14 hours which simulated flap compromise which may occur from hematoma, thrombosis, dressings, or venous outflow obstruction. The animals were separated into three treatment groups consisting of air, 100% oxygen or hyperbaric oxygen. The secondary ischemic time at which 50% of the flap survived was 6 hours for both the air and oxygen groups. For the HBO animals, the secondary ischemic time for 50% survival was increased to 10 hours.[52]

CATEGORY II - HEMORRHAGE / SHOCK

The physiology for using high-pressure oxygen as a blood substitute is well established. At three atmospheres absolute (ATA) pressure, the plasma content of dissolved oxygen is sufficient to support life without blood. Given the dwindling reserve of blood and the logistics of blood deployment, HBO offers a short-term solution, which permits rapid evacuation of injured troops to a more centralized location or short-term stabilization while blood is being transferred. However there is now evidence that

hemorrhagic shock sets in motion events that are not corrected by transfusion alone. The most prominent events are the elaboration of tumor necrosis factor (TNF) and interlukin-6 (IL-6), which are associated with increased mortality.[53] In a zymosan model simulating septic shock there is increased production of TNF and nitric oxide metabolites (NO_x) that are associated with increased mortality.[54] In both the hemorrhagic and septic shock model HBO reduces TNF, IL-6, and NO_x production and most importantly, it improves survival.

CATEGORY III – THERMAL BURNS

A substantial number of animal studies have clarified the benefits of HBO for the management of moderate and severe burns. These include shortened healing time, reduction of infection, reduced fluid requirements and reduced burn evolution from partial to full thickness loss. Clinical studies have affirmed much of the animal data. Cianci and others have documented shortened hospital stays, decreased fluid requirements, and reduction in surgical procedures.[55,56] Some burn centers are now following a strategy of early and aggressive surgical debridement. When this approach is used, the benefits of HBO are obscured. In a prospective trial by Brannan et al HBO failed to show any reduction in length of stay or surgical procedures.[57] However, both groups received very early and aggressive burn excision, which did not permit a clear delineation of HBO's salvage effect for "transitional" tissue. It should also be noted that early radical burn excision is very difficult for selected locations such as the face and hands and may not be possible in a mass casualty situation.

SUMMARY

Given that oxygen is one of the fundamental cornerstones of life, it is not surprising to find that it behaves in a multidimensional capacity. During acute microcirculatory failure it functions simply as a nutrient or metabolite. In this capacity, HBO must be provided several times per day. When there is a transient interruption of tissue perfusion, we find that high dose oxygen prevents the secondary deterioration of the microcirculation by containing reperfusion phenomenon. Likewise when the stress is more global such as hemorrhagic shock or septic shock, we again find a beneficial role of HBO in terms of reduced cytokine production and improved survival. Under these circumstances acute intervention is also important, however the requirements for HBO may be as few as three to six treatments. For the more chronic situation of a nonhealing wound associated with regional hypoxia, documented by oxymetric studies, we find that HBO behaves more as a cell signal requiring only once a day dosing.

For combat casualty management, logistical and operational issues have limited the widespread use of HBO. The recent development of the hyperlight chamber by the United States Airforce will permit a substantially more rapid deployment of this effective therapy in the theater of operation.

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USAF Experience with Hyperbaric Therapy of Altitude Decompression Sickness (1941-1999)

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Introduction

Decompression sickness (DCS) is characterized by a plethora of protean symptoms. It can range from mildly annoying to life threatening. Its etiology is tissue and/or vascular bubbles. Indeed, decompression sickness has been a recognized disease since its first report by Triger in 1841. (10) First noted in construction workers laboring in pressurized caissons and later in diving operations, decompression sickness was not even postulated in aviation until 1901 by von Schrotter. (8) Later (1917), Henderson popularized the concept. (11) Over the next forty years some 17,000 cases of altitude DCS were described. At least 743 were considered serious and at least seventeen were fatal. (6) However, altitude decompression sickness was not treated with recompression until Behnke employed it in 1941. (6) Despite his apparent success, supportive care remained the standard. Then, in 1959, under the most extreme of clinical circumstances (DCS shock), Donnell and Norton essentially plucked an aviator from the brink of death with recompression. Thirty-eight hours after entering the chamber the pilot emerged symptom free. (7) This spectacular success launched the research underpinning today's treatment regimen for altitude decompression sickness. Indeed, this paper describes the USAF treatment effort over the last fifty-eight years.

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Materials and Methods

In this review, 145 cases studied by Davis et al (1977) will be examined in conjunction with the 528 cases studied by Weien and Baumgartner (1990). (6,19) These cases represent USAF hyperbaric therapy for altitude decompression sickness from 1941-1986. Since that time no comprehensive examination of USAF hyperbaric therapy has been performed. As a result, the last thirteen years (1987-1999) of USAF hyperbaric therapy was examined.

The research records maintained at the Davis Hyperbaric Laboratory (USAF School of Aerospace Medicine; Brooks AFB, Texas) were reviewed. By regulation, all cases of decompression sickness treated with hyperbaric therapy are reported to the Davis Hyperbaric Laboratory. These reports consist of Air Force Form 1352 (Hyperbaric Patient Information and Therapy Record), Air Force Form 361 (Chamber Reactor/Treatment Report), and Standard Form 502 (Medical Record---Narrative Summary). In addition, other information sources include in-patient, transfer, and aeromedical summaries.

A list of DCS victims was generated from the laboratory's database. This list included every treatment case reported to the laboratory from 1 January 1987 to 31 December 1999. Each record was then individually recovered and information extracted using a detailed two-page survey. The records were found in three formats: scanned onto a CD-ROM (1987-1990), scanned onto Canonfile diskettes (1991-1994), and hard-copy paper (1995-1999). Tracking record numbers, patient names, and birth-dates proved inconsistent. As a result, every record within the laboratory database was examined and cross-referenced to the computer listing. Interestingly, the earlier records closely matched the computer listing; however, the later records did not come close. By individually examining each database record a significant number of cases (not on the computer listing) were discovered. Although missed records are not likely, it is possible.

Once a record was accessed, it was extracted onto the two-page survey. Here, demographic information, exposure data, predisposing factors, symptom onset, symptoms and signs, diagnosis, disease progression, treatment and outcome data, and complications were recorded. No identifying personal information was obtained.

A total of 729 records documenting treatment for decompression illness were scrutinized. Of these, nineteen proved not to have DCS. Another seven did not have enough information to be of any value. Twenty had arterial gas embolism and 203 were diving DCS. The remaining 480 cases were altitude decompression sickness.

The present effort incorporates not only the most recent 480 cases, but also the 145 cases of Davis et al and the 528 cases of Weien and Baumgartner. Thus, the substance of this review spans approximately 58 years and summarizes the therapeutic outcome of hyperbaric therapy for some 1153 cases of altitude decompression sickness.

Results and Discussion

Exposure

The bulk of altitude decompression sickness in the USAF results from chamber operations (93%). From 1941-1976 chamber operations accounted for 88% of cases. (6) From 1977-1986 chamber operations accounted for 92% of cases. (19) And, from 1987-1999 chamber operations accounted for 91% of cases.

Type of Altitude Exposure				
		Chamber	Operations	unclear
1941-1976		131	14	
1977-1986		507	21	
1987-1999		437	42	1
Totals		**93%**	**7%**	

It is interesting to note that 7% of the cases came from military operations. The earlier reports do not specify aircraft type; however, the most recent review found thirteen different aircraft. These ranged from a helicopter to a high altitude parachutist to a U-2. Of note, the U-2 was responsible fourteen of the forty-two operationally-attributed cases of DCS.

As expected, the maximum altitude attained during exposure reflected the training profiles. Almost a quarter of the cases were in the 20,000-25,000 feet range; almost a third were in the 30,000-35,000 feet range; and, again, almost a quarter were in the >35,000 feet range. For years the Type I "flight" to 35,000 feet was used for initial training. In addition, training in a Type II "flight" to 43,000 feet was routine for initial training. And, refresher training, FAA training, and flight nurse training all used "flight" profiles to 25,000 feet. (9) Clearly, the more common the "flight" profile the more common the altitude DCS. Interestingly, operational cases were more common below 25,000 feet.

Maximum Altitude of Exposure							
		< 20,000	20-25,000	25-30,000	30-35,000	> 35,000	unclear
1941-1976		5	14	11	51	63	1
1977-1986							
1987-1999							
----Chamber		11	118	61	147	87	14
----Operations		10	12	9	4	4	3
Totals		**4%**	**23%**	**13%**	**32%**	**24%**	**3%**

Demographics

When looking at chamber operations either the student or the inside observer (IO) can fall prey to altitude decompression sickness. There seems to be no clear predilection. Three time segments were studied and each had a different IO : student ratio. Exposure data was available from 1996 and 1997 at Brooks AFB. There was a four-fold difference in DCS rates between the student (0.422%) and inside observer (0.097%). In contrast, Davis et al (1973-1976) reported a three-fold greater incidence of DCS among inside observers (0.064% versus 0.020%) while Weien & Baumgartner showed no difference. (6,19)

Incidence of Chamber DCS (in percent)			
	1973-1976	1977-1987	1996-1997
Inside Observer (IO)	0.064%	0.058%	0.097%
Student	0.020%	0.058%	0.422%
IO : Student Ratio	**3 to 1**	**1 to 1**	**1 to 4**

Additionally, a review of the US Navy experience mirrors that of Davis et al. Only one study period (1959-1968) showed a student predominance. In fact, from 1972 through 1988 Navy inside observers suffered significantly more DCS than students. (3)

Why students might suffer more DCS stems from the routine training in hypoxia recognition. During the chamber flight students will remove their oxygen mask to identify their own special hypoxic symptoms. Thus, the DCS protection of oxygen is prejudiced. Of note, the inside observers do not go off oxygen. Why the inside observers might suffer more DCS stems from their activity during the training. When tissues move against one another there is a localized reduction in hydrostatic pressure creating a "bubble-friendly" milieu. (17) Thus, the DCS protection of inaction is prejudiced. Of note, the students remain dormant throughout the training. Clearly, no explanation for this contradictory data is readily apparent. In any event, the incidence rates for both the student and the inside observer (independent of time period studied) are very low.

The student-IO differences stimulate interest in the demographics of the DCS victims. The most recent review revealed no surprises. As expected, there was an overwhelming preponderance of young people. Over half were between 20-30 years of age and 85% were under 35 years. Eighty percent were Caucasian with almost 90% Air Force personnel. Interestingly, aircrew made up less than 20% of the cases. The vast majority was otherwise (ie, students, technicians, physiologists).

Gender Distribution of DCS				
		Male	Female	Female/Male Incidence
1941-1976		128	20	
1977-1986		334	95	4 to 1
1987-1999		318	162	
Totals		**74%**	**26%**	

The one demographic factor examined by all three studies was gender. Clearly, there is an overall male predominance of cases. However, over the last thirteen years a full third of the DCS was in females. Contrast this to the USAF in general. From 1980-1994 women made up only 12.7% of the active duty USAF personnel. (1) This certainly suggests an over-representation of DCS with women. Indeed, the concept of female predisposition is not new. Bassett, in a retrospective review, reported a ten-fold greater incidence of chamber-induced DCS in women. (4) Similarly, Weien and Baumgartner also observed a significant difference. They reported a four-fold greater incidence in females from 1977 to 1986 (0.206% versus 0.048%). (19) In addition, Bangasser, in a diving survey, discovered a three-fold greater incidence in female diving instructors and Leger Dowse et al, in a large diving survey performed in the United Kingdom, found a two-fold greater incidence. (2,14) These observed differences have been variously attributed to fat and/or hormones. (15,16,18) In any event, again, the actual rates of decompression sickness are very low.

Symptomotology

Symptom presentation certainly reflects the literature---almost all instances of decompression sickness present within the first 24 hours after an exposure. (10,12,13) In 1137 cases of altitude decompression sickness 60% presented at altitude or within two hours of exposure.

Onset of Symptoms

		Ground		
	at Altitude	< 2 hours	> 2 hours	unclear
1941-1976	72	43	23	7
1977-1986	123	173	225	
1987-1999				
----Chamber	94	158	186	9
----Operations	23	12	7	
Totals	**27%**	**33%**	**38%**	**1%**

This was more closely examined during the last thirteen years. Again, a full 61% of cases presented at altitude or within 2 hours of exposure. Within 10 hours of exposure 83% had symptoms and within 20 hours 94% had symptoms. At 25 hours 97% were symptomatic. Only 3% of cases appeared beyond the 25 hour point.

Over the past several decades the symptom patterns have changed. In fact, there seems to be an increasing variety of patterns observed. Excluding shock, Davis et al noted nine patterns, Weien and Baumgartner described eleven patterns, and, most recently, nineteen different patterns were encountered. This may well reflect a greater reliance on descriptive diagnosis.

Patterns of Altitude DCS

	Number of Patterns	Type I	Type II
1941-1976	14	61%	39%
1977-1986	11	80%	20%
1987-1999	19	75%	25%

Type I decompression sickness refers to skin involvement (itch, rash, lymphatics), “bends” (arthralgia, myalgia), and peripheral nervous system involvement (tingling/numbness/temperature sensations without focal findings). (6,19) The inclusion of peripheral nervous system in Type I decompression sickness is limited to altitude DCS. In no way should this symptom complex be considered Type I DCS in caisson or diving DCS. Type II decompression sickness refers to neurologic involvement (with focal findings), “chokes” (pulmonary involvement), abdominal/pelvic pain, and shock.

Although the number of symptom patterns have changed over the decades, the most common patterns have remained the same. *Bends alone* predominates at ~60%. The next most common pattern is *neurologic alone* at ~10% followed *by bends plus neurologic* at ~8%. Any combination of Type I and Type II symptom patterns make up the remainder of the case presentations.

Treatment

Throughout the 58 years of this review 95-98% of altitude decompression sickness has been successfully treated with recompression. Clearly, hyperbaric therapy works and remains the standard of care.

Most recently (1987-1999), hyperbaric therapy was 95% successful. However, there were 38 instances of recurrence and 48 instances of tailing treatments. Only 3.5% of cases had permanent residual (ie, joint ache, sensory deficit, headache). Interestingly, Treatment Table 5 (TT5) was 80% successful when applied within the first ten hours of symptoms. Of note, this does not include any delay to symptom presentation (~ 40% presented with a greater than 2 hour delay). Equally fascinating, Ground Level Oxygen (GLO) succeeded 20% of the time. Of note, effective use of GLO without hyperbaric therapy was not examined in this study.

Treatment Table Outcomes (percent success)

	TT 1-4	TT 5	TT 6	TT 8	other	**Overall Success**
1941-1976	78%	99%				**98%**
1977-1986		100%	98%	100%		**98%**
1987-1999		79%	89%	80%	43%	**95%**

Complications of Hyperbaric Therapy

As with any therapeutic intervention complications can happen. Over the last thirteen years only fifty-three complications were encountered. As expected, ear block (~50%) and pulmonary oxygen toxicity (~36%) predominated. There were two seizures (central neurologic oxygen toxicity) and two claustrophobic reactions. No permanent sequelae were documented.

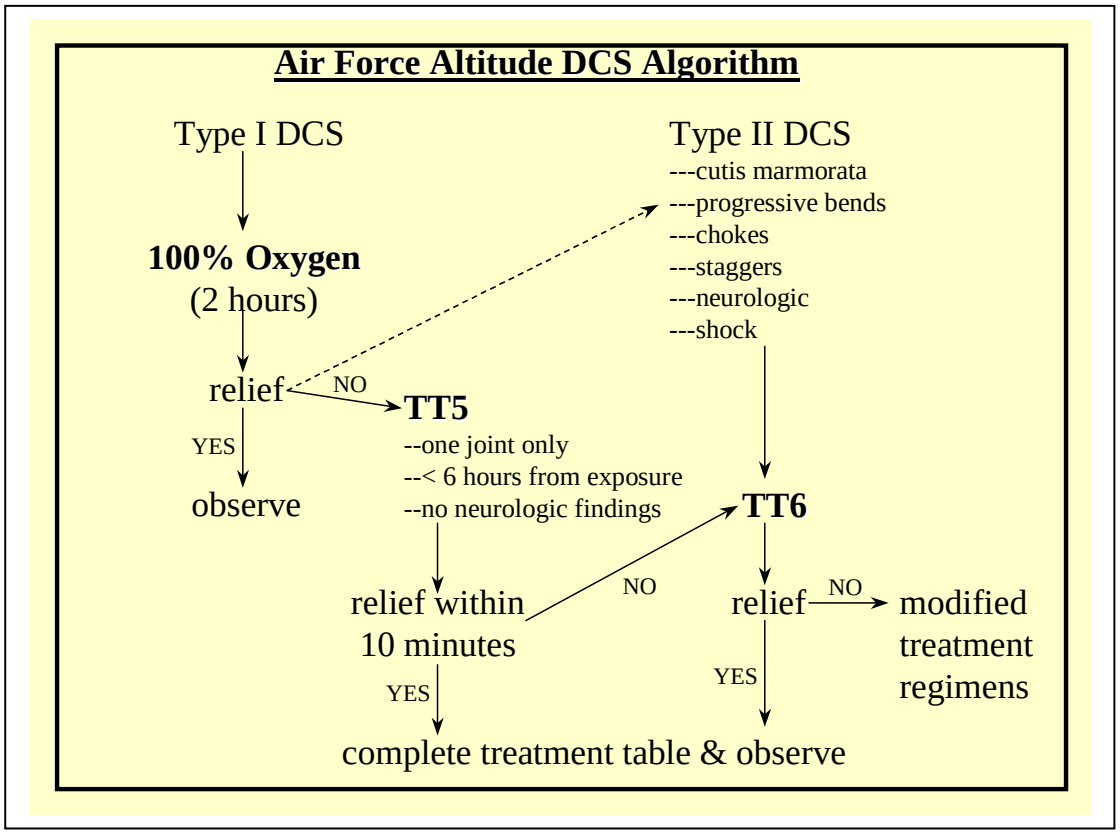
Complications of Treatment (1987-1999)

Ear Block		26
---myringotomy	2	
Pulmonary Oxygen Toxicity		19
CNS Oxygen Toxicity		6
---seizure	2	
Claustrophobia		2
Totals		**53**

Air Force Altitude DCS Treatment Algorithm

During the last half century an algorithm for the treatment of altitude decompression sickness has been developed by the USAF. It is apparent that the hyperbaric therapy portion of this algorithm works (95-98% successful).

Documented success with TT5 and anecdotal success with GLO outside the parameters of the algorithm suggest that more oxygen and less pressure might well be considered. A natural consequence of this thinking is to revisit both TT5 and GLO. (5) Indeed, future investigations may well demand a new iteration of the algorithm.



Summary

This study reviewed 58 years hyperbaric therapy for altitude decompression sickness in the USAF. It incorporates the studies of Davis et al and Weien and Baumgartner. (6,19) To their work (1941-1986) is added another report (1987-1999).

This study confirms the continued success of hyperbaric therapy for altitude decompression sickness documenting a 95-98% success rate. It also reaffirms that most cases are associated with altitude chamber training. In fact, the maximum altitude breakdown clearly reflects the chamber training profiles. Most symptoms appear within two hours of exposure and Type I symptoms predominate. Indeed, the most common symptom pattern is bends alone. And, as with any medical treatment, there are complications, but there were no sequelae of these complications.

This study did raise several interesting questions worthy of future attention. Are females more susceptible than males? If so, why? Why do inside observers and students have different rates of DCS? Furthermore, why are the observations to date conflicting? And, finally, can the Air Force treatment algorithm be tweaked to more efficiently use GLO and TT5?

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Headache and Decompression Sickness: Type I or Type II?

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Decompression Sickness (DCS) results from exposure to reduced environmental pressure. As a result, excess nitrogen evolves from tissues. This gas may then form bubbles that may localize in tissue or vessels. They then create symptoms that range from mild to severe. Commonly, mild symptoms are joint pains and are called Type I DCS. Severe symptoms can run a range of neurological manifestations and are called Type II DCS. Treatment for Type I may only require ground level oxygen, while Type II necessitates recompression with 100% oxygen (7).

Headache associated with DCS is not new. Ryles and Pilmanis reported an eleven-year period from the Armstrong Laboratory at Brooks Air Force Base, Texas. Out of 447 subjects, 0.9% reported headache (14). The German Air Force experience during World War II reported a 2.0% incidence rate (3). Bason searched the US Navy in-flight and altitude chamber experience. His incidence rates were 6.7% and 8.6% respectively (1,2).

The basis for this paper stems from two cases seen in the Davis Hyperbaric Laboratory and Air Force Research Laboratory at Brooks Air Force Base, Texas. This then prompted a review of headache DCS in the USAF. The traditional view has always been that a headache associated with DCS must be serious, Type II, or neurologic DCS. Yet in many cases there is no associated neurological symptoms. This begs the question, should headache always be considered Type II DCS? This paper will propose an alternative view.

Case 1

A twenty-one year old female was an altitude research protocol subject. She received no oxygen pre-breathe and subsequently went to 22,500 feet on 100% oxygen. She then developed an occipital headache at 135 minutes into the protocol. On return to ground level, she was nauseous with mild tenderness over the occipital suture. Her detailed neurological exam was normal. Recompression with 100% oxygen produced relief within fifteen minutes. Follow up revealed no recurrence.

Case 2

A twenty-seven year old female was an altitude research protocol subject. Her altitude chamber flight to 35,000 was uneventful. Nine hours later she developed a left lateral orbital headache. She did not present for evaluation and the next morning awakened symptom free. She then participated in another chamber flight to 43,000. Two hours later she developed the same left orbital headache. On evaluation she had mild discomfort to palpation over the left orbit yet no sinus tenderness. A detailed neurological exam was normal. She was given 100% oxygen, without recompression, and experienced relief in 45 minutes. Follow up revealed no recurrence.

Both cases pose an intriguing question. Should headache always be considered Type II DCS? DCS has a wide range of symptoms. This makes it difficult to diagnose and frequently can result in un-

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necessary grounding of a pilot. The traditional view has always been to classify headache as neurologic and hence Type II or serious DCS. Yet many cases, like these two, have no associated neurological symptoms. An alternative explanation is proposed for headache DCS. The skull has many suture joints. Bubbles within these sutures can cause headaches. Hence, some headaches can be considered joint pain or Type I DCS.

This prompted the current study. Thirteen years of headache in the USAF were reviewed and categorized for the years 1987-1999. Retrospectively, an attempt was made to identify and classify each case into Type I and Type II DCS. Perhaps the view of sutures as joints would re-classify some cases from Type II into Type I DCS. This paper provides these results along with the supporting basis for this alternative view.

The background for this paper is based on orthodontic and osteopathic medicine. For years craniofacial remodeling has relied on suture mobility. In fact, orthodontic remodeling capability during adulthood stems from the fact that the fronto-zygomatic suture persists as a functional articulation until late in life (6). Also for the past one hundred years, Osteopathic Medicine has regarded craniofacial sutures as joints. In fact, during cranial-sacral treatment, these sutures are actually manipulated or moved. The traditional view is that sutures are fused; they are not joints. An alternative view is that sutures are <u>not</u> fused--they are joints. Hence, a DCS headache can be joint DCS or Type I DCS. This contrasts with the traditional view that a DCS headache must be neurologic or Type II.

Literature Review

In order to understand this alternative view, it's essential to look at the anatomy and physiology of sutures. Numerous studies have explored the question of suture fusion. Upledger and Retzlaff examined cadavers (n=17) between the ages of 7-78 years and ten squirrel monkeys. Gross and microscopic evaluation revealed the sutures remained clearly identifiable structures without evidence of ossification (13). Kokich examined 61 human cadavers of age 20-95 years. The purpose was to evaluate changes in ossification at five-year intervals. This is important in orthodontics. It was essential to know at what age suture remodeling is no longer possible due to fusion. Extensive examination of the fronto-zygomatic suture was done by histological, radiological, and gross dissection techniques. Kokich found no synostosis (histologic changes that ultimately lead to fusion) until very late in adult life. In fact, there was no evidence of complete fusion until age 95! He concluded orthodontic remodeling was possible throughout adulthood since the fronto-zygomatic suture persists as a functional articulation until late in life (6).

Sutures are morphologically variable with different amounts of interdigitation. Jaslow wanted to know if sections of skull with sutures have different mechanical properties than adjacent sections without sutures. Also, he was wondered if these properties varied with different amounts of inter-digitation. In goats, he looked at the bending strength and impact energy absorption of sutures versus the surrounding cranial bones. He found sutures were not as strong as bone in bending. However, sutures were able to absorb 16-100% more energy per unit volume during impact loading than bone. This demonstrates the utility of patent sutures in adults as important shock absorbers (4).

The histology of sutures reflects the function -- a firm bond of union between two bones, yet allowing a little movement. At all ages, this motion is ensured by two uniting layers that adjoin the bones and five intervening layers (the sutural ligament) that allow movement (9). (See figure 1) The uniting layer is actually two layers of fibrous tissue, an external and internal layer. The five layers of the sutural ligament include two layers of fibrous capsule, two layers of cambial tissue, and a central zone of connective tissue that contains nerves and blood vessels (9). Essentially, this sutural ligament is periosteum and a matrix of very vascular connective tissue composed of collagenous, reticular, and elastic fibers (11).

It is important to understand that the developing skull contains both sutures and synchondroses. This distinction has histological importance. Synchondroses have cartilage interposed between the bony surfaces. In contrast, sutures have well vascularized, dense, fibrous connective tissue, segmented into distinct layers. Synchrondoses will show evidence of fusion by CT scan (8). In sutures, synostosis is prevented by the non-osteogenic nature of the central part that limits bone growth (9).

Sutures have four articular patterns that result in different types of movement. The plane suture has bony surfaces that abut one another. The squamous suture has beveled bone surfaces that overlap. Both of these types permit sliding and separation. Serrate sutures have saw-toothed edges where the bones meet. Denticulate sutures have teethlike bony projections that interlock with adjacent bone. Both these types allow for slight flexion (12).

Numerous studies have been done to evaluate suture motion. Squirrel monkey studies demonstrated suture movement as measured by force displacement transducers attached to the mid-point of the parietal bones. This movement was found to be associated with respiratory and cardiac activity. (See figure 2) Flexion and extension of the spine caused the parietal bones to move relative to the spinal movement. (See figure 3) It is suspected this movement is caused by changes in the cerebrospinal fluid pressure. Additionally, there was motion independent of respiratory or cardiac activity (10). (See figure 2)

If sutures may be considered as joints, then a slightly different approach to potential DCS patients with a headache may be followed. A detailed neurologic exam must be done to rule out a neurologic component. The differential diagnosis may include sinus block, pain from an oxygen mask or helmet, and dehydration. Additionally it is necessary to localize the pain, if possible, to a suture. What is produced is a potential criteria for Type I instead of Type II DCS. This includes no clear alternative diagnosis, a localized headache along the suture, and no nerologic findings. With this understanding of sutures as joints, it seemed reasonable that some DCS headaches could be considered joint pain of Type I DCS. This prompted a look at thirteen years of headache DCS in the USAF.

Materials and Methods

The research records maintained at the Davis Hyperbaric Laboratory (USAF School of Aerospace Medicine, Brooks AFB, Texas) were reviewed. By regulation, all cases of decompression sickness (DCS) treated with hyperbaric therapy are reported to the Davis Hyperbaric Laboratory. These reports consist of Air Force Form 1352 (Hyperbaric Patient Information and Therapy Record), Air Force Form 361 (Chamber Reactor/Treatment Report), and Standard Form 502 (Medical Record---Narrative Summary). In addition, other information sources include in-patient, transfer, and aeromedical summaries.

A list of DCS victims was generated from the laboratory's database. This list included every treatment case reported to the laboratory from 1 January 1987 to 31 December 1999. Each record was then individually recovered and information extracted using a detailed two-page survey. The records were found in three formats: scanned onto a CD-ROM (1987-1990), scanned onto Canonfile diskettes (1991-1994), and hard-copy paper (1995-1999). Tracking record numbers, patient names, and birth-dates proved inconsistent. As a result, every record within the laboratory database was examined and cross-referenced to the computer listing. Interestingly, the earlier records closely matched the computer listing; however, the later records did not come close. By individually examining each database record a significant number of cases (not on the computer listing) were discovered. Although missed records are not likely, it is possible.

Once a record was accessed, it was extracted onto the two-page survey. Here, demographic information, exposure data, predisposing factors, symptom onset, symptoms and signs, diagnosis, disease progression, treatment and outcome data, and complications were recorded. No identifying personal information was obtained.

A total of 729 records documenting treatment for decompression illness were scrutinized. Of these, nineteen proved not to have DCS. Another seven did not have enough information to be of any value. Twenty had arterial gas embolism and 203 were diving DCS. The remaining 480 cases were altitude decompression sickness. Of these, the seventy cases of DCS associated with headache were examined for this report.

Results

A retrospective review of seventy cases was performed. Normally headache associated with DCS is considered Type II DCS. Recall the original seventy cases would be considered Type II DCS. Additionally, recall the prospective criteria included no clear alternative diagnosis, localized headache along a suture, and no neurologic findings. The retrospective data made it impossible to rule out an alternative diagnosis. So, this one criteria was substituted with rapid resolution of symptoms within thirty minutes of recompression treatment. Using the three criteria, sixteen cases or 23% might be considered Type I DCS. Because of the limitations of retrospective data, the criteria was loosened to only include the headache cases with a negative neurologic exam. The cases that met the criteria that could be classified as Type I were 63% or 44 cases!

Discussion

Having established that sutures are joints, DCS headaches may be considered joint pain. However, it is imperative that a thorough history be obtained to rule out other causes of headache. The differential diagnosis may include sinus block, pain from an oxygen mask or helmet, and dehydration. Additionally, a detailed neurological exam must be done to rule out a neurological component. The physical exam should confirm that the headache is localized to a suture. This suggests potential criteria for categorizing headache as Type I instead of Type II DCS. These criteria include no clear alternative diagnosis, no neurological findings, and a headache localized to a suture.

Recent stroke studies demonstrate the use of neurologic damage markers to aid in diagnosis. It is possible that these markers may be sensitive enough to help confirm true neurological DCS from joint pain. Use of neurological damage markers combined with physical exam findings of headache localized to a suture suggests a method to confirm this alternative view.

This retrospective study certainly cannot validate this alternative view. However, it does strongly suggest a prospective study be done. Acquisition of detailed data would include the three criteria: no alternative diagnosis, a headache localized to a suture, and a negative neurologic exam. Additionally, recent stroke studies demonstrate the use of neurologic damage markers to aid in diagnosis of various neurologic emergencies. These markers, specifically neuron specific enolase and tau protein are released from dying and ischemic neurons into the CSF. Crossing the blood brain barrier, they can be measured in the serum. (5) The use of neuron specific damage markers combined with this criteria suggests a method to confirm this alternative view. Additionally, a marker to identify neurologic DCS might be confirmed.

The aeromedical implications of Type I versus Type II DCS can be very different. In the USAF and the US Army, Type I DCS requires grounding for 72 hours. Type II DCS without residual signs and symptoms additionally requires a normal neurology consultation before returning to flying status. The USN is more restrictive. Type I DCS is grounded for one week. Type II DCS is grounded for one month followed by waiver action considered on a case by case basis. The FAA grounds both Type I and Type II until cleared by a qualified medical official.

Many military theaters today are remotely located. Type II DCS requires recompression treatment and a neurologic consultation before being returned to flight status. If cases could safely be classified as Type I instead of Type II DCS, this simplifies the process. Return to duty would be accelerated--essential in today's military operations.

In conclusion, the problem is due to an exposure to reduced ambient pressure. A headache develops that is localized without associated neurological findings. Our question is, must this always be considered Type II DCS or can it be considered Type I? The answer depends on following a traditional or a newer alternative view of headache DCS. The traditional view states the skull is without joints; hence bubbles causing a headache must be neurologic DCS, Type II, or serious DCS. The alternative view suggests the skull has many suture joints; thus, bubbles causing a headache may be joint DCS, Type non-serious DCS or I!

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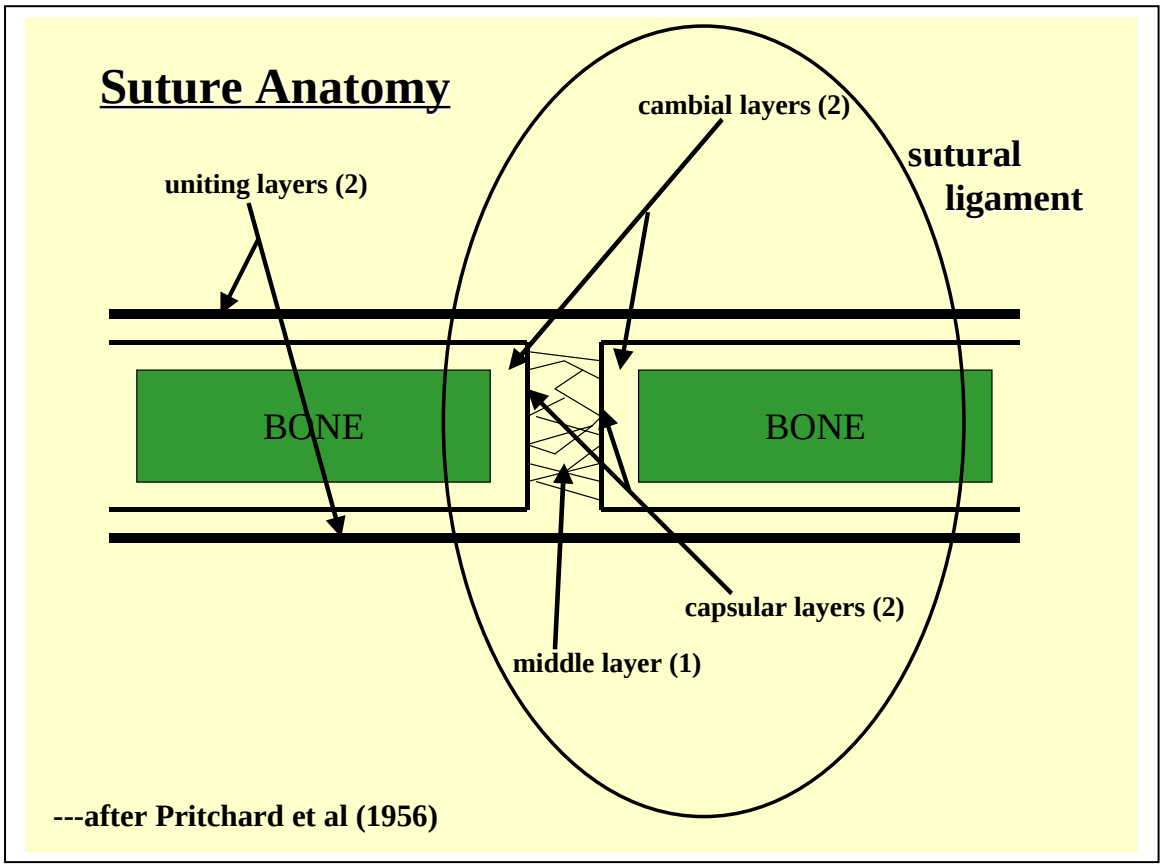

Figure 1. Sutural Anatomy

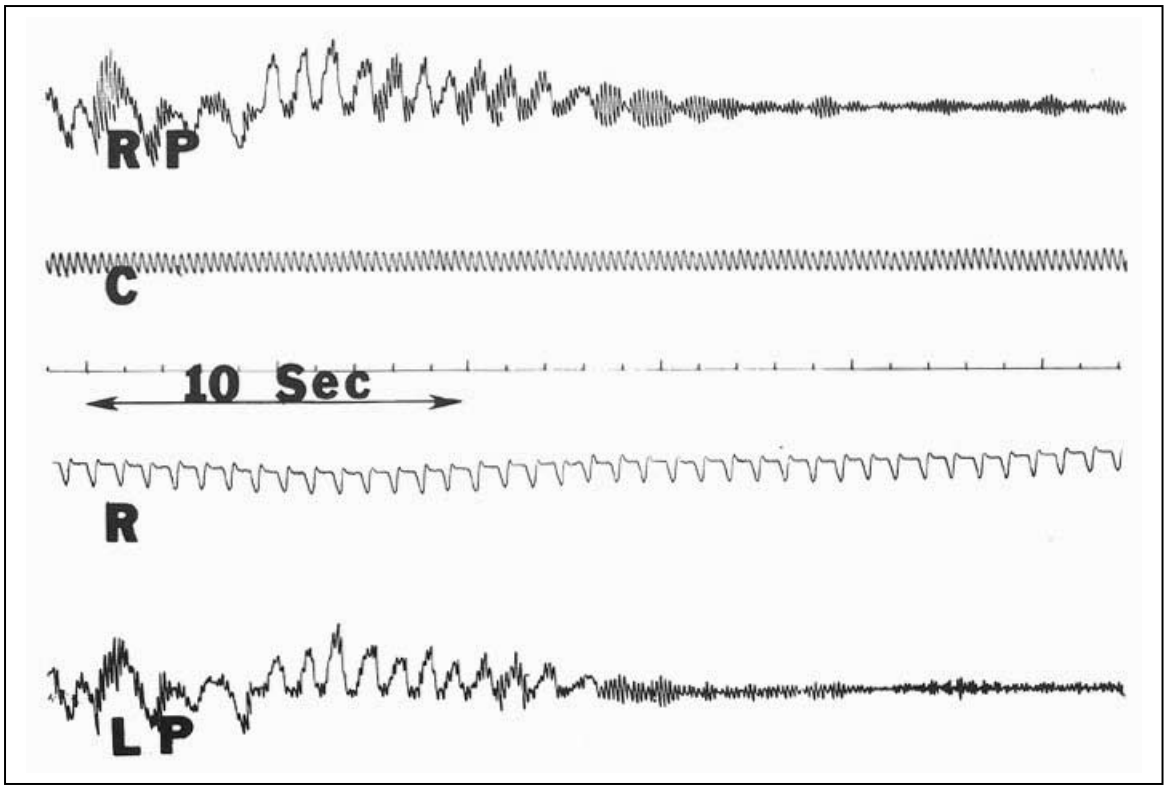

Figure 2. Sutural Movement with Spinal Flexion/Extension
Note the large oscillating waves associated with spinal flexion/extension ("RP" = right parietal bone motion and "LP" = left parietal bone motion). Also, note the rhythm patterns associated with cardiac ("C")and respiratory ("R") activity. Used with permission from *The Journal of the American Osteopathic Association*.

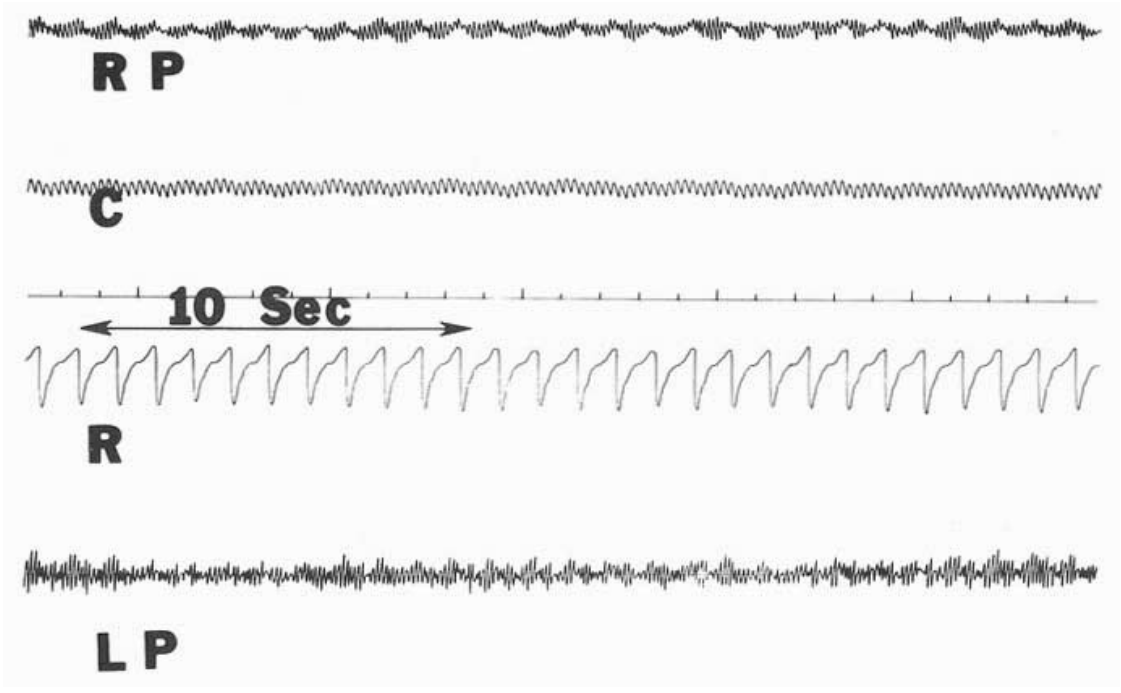

Figure 3. Sutural Movement with Cardiac and Respiratory Motion
Note the small oscillatory movement waves (cardiac) that superimpose on larger less frequent oscillatory waves (respiratory) ("RP" = right parietal bone motion and "LP" = left parietal bone motion). Also, note the rhythm patterns associated with cardiac ("C") and respiratory ("R") activity. Used with permission from *The Journal of the American Osteopathic Association*.

Patent Foramen Ovale as a Risk Factor for Altitude Decompression Illness

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Abstract

The relation between the presence of a patent foramen ovale (PFO) and the risk of decompression illness (DCI) remains controversial. PFO is a common finding in the general population, with an autopsy prevalence of about 25%. Recent review articles in the diving literature have concluded the presence of a PFO may increase the relative risk for DCI but the absolute risk remains low. In space operations, DCI is a significant concern for extravehicular activities (EVA) because of the low suit pressure (the NASA EMU-suit pressure is 4.3 psia, equivalent to about 30,000 feet). The Canadian Space Agency (through contract to DCIEM) is participating in NASA-led Prebreathe Reduction Protocol (PRP) studies to assess the safety and efficacy of reducing EVA oxygen prebreathe time. Reduction in prebreathe time is accomplished by incorporating exercise protocols during a two hour oxygen prebreathe prior to decompression to EVA suit pressure. As for NASA astronauts, DCIEM PRP subjects are screened with a trans-thoracic echocardiogram (TTE). In 48 volunteers at DCIEM screened for the PRP studies with a TTE, 14 (29%) were found to have an echo-probable PFO. In 29 altitude-exposed subjects who had a TTE, there were 5 echo-probable PFOs. None of these 5 subjects experienced DCI. Two of these subjects had a high bubble load with grade IV bubbles on precordial Doppler monitoring. In total there were four cases of Type I DCI and no Type II DCI. None of these subjects had an echo-probable PFO.

Introduction

Decompression illness (DCI) represents a significant health risk for underwater divers, caisson workers, pilots of high performance aircraft and astronauts who perform EVAs, with symptoms ranging from local joint pain (Type I), to neurological symptoms (Type II), to circulatory collapse and death. Of particular concern are the serious neurological manifestations of DCI (Type II DCI) which untreated, may lead to system collapse and death. DCI occurs as a result of the evolution of nitrogen dissolved in the body fluids and tissues when ambient pressure is decreased to the point that gas phase separation occurs. Inert gas bubbles are generally believed to form extravasculary in tissue, or intravascularly in the venous side of the circulation. Intravascular bubbles in the venous system, or venous gas emboli (VGE), circulate to the right side of the heart and eventually travel to the pulmonary circulation where they are filtered out due to the very large concentration gradient between the pulmonary capillaries and the alveoli.

Neurological complications in DCI are thought to occur as a result of the formation of gas bubbles in the tissues of the brain or spinal cord, or of arterial gas embolism (AGE). AGE may then flow to the brain and spinal cord, obstructing circulation in these tissues, causing mechanical damage, and altering biochemical and hematological balances. The presence of gas bubbles in the arterial side of the circulation is thought to occur by three possible mechanisms: 1) rupture of small airways in the lungs resulting in air embolism; 2) generation of inert gas bubbles in the arteries (de novo genesis or tribonucleation); or 3) cross-over of gas emboli from the venous to the arterial side of the circulation. Right-to-left cross-over may occur by: 1) anatomical shunts within the lung, or 2) intracardiac shunts including atrial septal defect (ASD) and patent foramen ovale (PFO).

Recently, atrial septal defects amongst divers, particularly in the form of patent foramen ovale (PFO), have been associated with the right-to-left crossover of inert gas bubbles resulting in neurological DCI (Moon *et. al.*, 1989 and Wilmhurst *et.al.*, 1989). PFO is a common finding in the general population, with an autopsy prevalence of about 25-34% (Hagen *et.al.*, 1984) and recent reports in the diving literature have concluded that the presence of a PFO increases the relative risk for DCI but the absolute risk remains low (Cross *et. el.*, 1994 and Bove, 1998).

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The relationship between Type II DCI and PFOs is less clear in the altitude environment largely due to the lack of data. Clarke & Hayes (1991) found a 16% incidence (by TTE) of PFO amongst 24 cases of Type II altitude DCI using trans-esophogeal echocardiography (TEE), suggesting that there was no significant relationship between PFO and Type II DCI. Powell *et. al.*, (1995) report a single case of a research subject who displayed a patent foramen ovale using contrast trans-cranial Doppler (TCD) and trans-thoracic echocardiography (TTE) without Valsalva maneuver. Following decompression no gas bubbles were detected in the left ventricular outflow tract or the middle cerebral artery despite numerous gas bubbles in the right heart. In addition, Pilmanis *et. al.* (1996) studied six USAF subjects who were found to have left ventricular gas bubbles at altitude in addition to high VGE scores. Of the six subjects, three had no septal defect, one had a PFO, one had a small sinus venosus, and one subject was not evaluated. Five of the cases became symptomatic at the time of AGE. The authors demonstrated that VGE can cross over to the arterial side by a number of mechanisms and suggest that altitude exposures that result in high VGE loads should be avoided by aviators.

In space operations, DCI is a significant concern for extravehicular activities (EVA) because of the low suit pressure (the NASA EMU-suit pressure is 4.3 psia, equivalent to about 30,000 feet). The Canadian Space Agency (through contract to DCIEM) is participating in NASA-led multi-centre Prebreathe Reduction Protocol (PRP) studies to assess the safety and efficacy of reducing EVA oxygen prebreathe time for International Space Station construction and maintenance EVAs. Reduction in prebreathe time is accomplished by incorporating exercise protocols during a two hour oxygen prebreathe prior to decompression to EVA suit pressure.

At DCIEM, a trans-thoracic echocardiogram and colour flow study (cardiac ultrasound) is performed on subjects as part of their medical screening. The echocardiograms are performed to detect the presence of signficant intracardiac shunts such as atrial septal defects which could put subjects at increased risk for serious decompression illness. Incidental note was made during the studies as to the possible presence of a PFO. Subjects were not excluded from the PRP study due to the echocardiographic/colour flow findings of a possible PFO. This paper presents a preliminary analysis of the incidence of PFOs amongst the DCIEM subject pool who underwent trans-thoracic echocardiography, and the occurrence of precordial bubbles and decompression illness in subjects with and without PFOs.

Methods

Volunteer subjects were recruited from DCIEM staff and from the general population, with special efforts to obtain subjects from local diving clubs, police and firefighting associations as individuals from these populations tend to more closely fit the older healthy astronaut population. In addition, many of these individuals have a general understanding of DCI and/or have experience in physiological stressful environments and in the use of breathing systems.

Prior to participating in the study, subjects underwent a trans-thoracic echocardiogram and colour flow study to exclude subjects with significant intracardiac shunts. Scans were performed by a certified ultrasound technician using a Hewlett Packard Sonos 5500. The echocardiographic study included careful colour flow interrogation of the atrial septum specifically looking for trans-septal flow. Studies included a Valsalva manoeuver. A diagnosis of “probable PFO” was made if a trans-septal colour flow pattern could be identified on several cardiac cycles.

The DCIEM altitude chamber was used to simulate the pressure changes astronauts will be exposed to within the ISS and the EVA suit. Tests involved simulating an EVA day starting 90 minutes prior to the prebreathe period up until the end of a 4 hour simulated EVA excursion to 0.3 ATA. Figure 1 displays the major events that occur throughout the EVA day.

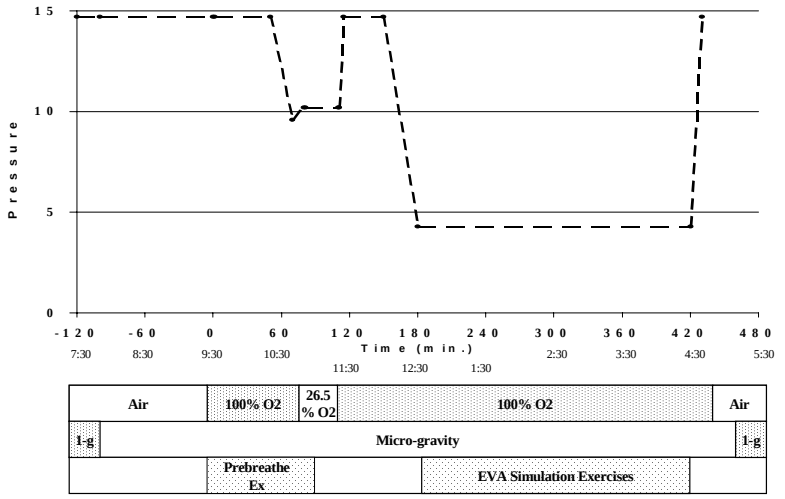

Figure 1: Graph of pressure profile (in psia) during EVA simulation day. Bottom box indicates occurrence of breathing mixtures changeovers, duration of adynamia (microgravity) and periods of exercise.

Subjects arrived at DCIEM the morning of testing and began a bedrest period for

90 minutes prior to the start of the prebreathe period. The purpose of this bedrest period (adynamia) was to simulate the weightlessness conditions of space. Subjects then donned a breathing mask and begin prebreathing 100% oxygen. Minutes after the start of prebreathe, subjects began a series of prebreathe exercises. Prebreathe exercises consisted of either high intensity short duration dual/arm leg ergometry exercises or a series of light, primarily upper body exercises performed on the cot (Figure 2).

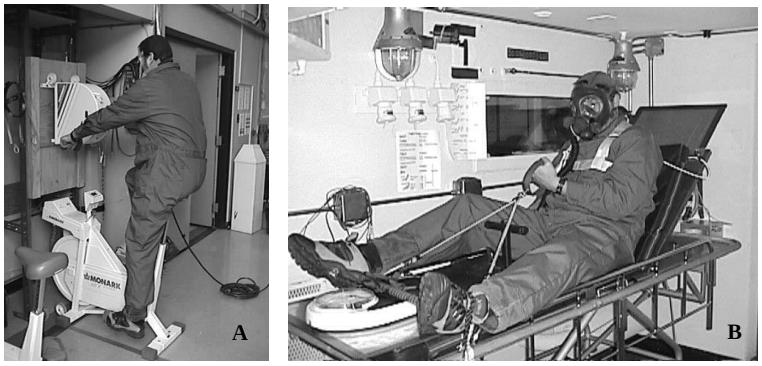

Figure 2: Photographs of two types of prebreathe exercises used to augment nitrogen washout. Figure 2a shows the dual arm/leg ergometry used in Phase II. Figure 2b shows Phase IV prebreathe exercises.

For a short period during the prebreathe exercises the pressure in the altitude chamber is reduced to 0.7 ATA (10.2 psia) and the breathing gas changed to 26.5% oxygen. This reduction in pressure and breathing gas was performed to simulate the operational environment. Following the prebreathe period, the altitude chamber pressure is reduced to 0.3 ATA (4.3 psia) to simulate the EVA environment. Throughout the EVA simulation to 0.3 ATA, subjects were monitored for symptoms of DCI. In addition, subjects were also monitored for the presence of precordial bubbles using an ultrasound unit (Model No DBM 9008, Techno Scientific Inc.) and array probe (TPI DSA7). Bubble signals were graded according to the Kisman-Masurel grading system which were then converted to the Spencer Grade Bubble Scale to allow comparison between participating laboratories (Nishi, 1993).

Results

PFO screening was not performed in the first few tests as screening was not initiated until shortly after testing began. Data presented in this paper will be is only for subjects who underwent PFO screening. In total, 48 potential subjects volunteered to participate in the study and were screened with echocardiograms (age = x ± x yrs). There were no significant cardiac abnormalities identified in any of the subjects. Fourteen of the 48 potential subjects (29.1%) had detectable PFOs (Table 1). Only 29 of the 48 volunteers participated in the chamber tests, the remaining were either unable to participate due to schedule conflicts or were eliminated from participation for medical reasons other than cardiac. Only 5 (17.2%) of the 29 participants had detectable PFOs. During altitude decompression, three of these subjects had no precordial bubbles as measured with the Doppler ultrasound unit. The remaining two subjects had detectable precordial bubbles, with one subject experiencing Grade III bubbles and the other Grade IV bubbles. None of the subjects with detectable PFOs experienced symptoms of DCI. In the total subject pool there were 4 cases of Type I DCI with no incidence of Type II DCI. Of the 4 subjects with type I DCI, none had PFOs detected by TTE.

Table 1: PFO, DCI and bubble grade incidence.

	Total Volunteers n=48	All Test Subjects n=29	Test Subjects with PFOs n=5
PFO	14 (29.1%)	5 (17.2%)	-----
DCI Type I	-----	4 (13.8%)	0
DCI Type II	-----	0	0
Bubble Grade 0		13	3
Bubble Grade I		1	0
Bubble Grade II		0	0
Bubble Grade III		6	1
Bubble Grade IV		9	1

Discussion

This study reports on PRP Phase II and Phase IV volunteers who were screened for intracardiac shunts with a trans-thoracic echocardigraphic and colour flow study. In this study, 29% of individuals who volunteered for the study and 17% of those who underwent altitude decompression were found to have a PFO based on colour flow findings of a trans-atrial septal flow pattern using TTE. None were found to have atrial septal defects or other significant cardiac abnormalities. Our reported TTE PFO incidence is higher than earlier reports and may reflect improvements in echocardiograph technology and statistical clustering. For example, autopsy results reported by Hagen *et. al.*, (1984) have revealed an incidence of 27.3% in the general population whereas studies in the early-to-mid 1990s comparing TEE and TTE have reported incidence of 11-45% using TEE and 6-9% using TTE (Siostrzonek *et. al.* 1991, Belkin *et. al.* 1994, Fischer *et. al.* 1995).

The drop in incidence from 29% in volunteers to 17% in those individuals who underwent decompression testing indicate that a larger proportion of the volunteer subject pool without PFOs went on to become test subjects than those with PFOs. The test subjects were selected from amongst the 48 volunteer based only on: 1) medical clearance by the diving medical officer, and 2) availability to participate on the scheduled test days. Medical histories resulting in exclusion from decompression testing included high blood pressure and history of complicated joint injury. No subjects were excluded from the study and none refused participation based on a positive PFO result. As a result, the lower incidence amongst test subjects is believed to be a result of statistical clustering.

Although 4 incidents of Type I DCI were diagnosed during the altitude decompressions, no subjects developed Type II DCI and none of the PFO positive subjects developed DCI. Two of the PFO positive subjects developed high levels of precordial Doppler bubbles during altitude exposure, one grade III, and the other grade IV, highlighting the fact that Type II DCI does not necessarily result from high bubble grades in the presence of a PFO.

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The Relevance of Patent Foramen Ovale to Type II DCS: An Overview of the Literature

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The significance of patent foramen ovale (PFO) in the pathophysiology of Type II decompression sickness (DCS) remains controversial. PFOs are common, occurring in approximately one quarter of the normal population, thus making right-to-left shunting of venous gas emboli (VGE) a theoretical concern in both hyper and hypobaric situations. Despite this high prevalence of PFO in the general population, and the relatively common occurrence of venous gas bubbles in diving and altitude exposures, the incidence of Type II DCS in diving or with altitude is remarkably low. Although the literature supports a relationship between the presence and size of PFO and cryptogenic stroke, and an increased relative risk of Type II DCS with a PFO in divers, the absolute increase in risk accrued is small. Hence, the value of screening is also controversial. This paper presents a brief summary of the literature on PFO's and DCS in altitude and diving, focussing on the latter; as well the analogous literature on cryptogenic stroke; and the results of an examination of the literature on detection of, screening for, and treatment of PFOs.

The foramen ovale develops as part of the process of atrial septation in which two apposed incomplete septa form with partially overlapping fossae. The foramen ovale represents the opening that remains patent between the septae. Post-natal increases in left atrial pressure usually force the interseptal valve against the septum secundum and within the first 2 years of life the septae permanently fuse due to the development of fibrous adhesions (1). However, autopsy studies have shown that in approximately 25% of cases in an adult population the foramen ovale fails to fuse (2).

This is generally of no significance since the higher left atrial pressure keeps the valve functionally closed. However, in situations where the right atrial pressure becomes significantly higher than the left, a gradient reversal can occur, causing right-to-left shunting through the foramen. Gradient reversal can occur when pulmonary vessels are obstructed (e.g. from overload of venous bubbles), when left atrial pressure is decreased (eg. after vasoconstriction causes increased pulmonary vascular resistance and subsequent decrease in cardiac output), on release of Valsalva or with strain, coughing, negative pressure breathing, cessation of positive pressure breathing, restricted breathing, or any other situations leading to substantial increase in venous return to the right heart. Such situations are common in both diving and air operations, including anti-G straining maneuvers, Valsalva for pressure equalization, and positive pressure breathing. Moon et al (3) speculate that immersion in water might increase a shunt as a result of increased right atrial pressure and cardiac dilation, and that the prevalence of shunting in divers may therefore be underestimated by assessments performed in the lab.

In some cases, right-to-left shunting has been shown to occur occasionally during quiet breathing without complication (4-6) and generally such intermittent shunting in a normal individual may cause transient decreased oxygen saturation, but little else. Of greater concern is when right-to-left shunting causes paradoxical embolization to occur. A patent PFO is a potential conduit for vessel-obstructing material such as blood clot in the case of stroke, or venous gas bubbles. However, there has been considerable controversy about the significance of a PFO as a possible mechanism for Type II decompression sickness.

Decompression sickness is a syndrome considered to be due to the presence of blood or gas in the tissues as a result of reduction in ambient pressure, resulting in a variety of symptoms depending on the location of the blood or gas. Gas entering the arterial system as a result of overpressurization of the lungs (pulmonary barotrauma) results in arterial gas embolism. Because overlapping pathologic mechanisms may result in confusion as to cause, the term decompression illness has come into favour as a descriptive term to cover all manifestations of decompression barotrauma and/or decompression sickness. In this paper, we use the term decompression sickness to refer to the syndrome due to

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evolution tissue gas and venous gas emboli with right-to-left shunting as distinct from that caused by arterial gas embolism.

The phenomenon of paradoxical embolization has been well-studied among stroke patients, particularly among those who experience stroke despite having no risk factors. This situation is referred to as cryptogenic stroke. Although there are some studies which report that the prevalence of cerebral ischemia in PFO patients is not different from that in controls (7,8) in general, the prevalence of PFO has been shown to be higher among stroke patients than among controls (9,10). When classifying by the cause of stroke i.e. known cause, known risk factor, or no risks ie cryptogenic, the prevalence of PFO rises respectively (11-14).

Although PFOs are more common among both cause-known and cryptogenic stroke patients than in controls, the size of the PFO in cryptogenic stroke is generally larger than in cause-known cases (15,16) indicating an association between shunt size and risk of future embolic events, and suggesting that the clinical significance of individual foramina may be in part determined by echocardiographically identifiable characteristics.

It is clear that PFOs can lead to stroke if clot passes paradoxically through a functional right-to-left shunt, but the question remains whether one can now extrapolate what is known in the cryptogenic stroke situation to that of decompression. In fact, as early as 1969, reports existed suggesting that early neurological symptoms after diving could be caused by intracardiac shunts, and specifically by PFOs (17). Although gas emboli behave differently than clots in that they are not rigid and so can conform to vessel shape, their presence remains a key factor in the explanation of Type II decompression sickness.

In both diving and altitude, venous gas bubbles may develop when dissolved gas comes out of solution as the ambient pressure decreases during ascent, and the depressurized gas volume expands. The filtration of bubbles by the lung means they usually do not enter the arterial circulation. However, if the lungs are overwhelmed, or if there is a right to left shunt as would exist with PFO (or other atrial-septal defects) then venous bubbles could bypass the lung filter and directly enter the arterial circulation and thus travel to the brain.

Spencer (18) found that venous gas emboli were detectable in 4/11 divers (36%) after a no-decompression (USN tables) 18 m chamber dive for 60 min. He also noted that for the same profile, bubbles were more likely in open water rather than chamber dives. Later, Dunford et al (19) found venous bubbles in 17% of a sample of sport divers undertaking dives between 6 and 39 msw. Gas bubbles have been found in the venous circulation after ascents from as shallow as 3 m (20).

Eckenhoff et al (20) studied the dose-response relationship for decompression magnitude and endogenous venous gas bubble formation in humans. Subjects were exposed to pressure of 12, 16, and 20.5 fsw for 48 hrs then returned to surface in less than 5 minutes. There were no DCS cases but a large incidence of venous bubbling. Using the Hill equation to calculate the saturation depth pressure at which there is a 50% probability of detectable VGE, they found that with subclavian doppler 50% of humans would be predicted to generate endogenous bubbles after exposure to only 11 fsw.

Despite a clear relationship between decompression and development of venous bubbles, the relationship of VGE to DCS is less conclusive (21, 22). Recent and extensive work by Nishi at DCIEM (23) concludes that although large numbers of bubbles are not necessarily accompanied by DCS, the opposite is usually true i.e. DCS is usually accompanied by venous bubbles.

Pigs are increasingly being used in research because of their physiological similarity to humans particularly with respect to the cardiovascular system (24). In animal studies using pigs, Vik et al (25) investigated whether arterial gas was more likely when a PFO was present. The incidence of paradoxical air embolism tended to be higher in the PFO pigs compared to controls. In addition, less air needed to be infused (into the right heart) of the PFO pigs before arterial bubbles were seen. Finally, the size of the PFO was found to be unrelated to the occurrence of arterial gas.

They also tested the hypothesis that after rapid decompression pigs with a PFO would be more likely than those without one to have arterialized bubbles (26). Bubbles were found in all 6/6 of the PFO pigs, but only 2/8 in the non-PFO group ($p<.009$). In addition, venous bubble counts in the PFO pigs were lower than in non-PFO pigs. Thus, arterial gas bubbles occurred at lower venous bubble loads in PFO pigs, and pigs with a PFO were more likely to have arterialized gas.

In a human population, Glen et al (27) used transcranial Doppler to determine the incidence of bubbles in the cerebral circulation of divers with and without PFO at various times during safe decompression from air dives. They found 4/17 divers with shunts identifiable by TCD, but none of the divers either with or without PFO had detectable bubbles in the cerebral circulation.

Considering that the prevalence of PFO in the population is about 25%, the incidence of Type II DCS is less than might be expected given the known prevalence of PFOs and the documented common occurrence of decompression-induced venous gas bubbles. Bove (28) calculated the frequency of military, sport, and commercial occurrences of Type II DCS to be 1.33, 2.52, and 2.09 per 10,000 dives respectively, with a combined frequency of 2.28 per 10,000 dives. Cross et al (29) note that of approximately 50,000 divers in Britain 15,000 (30%) might be expected to have a PFO, yet the number of neurological DCS cases per year is only about 100.

Much less research on the phenomenon of paradoxical gas embolism and the relationship between PFO and DCS has been reported in the altitude literature than in the diving literature so it will now be discussed first, the focus on the latter to follow. In fact, there has been some suspicion that DCS symptoms in altitude situations tend to be underreported to a greater extent than they do in diving due the perceived negative career-related consequences.

Because altitude DCS is related to decompression from saturation, it is thought that more venous bubbling occurs in altitude than with subsaturation decompression in diving, the result being a greater likelihood of paradoxical cross-over. Thus it is reasonable that one finds more cerebral symptoms among altitude than diving decompressions (30).

Clarke & Hayes (31) examined the prevalence of PFO among 24 cases of Type II altitude DCS in naval aviation personnel. They identified 4 cases (16%) of PFO by contrast TTE. They used Moon's (3) control data to conclude that there was no significant relationship between PFO and Type II altitude DCS.

Pilmanis et al (32) presented the first documented right-to-left shunting of venous bubbles after exposure to altitude. Retrospective examination of a 1500-subject database identified 6 subjects who demonstrated left ventricular gas emboli. Despite known embolization, PFOs were found in only 2 of the 3 cases investigated with TEE. In light of the fact that in all cases the venous gas score was high at the time of embolization, overload of pulmonary filtration was a second suspected mechanism for arterialized gas. The conclusion was that situations which expose subjects to altitudes known to produce high venous bubble loads should therefore be avoided.

Webb, Pilmanis, and O'Connor (33) went on to determine at what altitudes high bubble loads occur. They exposed 124 subjects to altitudes ranging from 11,500 to 25,000 feet for 4 to 8 hours, monitoring for DCS and venous bubbling. Venous bubbles were first seen at 15,000 ft and were present in 70% of cases above 22,500 ft. In terms of DCS symptoms, the 5% threshold for symptoms was 20,500 ft with an abrupt increase in symptoms beyond 21,200 ft. These results led the authors to recommend reconsideration of current US altitude exposure guidelines.

As previously mentioned, the suggestion that early neurological symptoms after diving could be caused by intracardiac shunts was made as early as 1969 (17). The majority of studies however were not undertaken to investigate this hypothesis until after 1986 when Wilmshurst et al (34) suggested that Type II DCS in a diver with an atrial septal defect (ASD) resulted from venous gas passing through the defect. If there was a right-to-left shunt as would exist with PFO then venous bubbles could directly enter the arterial circulation and migrate to the brain, particularly if the normal pressure gradient is reversed.

Unfortunately, there are several factors which limit the generalizability and hence the conclusions which can be drawn from studies that have attempted to determine the relationship between PFO and DCS in diving. These limitations include variation in study groups used (i.e. sport, commercial, or military divers), variation in control groups used (i.e. matched vs unmatched, diver vs non-diver), differing techniques for PFO detection (i.e. TTE vs TEE), and variability in definition of DCS or severity of cases selected to be members of the study group. Nonetheless, some trends occur in the examination of the findings of multiple studies although individually many studies have nonsignificant results.

First, the prevalence of PFO in non-DCS divers appears to be similar to that in the non-diving controls (35,36). Second, PFOs appear to be more common among DCS divers than non-diving controls (36,37). Third, PFOs seem to occur more commonly in divers experiencing Type II DCS than control divers (38,39). Finally, PFOs seem to be more frequent among divers with more serious DCS symptoms (3,38).

A meta-analysis of 3 previously published studies by Bove (28) mitigates some of the limitations of the individual studies by increasing the sample size. The results of this analysis show that the presence of PFO significantly increases the risk of all DCS in divers with PFO by 1.93 times compared to divers without PFO. For Type II DCS the risk was found to be 2.52 times higher in those with PFO.

Reconsidering Bove's calculation that PFO increases the risk for Type II DCS by 2.52 times; in a population of military divers in which the baseline incidence of Type II DCS is 1.33 per 10,000, an increase of 2.52 times 1.33 would lead to an absolute number of 3.4 per 10,000 cases of Type II DCS. With an absolute increase of 2 cases per 10,000, is screening for PFO warranted and if so what is the best screening method?

Although Bove (28) concludes that the absolute risk is small enough that screening is not warranted, and there is no basis for recommendations against diving in those with PFO, the decision to screen or not may vary based on the needs of a particular organization. In deciding whether or not to screen, one should also take into consideration the anticipated bubble load. With this in mind, screening of the shallow water sports diver is probably unnecessary, but in military or commercial divers, when high bubble loads are likely, screening might be useful. Any organization should consider following characteristics of a useful, albeit population-based screening measure prior to implementation (40).

1) Conditions for which screening is used should be important health problems i.e. The incidence should be sufficiently high that the cost of screening is not prohibitive.
2) Facilities for diagnosis and treatment should be available.
3) Effective, non-controversial treatment for patients with confirmed condition should be available.
4) Tests should have high sensitivity and specificity; screening must be safe, rapidly applied, and acceptable to the population being screened.
5) The natural history of the condition should be understood, such that if detection and treatment do not alter the natural history, screening should not be implemented.
6) Policy must stipulate what action will be taken in borderline cases to avoid overdiagnosis.
7) Maximum benefit for minimum cost must be achieved by comparing the costs and efficiency of various screening methods.
8) Control and screened groups should be compared at regular intervals to determine whether the screening procedure and subsequent investigations have an effect on the control group that is greater than just regular observation (placebo effect).
9) Compliance with screening recommendations should be ensured.
10) Screening programs should be a continuous process.

Should one then decide to go ahead with screening, transesophageal echocardiography (TEE), not transthoracic echocardiography (TTE) has been considered the gold standard for detection of PFO, although many other detection methods have been assessed. Generally any TEE modality is better than either contrast or colour flow TTE. Detection of PFOs with bubble contrast TEE is significantly better than with contrast TTE (12,41,42). With contrast TTE there tend to be more false negatives and undetermined cases than false positives, and most patients with a positive TTE study will also have a positive TEE. Thus an unequivocal contrast TTE study negates the need for further TEE imaging but a negative TTE does not. Among the different types of TEE examination, some studies suggest that bubble contrast detects more PFOs than does colour flow (8), whereas others suggest the opposite, that colour flow is better (42,43).

Although TEE provides better resolution than TTE, it is not without risks. These include esophageal injury, laryngospasm, aspiration, hypoxia, bronchospasm, dysrhythmias, and transient neurological side effects (44,45). Still, the morbidity rate of contrast TEE is only .07%, which is less than that of the exercise stress test, a well-accepted screening test, which has a complication rate of .09% (46). Nonethless, TEE is generally considered an unpleasant procedure and IV sedation is often required. In addition, many find performing a Valsalva maneuver difficult with the probe in place.

Considering the low sensitivity of TTE and the relative complexity of TEE, a simpler, but acceptably sensitive method for PFO screening is transcranial Doppler (TCD). Studies comparing TCD of the middle cerebral artery to TEE demonstrate sensitivities ranging from 68 to 100%, with specificities repeatedly in the order of 100% (12,47-49). TCD is an ideal method for screening for PFO because the high sensitivity could spare patients a TEE exam. Furthermore, TCD costs less, and one can easily monitor effectiveness of the Valsalva by observing decreased cerebral blood flow (12). Other less well-studied methods of PFO detection which will not be discussed include carotid duplex monitoring (50), dye dilution and oximetry (51).

Studies evaluating PFO detection methods specifically among divers are few. Kerut et al (52) compared the ability of TTE, TEE and TCD to detect PFOs in both control subjects and divers referred for possible, probable, and definite neurological DCS. TEE was the most sensitive method for detecting PFOs in both controls and divers. However, only the TCD method of imaging differentiated between divers and controls. The authors suggest that the TCD method only detects clinically significant PFOs since only strongly positive TEE also had positive TCDs. They calculated the positive and negative predictive values for detection of shunts in DCS divers for all 3 imaging modalities. The positive and negative predictive value for each respectively was 52% & 59% (TEE), 62% & 58% (TTE), and 65% & 64% (TCD). Unfortunately the authors do not define "clinically significant" and in fact when "possible DCS cases" were removed from the sample, TCD no longer differentiated between DCS and control groups.

The implications of Bove's conclusions are that divers need not be screened prior to initiation of diving, and that those who already know that they have a PFO can still go ahead and dive. But what about the situation in which DCS has already occurred. Obviously, one must then consider evaluation for a shunt. If present, how does one reduce the risk of recurrent DCS in a diver with known PFO?

In Britain, professional divers with PFO are required to have transcatheter closure. Likewise the Allied Guide to Diving Medical Disorders published by NATO (53) states that "significant right-to-left shunts are incompatible with diving unless surgically corrected". Several risk reduction options to consider in PFO-positive divers include complete cessation of diving, reducing venous bubbling by either shallow diving only, altering the breathing gas used (eg choosing nitrox), or by using conservative decompression tables/methods, or finally closing the defect either by open surgery or by transvenous closure.

In the stroke literature, several methods of prevention of recurrent stroke have been used in patients with PFOs, which include no intervention, antiplatelet medications, anticoagulants, transcatheter closure, and surgery. Mas (54) argues that closure is the best option in cases of known paradoxical embolism.

Although surgical closure is easy to perform, it does not guarantee prevention of recurrence. Several studies have assessed open surgery as a method of closure. Giroud et al (55) studied 8 stroke patients and found no surgical complications, no recurrence of neurological events, and no residual shunting after PFO closure without post-op anticoagulation. Ruchat et al (56) also found no post-op complication among 32 patients, although residual shunts were present in 2/32 cases. Homma et al (57) followed 28 patients with a history of cryptogenic stroke and who underwent surgical PFO closure and found recurrence rate for neurological events of 19.5% overall. This rate was variable when age was considered and proportional hazards regression analysis revealed an increase in relative risk of recurrence of 2.76 per 10 years of age.

Nendaz et al (58) considered risk of stroke recurrence, complications, quality-adjusted life years, and death after 5 years in their decision analysis model assessing secondary stroke prevention options. They determined that if the risk of recurrence was .8 to 7% per year, defect closure was the best management strategy. At risk levels of .8% and 1.4% per year, anticoagulation and antithrombotic therapies were better than therapeutic abstention. If however, the risk of recurrence was low (i.e. less than .8% per year) then the best management option was no treatment.

Non-operative closure of atrial septal defects has been reported since 1976 (59,60). Transcatheter closure options are also possible for PFO and include button devices, clamshell umbrella devices and septal occluders (Amplatzer). Although the least expensive, the former method has been shown to have residual shunting (61), long recovery times, and higher numbers of complications compared to other methods (59). The double umbrella Clamshell had to be redesigned after device arm fracture in 71% of cases. Evaluation of the new version (Cardio SEAL) by Kaulitz et al (62) indicates improved device function, but in residual shunting in 57% of cases.

Formigari et al (59) report on the techniques and results of 28 ASD closures using three different percutaneous devices: the Sideris "Buttoned Device", the Das "Angel Wings", and the "Amplatzer". For all groups, fluoroscopy times were similar, but procedure time was shortest for the Amplatzer and longest for the buttoned device. Definitive closure occurred in all cases except 1 buttoned device. Followup times were longest for buttoned devices (at 40+/- 2 months, compared with 27+/- 2 mo for the Angel Wings, and 5+/3 mo for the Amplatzer). In terms of complications, there were 2 cases of transient myocardial ischemia secondary to coronary air embolism in the buttoned devices, and 1 case of pericardial tamponade with the Angel Wings. Others have reported failures with this device also requiring emergency surgical intervention (63). There had been no complications with the Amplatzer device. Cost, was least expensive for the buttoned devices. Overall they concluded that the Amplatzer device is preferable.

Preliminary results of the World Study on closure with the Amplatzer from November 1998 (64) indicate that a total of 936 ASDs have been closed as well as 86 PFOs. Closure rates for PFOs are good, with 100% being closed at 24 hours, compared with 100% at 1 year for the ASD cases (98.9% at 1 month). There were 24 complications among these approximately 1000 patients, the majority of which included device embolization (9/24), TIA/embolization (4/24), and arrhythmia (3/24).

Wilmshurst et al (65) write about 2 cases of PFO in divers with neurological DCS who were successfully treated with an inverted adjustable button device, one with no residual and the other with a tiny residual shunt. Both divers returned to diving. There is no mention of whether either diver experienced repeated DCS post-procedure.

Closure by transcatheter methods remains impossible for some defects especially those greater than 25 mm in size. In addition there are relative contraindications for closure, particularly morphological constraints. Johnston et al (66) believe that wider application of invasive shunt closure methods should not occur before the relation between PFO and DCS is further delineated, noting that one must consider the shunt size and not just patency in DCS risk evaluation.

Conclusions

In summary then, several conclusions can be tentatively drawn on the basis of available research:

1) Animal studies show increased arterial bubbles at lower venous bubble loads in pigs with PFO than in those without.
2) High bubble loads in either altitude or diving decompression increase the risk of pulmonary overload as a mechanism for arterial embolization.
3) There seems to be a relationship between crypogenic stroke and the presence of PFO, as well as the size of the PFO.
4) The weight of evidence favours an association between diving DCS and PFO. This association remains less clear in the case of altitude DCS, with less studies available on this topic.
5) The absolute increase in risk of DCS as a result of PFO seems small.
6) The issue of screening remains controversial and the decision to screen for a PFO should not be based on the absolute risk alone, but should also take into consideration decompression stress, professional status and employer responsibility, and the availability of adequate treatment.
7) For detection of PFO, contrast TEE is the gold standard, but as a screening tool, TCD in combination with contrast TTE is preferable to TEE.
8) Should closure be chosen for management, the transvenous Amplatzer appears to be the best available option, particularly for large PFOs.

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Altitude DCS Susceptibility Factors

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Introduction

Altitude decompression sickness (DCS) susceptibility factors include environmental parameters that influence the incidence and onset of DCS. These parameters include: altitude, time at altitude, exercise during exposure, level of denitrogenation (preoxygenation/prebreathe time), ascent rate, and breathing gas composition. The parameters with the most effect on DCS are altitude, time at altitude, exercise during exposure, and level of denitrogenation. These four environmental parameters are determined by mission requirements and can yield 0% to approximately 100% risk of DCS depending on interactions with the other parameters.

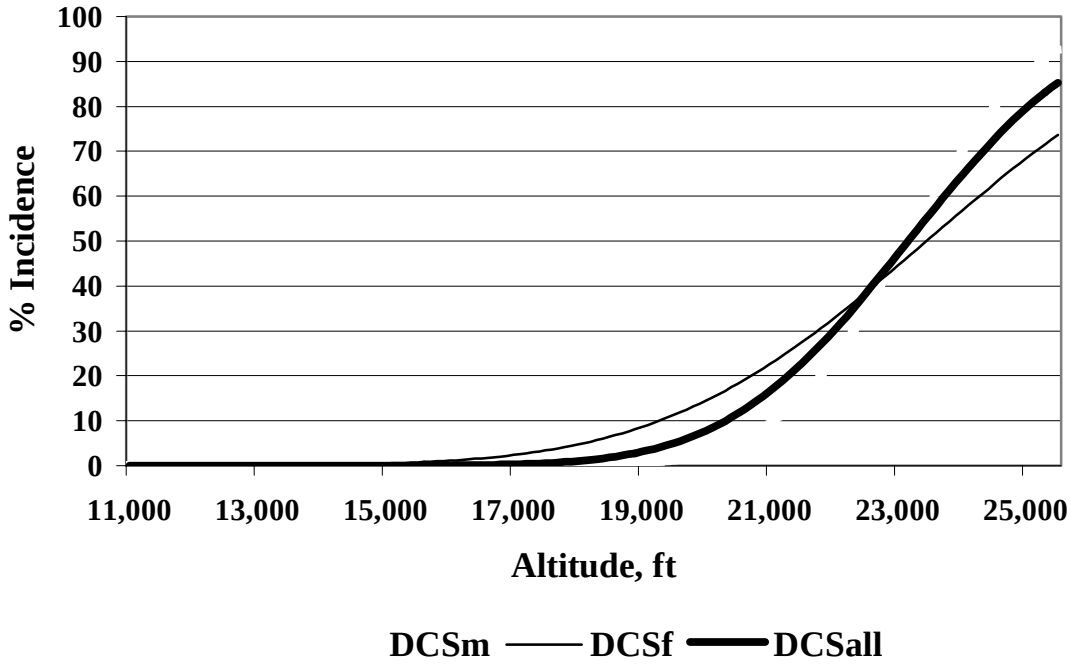

Figure 1. Altitude DCS threshold curves

The environmental factor of increasing altitude can rapidly increase the incidence of DCS symptoms (see Fig. 1; Webb and Pilmanis, 1995; Webb et al., 1998). These data came from different subjects decompressed, without prebreathe, to 9 altitudes from 11,500 ft to 25,000 ft while performing mild exercise. The 'best fit' probit curves and the individual Chi Square comparisons by altitude or as a total group of males and females did not show any differences in DCS incidence despite an apparent difference in slope of the male and female sigmoidal curves. The altitude DCS threshold curve for all subjects (DCSall) in Figure 1 shows DCS symptoms appearing below 20,000 ft and reaching 50% below 24,000 ft. The mean DCS incidence for all 182 female exposures was 47.3%, versus 51.1% DCS observed during the 360 male subject-exposures (N.S.). The effect of increasing altitude can also be shown following prebreathe. Exposures to 35,000 ft showed decreased onset times and increased symptom incidence compared to exposures at 30,000 ft and 25,000 ft despite a slightly longer prebreathe prior to the 35,000-ft exposures (Fig. 2). However, symptom severity did not increase at the highest altitude (35,000 ft), probably due to immediate recompression of subjects following any report of symptoms.

Paper presented at the RTO HFM Symposium on "Operational Medical Issues in Hypo- and Hyperbaric Conditions", held in Toronto, Canada, 16-19 October 2000, and published in RTO MP-062.

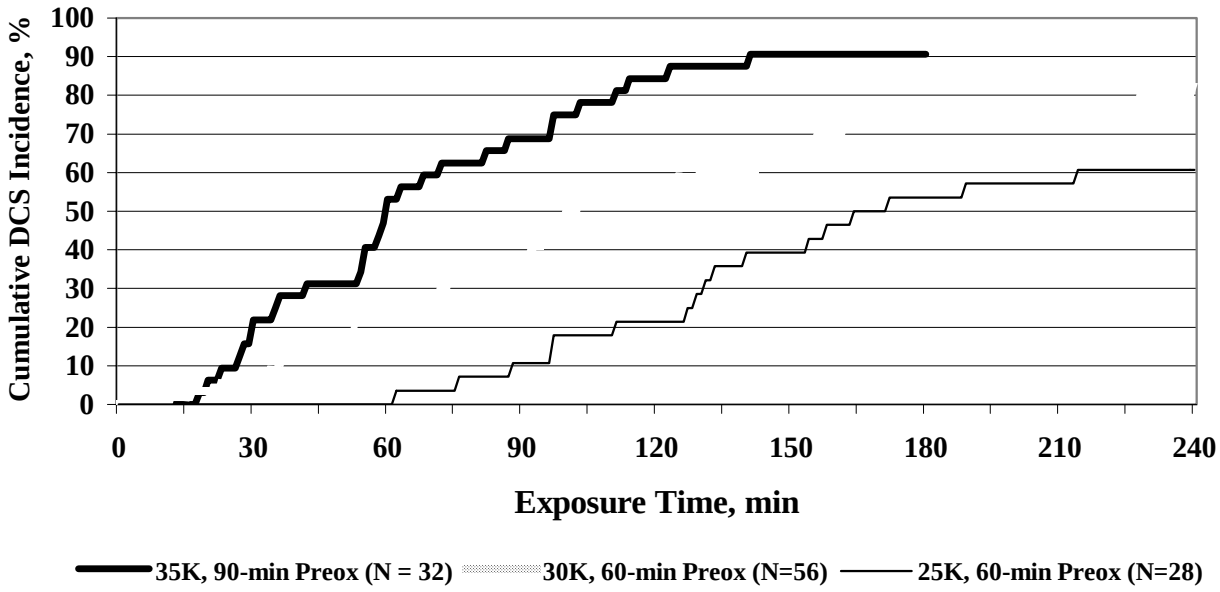

Figure 2. Cumulative DCS incidence versus time at altitudes of 25,000 to 35,000 ft; mild exercise.

Duration of exposure also increased the incidence of symptoms albeit highly dependent on altitude (Fig. 2 and Webb and Pilmanis, 1995; Webb et al., In Press). Figure 2 clearly shows that it takes longer to develop 50% DCS at a lower altitude (curve on the right) than at any of the higher altitudes where the depicted curves are displaced to the left.

The role of exercise in DCS susceptibility is also well accepted, although Pilmanis et al. (1999) reported no significant difference in DCS incidence based on whether arm or leg exercise was accomplished at altitude or whether isometric or dynamic exercise was performed (Fig. 3). Webb et al. (In Press) reported no difference between the effects of mild or strenuous exercise performed at 35,000 ft (Fig. 4). Both studies reported considerable increase in susceptibility in all comparisons of seated rest to exercise as reported throughout the literature.

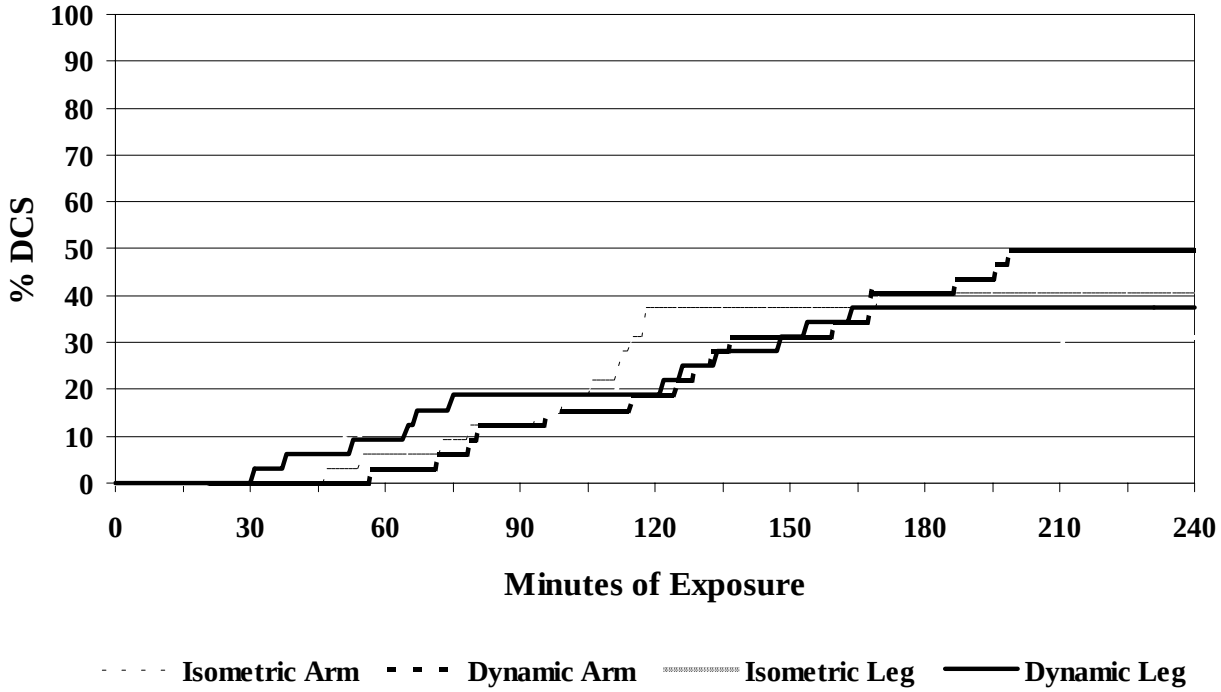

Figure 3. The effect of exercise mode on altitude DCS incidence and onset (Pilmanis et al., 1999).

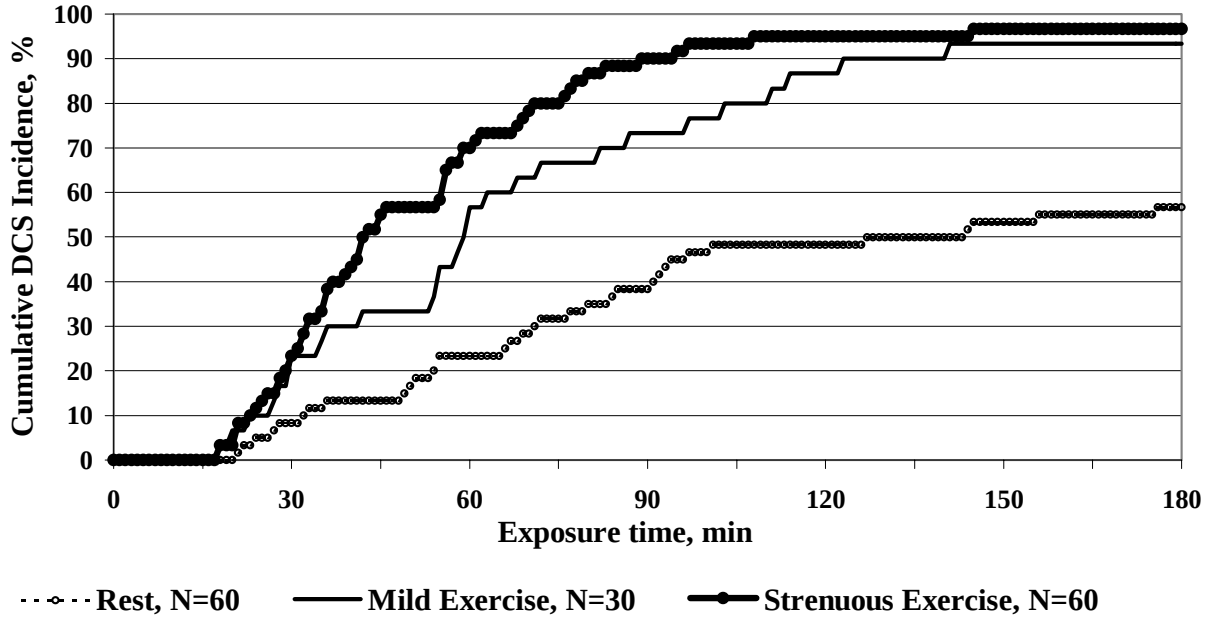

Figure 4. The effect of exercise intensity on altitude DCS incidence and onset at 35,000 ft (Webb et al., In Press).

Exercise during preoxygenation can apparently enhance denitrogenation as evidenced by significant reduction of DCS incidence compared to the incidence of symptoms following standard, resting preoxygenation (Webb et al., 1996; Paper #46, this symposium). The protective value of resting preoxygenation is better known, but its effectiveness decreases with time (Webb, et al., 1999). Predictions from the recently-developed Altitude DCS Risk Assessment Computer model (ADRAC) show decreasing efficiency of prebreathe in Figure 5. Beyond 1 h of prebreathe, only about 12% additional protection from DCS at 25,000 ft is acquired with each additional h of prebreathe.

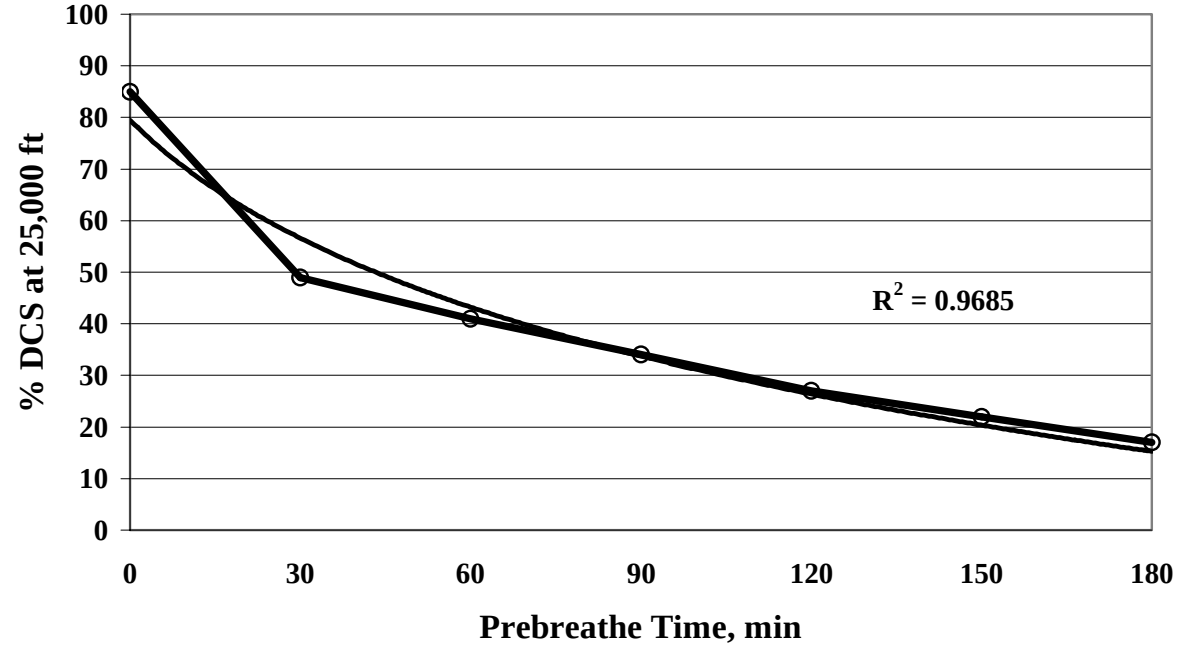

Figure 5. Resting preoxygenation time versus DCS incidence; 25,000 ft, mild exercise, ADRAC predictions

Comment

Modest alterations in environmental parameters, e.g. altitude, time at altitude, exercise at altitude, or level of denitrogenation, could significantly increase protection from DCS. Flexiblity in mission planning may be able to accommodate these alterations in the interest of avoiding DCS symptoms; i.e. flight safety.

Although the mission may involve a need for exercise while decompressed, limiting the exercise level to that needed for mission accomplishment can provide some advantage. Although we did not show that the type of exercise relates to susceptibility, the threshold exercise intensity for observing an effect on DCS incidence appears to be lower than previously believed.

Environmental susceptibility factors have provided sufficient variance to confound most attempts at risk prediction. To predict a population risk requires incorporation of at least four environmental parameters; altitude, time at altitude, exercise during exposure, and level of denitrogenation (preoxygenation time). The ADRAC model does incorporate these factors and may provide a resource for mission planning.

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Pharmacological Correction of the Human Functional State in High Altitude Conditions

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Summary: The effect of *Bemithylum* on metabolic changes of glucose, lactate, pyruvate, inorganic phosphate, uric acid, cholesterol, bilirubin, urea and creatinine in human blood during short-term residences in high mountain regions of Tien Shan and Pamir was investigated. To evaluate effectiveness of *bemithylum* for correction of metabolism, physical and mental workability of military personnel during short-term residence at 2800m altitude the subjects were tested by 2,5-kilometer marsh with fast temp in mountain canyon as a maximal physical exercise and by psychophysiological test "The Disarranged Lines" which were carried out before (as control exercise) and after pharmacological procedures. The subjects were separated to two groups: for first one (n = 7) was prescribed to take *bemithylum* in the dose of 750 mg per day by one or two 5-day treatments during initial period of high altitude adaptation, for second one (n = 8) was prescribed to take *placebo* in the same dose and period of the prescription. All the metabolic indicators mentioned above (excepting lactate and pyruvate) were measured spectrophotometricaly in the dried acid extracts of blood samples with standard monotests. It was shown that *bemithylum* makes essential psychoenergizing and stimulating effects on the processes of concentration and mental workability in conditions of high altitude hypoxia for the sake of direct influence on hemoprotein catabolism, i.e. preventing increase in bilirubin formation to the levels promoting its penetration through blood-brain. Excessive increase of blood cholesterol during physical exercises causes negative influence on human organism and significantly decreases his workability at 2800m altitude. *Bemithylum* prevents significant cholesterol accumulation in blood and simultaneously increases human physical workcapacity in conditions of high altitudes. In persons treated with pharmacological correction with *bemithylum*, time of making maximal physical exercise decreased more than by twice in comparison with the data received in subjects with *placebo*-effect. To approve action of *bemithylum* on increase of human hypoxic resistance and on prompting human adaptation and widening its limits in conditions of high mountain hypoxia was studied character of metabolic adaptation of persons with low hypoxic resistance with treatment of two 5-day correction procedures during 30-day residence at 3600 m altitude. The first 5-day procedure with *bemithylum* significantly decreased lactic acid accumulation (for 72.3%, $P<0.01$) and value of excess lactate (for 76.9%, $P<0.01$) in blood of subjects (n = 10) in comparison with group of low resistant persons who took *placebo* (n = 10). Increase of creatinine, cholesterol, uric acid and especially urea was also lowered for 22.5% ($P<0.01$), 27.1% ($P<0.01$), 59.8% ($P<0.01$) and 122.1% ($P<0.01$) in these persons accordingly. Further after two 5-day procedures this actoprotector reduced increase of glucose for 17.6%, lactic acid for 33.8%, uric acid for 19.3%, creatinie for 21.2%, urea for 179.3% and cholesterol for 74.3% in comparison with subjects with *placebo*-effect. The scheme of one 5-day treatment with *bemithylum* seems to be the most effective both for reducing of terms in achieving urgent adaptation to acute phase of high altitude hypoxia and for transfer of passive form of adaptation into active one. It is necessary to increase treatment with *bemithylum* to two 5-day procedures with obligatory one-day interval between procedures to rise adaptability and resistance of human organism to long-term residence in high altitude conditions.

Key words: High Altitude Hypoxia, Bimethylum, Exersise, Workability, Glucose, Bilirubin, Cholesterol, Adaptation

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INTRODUCTION

The problem to rise adaptive potential to the input of extreme environmental factors, to provide for optimal workability of a healthy human in taxing conditions of activities, attracts careful attention of many scientists and medical researchers both in our country and abroad in connection with practical importance and demands of military medicine and human applied physiology. Our previous studies [V.P.Mahnovsky et al., 1985a; V.P.Mahnovsky and R.V.Bolshedvorov, 1986] showed that preliminary individual selection of military personnel with low hypoxic resistance and their further dismissed from military service in high mountains (with transfer for serve in other conditions) allowed to decrease by 18% the number of illness among military personnel a serving at frontier posts in high mountains conditions. Also, the number of disadaptive disorders' cases among selected personnel decreased from 70-75 to 35 cases per year, practically there were no mortal cases from acute mountain sickness. However, there are still some cases of illness connected with disadaptive disorders among selected personnel with average (to 5%) and high (to 3%) hypoxic resistance, and particularly with low hypoxic resistance (10%), who were sent to serve on high mountains posts.

So, for more effectiveness to disclose and prevent disadaptive disorders we have to develop in parallel both the methods of diagnostic control of functional systems of human organism in conditions of high altitude adaptation and schemes of correctional procedures.

At present two main ways have been developed to rise a human hypoxic resistance. First, application of high mountain or pressure chamber training. Second, one includes use of pharmacological remedies and various biologically active substances which allow to reorganize quickly metabolism in conditions of oxygen deficiency.

In implementation of this prophylactic method the knowledge of biochemical mechanisms of adaptation is of great importance. Here the prospective way of biochemical prophylactics is believed to be the regulation of the processes of organism resistance rising with the help of natural protective compounds of close or equal to endogenic substances, participating in support of constant internal condition of organism. In a certain extent this is achieved with the help of natural protective endogenic substances (vitamins, neuromediators, hormones, antioxidants, etc.) or compounds with similar specter of activity which have regulative impact on different metabolic processes both on cellar and system levels, take part in the process of homeostasis and are capable to rise protective and adaptive opportunities of organism. With this it is necessary to take in mind that, first, it is necessary to have remedies (for pharmacological correction of hypoxia of different genesis) which selectively gave impact onto different chains of complicated mechanism of oxygen supplies, i.e. onto: (1) support of functions of respiratory system; (2) correction of functions of cardiovascular system; (3) effectiveness of organism transport system functioning (rheologic functions of blood, erythrocyte functions); (4) tissues energetic metabolism; and (5) functions of cellular and mitochondrial membranes [P.P.Denisenko, 1984].

The second, during period of hypoxic damage of different genesis and intensiveness in all organs and tissues without any exclusions there occur changes affecting realization of its functions. But the main changes are the changes in energetics, in keeping membrane structure and enzymatic ensembles unchanged, and in energy-related transformation of metabolic ways, so correction of these processes and states with pharmacological agents, capable targetly to interfere into these processes, is the most prospective direction of pharmacological correction of adaptation [A.S.Losev et al., 1986].

The third, pharmacological correction of hypoxic states is possible mainly on compensatory stage of hypoxia. It can be made both with substances recovering the flow of revitalizing equivalents through NAD-dependable part of the respiratory chain, and substances capable to shunt the electron flow in the same point [L.D.Lukyanova, 1984]. And it is necessary to take into account here that maximal protective effect of antihypoxic remedies occurs in organisms which are non-resistance to hypoxia, and that it is minimal for high resistant ones [L.D.Lukyanova, 1988; G.N.Chernobaeva, V.E.Romanova, 1988].

The most prospective compounds, having exposed antihypoxic abilities, are actoprotectors, whose activity more often combines with adaptogenic and anabolic effects of the

metabolic regulation remedies [A.S.Losev, 1991]. *Bemithylum*, membrano-active antioxidant has very important value among the compounds of this class.

Bemithylum (2-benzilidazol-thioethyl) is an original actoprotector which was obtained in the Research Institute of Pharmacology of the Russian Academy of Medical Sciences (Moscow) and is permitted for wide clinical use to rise human physical and mental workability in the taxing conditions by the State Pharmacological Committee of the Russian Federation. *Bemithylum* exposes positive effects with one-time treatment in the dose of 500-700 mg. By its pharmacological specter *bemithylum* makes some psychostimulating, antiastenic and adaptogenic effects, rises organism resistance to functional hypoxia and overheating, increases and rehabilitates organism workability during physical exercises.

Mechanism of *bemithylum* effect is connected with promoting cellular energoplastic supplies, gluconeogenesis activation and lactate utilization, increase of anabolic processes by means of direct influence RNA synthesis in cells and more economic oxygen utilization [A.V.Smirnov et al., 1990; S.A. Kryzhanovski et al, 1994]. Increase of RNA synthesis reactions is connected with the ability of *bemithylum* and its similar substances to interact with genom of different cells, which is explained by structural equality of benzilidazol derivatives and purines of nucleic acids [A.V.Smirnov et al., 1988]. Membrano-stabilizing and antioxidant effects was exposed in the specter of mechanism of *bemithylum* effect. It was proved that *bemithylum* is an active immunostimulator both on cellular and humoral levels. Possibly, it is specific and obligatory characteristic of all actoprotectors class. This compound also has exposed antimutagenic effect.

By the experiments with animals it was shown that *bemithylum* is capable to increase their physical workability, to make an ‘economizing’ effect on energetic metabolism which provides increase of cellular ATP concentration and lactate utilization [G.V.Morozov et al., 1987]. Smirnov A.V. [1991] showed that it decreases effects of motor hypoxia in animals during physical exercises by means of decreasing level of lactate in tissues and blood, and decreasing use of energetic resources.

Interesting data was received during study of *bemithylum* effect onto development of adaptive processes in animals and humans in conditions of pressure chamber hypoxia. So, with experiments on animals it was shown that use of this compound during 3-day impulse hypoxic training in pressure chamber increased the development of cross adaptation to physical exercises [A.V.Smirnov et al., 1991]. During these experiments the authors saw additional increase of endurance of the animals, improvement of biochemical indicators' values and increase of antioxidant enzymatic activity. A.Z. Zurdinov [1998], examining concentration of metabolites in animal blood after injections of *bemithylum* in normal conditions during 10 days and in combination with pressure chamber training at the "altitude" of 6,500 m, showed that after injection of the remedy there was mentioned the development of the new, more economic level of metabolic supplies of adaptive processes.

Clinical evaluation of *bemithylum* effectiveness, made during experiments with healthy volunteers in climatic pressure chamber showed that this actoprotector (in the dose of 500 mg) increases coefficient of oxygen utilization and level of aerobic-anaerobic switch [L.I.Voronin et al., 1988]. According to A.V. Smirnov et al. [1990], under dosed physical exercise it increased effectiveness of external breathing for 25-30% and decreased the increase of lactate in blood for 30%, and moderated subjective symptoms of mountain sickness. A.S. Shanazarov et al. [1988, 1999] studied *bemithylum* effect on antioxidative activity of superoxidedismutase (SOD) and some products of lipid peroxidation (LP) in blood serum of healthy young people placed at the altitude of 2100 m in Tien Shan mountains. It was shown that by mean of normalization of SOD activity the actoprotector prevents significant increase of malondialdehyde (an intermediate product of LP) in erythrocyte membranes and thereby it prevents cellular destruction.

The object of the present research was to study effect of *Bemithylum* on human metabolic changes in acute period of adaptation in high mountain regions of Tien Shan and Pamir. The goals were: (1) to evaluate effectiveness of *bemithylum* for correction of physical and mental workability of military personnel during short-term residence at 2800m altitude, (2) to approve action of this actoprotector on increase of human hypoxic resistance and on

prompting human adaptation and widening its limits in conditions of high mountain hypoxia (at 3600 m altitude).

METHODS

Subjects, protocol and data treatment*:* two seria of researches were conducted in mountain conditions:

- The first series: the purpose was to study *bemithylum* effect on military personnel capacity for work in process of high altitude adaptation. It included a study of the actoprotector influence both metabolism and mental workability of 15 normal males (with age of 18-20 years old) in the real conditions of military service activity in the first 10-day period of their residence at altitude of 2800 m over sea level (Tien Shan) and their endurance of maximal physical exercise. The subjects were separated to two groups: for first one (in the number of 7 persons) was prescribed to take the actoprotector in the dose of 750 mg per day during five days, for second one (in the number of 8 persons) was prescribed to take *placebo* in the same dose and period of the prescription.

Maximal physical exercise: 2,5-kilometer distance marsh with fast temp in mountain canyon. This marsh was carried out with the two groups of subjects in two times: before (as control exercise) and after the treatment of the pharmacological procedures.

Mental workability: for evaluation of concentration processes of the subjects was used a well-known psychophysiological test *"The Disarranged Lines"*, on the basis of results of which were calculated a time of solving the tasks and a number of mistaken solutions.

Indicators: an individual time of the distance overcoming by the subjects was measured. The some physiological (heart rate and arterial blood pressure) and biochemical (glucose - *Gl*, inorganic phosphate - Ph_i, cholesterol - *Ch*, bilirubin - *Br*, urea - *Ur*, creatinine - *Cr*) indicators' levels of these subjects were measured in blood samples before the pharmacological treatment and the maximal physical exercises - as control values, and after these ones. A rate of concentration change of metabolic indicators in blood was calculated.

- The second series included to study *bemithylum* effect on metabolism of 20 males with low hypoxic resistance (with age of 18-20 years old) in the real conditions of military service activity. This research was carried out in middle mountain conditions (at altitude of 1700 m over sea level) and then at 3600 m over sea level (Pamir): on 3, 7, 15 and 25 days of their adaptation. These subjects were separated to two groups: for 1st group (in the number of 10 persons) was prescribed to take *bemithylum* in the dose of 750 mg per a day by two 5-day treatments (with one-day break) during first eleven days of residence at 3600 m, for 2nd group (in the number of 10 persons) was prescribed to take *placebo* in the same dose and period of the prescription.

Indicators: glucose, lactic acid (lactate), pyruvic acid (pyruvate), uric acid (*U.A.*), cholesterol, urea and creatinine levels of these subjects were measured in blood samples before and after first- and second five-day treatments of *bemithylum* and *placebo* at altitude of 3600 m. The biochemical data of these subjects received in the middle mountains were used as control.

Selection procedure of the subjects with low hypoxic resistance was preliminary conducted on the basis of results of the dosed Flack test by our method [V.P. Mahnovsky, 1991]. These persons were there selected from majority of healthy military contingent located at altitude of 1700 m.

Data treatment: (1) for evaluation of character of hemodynamic changes the heart rate and arterial blood pressure (AP) were measured with the portable monitor of pulse and AP (made in Hungary); (2) for evaluation of character of changes of indicators of carbohydrate, lipid and nitrous metabolism in mountain conditions we used standard methods of spectrophotometric analysis. All the metabolic indicators mentioned above (excepting lactate and pyruvate) were measured in the dried acid extracts of blood samples with standard monotests of firm "Baker Instruments Limited" (USA) and firm "Boohringer Mannheim" (Germany) by centrifugal analyser "Centrifichem-600" (Baker Instruments Limited, USA). Calculation of these indicators was made in the relative units. Concentrations of lactate and pyruvate were measured in arterial blood simples accordingly W.E. Huckabee [1957]. On the

basis of these indicators there were calculated a ratio of lactate to pyruvate (*K*) and an excess of lactate (*ExL*) accordingly the following formulas:

$$K = L_i / P_i$$

K - coefficient of ratio of lactate concentration to pyruvate concentration, L_i - lactate concentration, P_i - pyruvate concentration

$$ExL = (L_e - L_c) - ((P_e - P_c) \times L_c \times P_c)$$

ExL - excess lactate (in relative units), L_c and L_e - concentrations of lactate before and after exercise, P_c and P_e - concentrations of pyruvate before and after exercise accordingly.

Statistical analysis of experimental data: Analysis of experimental physiological and biochemical data was made by parametrical statistics methods (T- and F-criteria) with standard programmes: "Biostatistics-2" and "Biostatistics-3" on personal computer "Apple". Coefficients of correlation between parameters were calculated depending on special research goals. For mathematical estimation of character and forces of correlation of these biochemical indicators and antihypoxic effect of *bemithylum* on metabolic system, human resistance and physical capacity in high altitude conditions a method of correlation analysis (with arranging the values of links between indicators and constructing correlation structures) was used.

RESULTS AND DISCUSSION

In table 1 means of the metabolic indicators are shown before and after maximal physical exercise in the acute period of adaptation to the altitude of 2800m taking into account of factor of *bemithylum* effect.

As our observation showed during the first day of residence at this altitude a significant increase of glucose level in blood for 11.5% ($P<0.01$) in all examined persons after control maximal physical exercise was registered. It is known that glucose level in blood during physical exercises may rise, decrease or stay the same as in rest condition. In working muscles a consumption of glucose increases and glycogen decay, glycolysis and lactic acid genesis are intensified as well, the lactic acid being as a substance of gluconeogenesis may stimulate glucose produce in lever [E. Newsholm and K. Stark, 1977].

At the same time it was found that bilirubin and especially cholesterol concentrations in blood increased accordingly for 9.9% ($P<0.05$) and 84.6% ($P<0.01$). Seems it shown that level of total cholesterol (and triglycerides) in blood plasma often correlates negatively with the level of physical activity [P.D. Wood et al., 1985; A. C. Arutzenius et al., 1985], sharp increase of this metabolite may certify significant decrease of physical tolerance in examined persons and their work capability in the initial period of high mountain acclimatization.

Changes in the other metabolic indicators concentrations (i.e. inorganic phosphate, urea and creatinine) in blood after making control maximal physical exercise in the first day of residence at the altitude of 2800m appeared to be statistically non-significant ($P>0.05$). Nevertheless, application of method of correlation structures for the analysis of the biochemical data of this physical exercise allowed to define general features and effect of the concentration level of these indicators on the process of biochemical adaptation and human resistance formation to the combined effect of maximal physical exercise and acute high altitude hypoxia.

So, in scheme 1 we see that the majority of the metabolic indicators after maximal physical exercise has significant correlation both with glucose level (Ph_i: $r = 0.698$; *Cr:* $r = 0.811$) and with rate of its concentration change in blood (*Cr:* $r = 0.761$). Simultaneously, significant correlation between individual time of the distance overcoming by the subjects (T) and rate of glucose concentration change ($r = -0.515$), showing that increase of glucose exchange rate in blood results to significant decrease in individual time making maximum physical exercise in conditions of high altitude hypoxia. Discovered interconnection of these indicators may be explained on the basis of the following data in literature.

It is well known that even in conditions of normal barometric pressure beginning from the first minutes of physical exercise the blood glucose plays important role as energetic

substrate for the oxidative process in muscles, because local amounts of carbohydrate there significantly decrease [J. Wahren et al., 1971]. During maximal physical exercises an ATP consumption for muscle contraction is so bigger that rate of substrate and oxygen supplies by blood is inadequate. Utilizations of blood glucose and muscle glycogen as prompt mobilizing energetic resources for muscle work increase sharply in these conditions. Thereby adrenaline secretion increases, that stimulates both producing glucose from glycogen in lever and splitting the glycogen to lactate [N.N.Yakovlev, 1974; A.L. Lehniger, 1982].

Time of adaptation	Phase of research		Glucose	Inorganic phosphate	Urea	Creatinine	Bilirubin	Cholesterol
Day 1	Control	Rest	6,95 (1,66)*	0,821 (0,188)	2,14 (0,67)	0,157 (0,002)	1,31 (1,00)	0,039 (0,002)
		Excercise	7,75 (3,56)	0,819 (0,048)	1,79 (0,82)	0,153 (0,003)	1,44 (2,06)	0,072 (0,018)
		P	<0,01	>0,01	>0,5	>0,5	<0,05	<0,01
Day 6	Bemithylum	Rest	8,35 (9,55)	0,720 (0,012)	1,86 (0,29)	0,172 (0,003)	1,75 (0,83)	0,048 (0,0015)
		Excercise	9,87 (3,58)	0,850 (0,25)	3,07 (1,93)	0,226 (0,016)	1,73 (1,93)	0,109 (0,0035)
		P	>0,05	<0,001	<0,01	<0,01	>0,05	>0,05
	Placebo	Rest	5,03 (0,66)	0,497 (0,004)	2,29 (2,1)	0,108 (0,0007)	0,68 (0,02)	0,023 (0,0002)
		Excercise	8,3 (8,58)	0,819 (0,09)	2,33 (0,3)	0,162 (0,001)	1,01 (0,09)	0,059 (0,0018)
		P	<0,001	<0,001	<0,01	<0,01	<0,01	<0,01

* dispersion

Table 1. Effect of *bemithylum* on metabolic indicators in acute period of subjects adaptation to the altitude of 2800m.

At the same time blood lactate, some amino acids and glycerol are converted by gluconeogenesis into glucose which then is transfered by blood to muscles and using both in recovery of glycogen reserves and in liquidation of oxygen debt. Another way on supplies of maximal ATP amount of skeleton muscles in critical circumstances is a splitting of creatine phosphate, - a high energetic compound which is a reserving donor of high energetic phosphate groups in filling uncoupled end-phosphate groups of ATP during muscle contractions. The creatine phosphate supplies exhaust promptly in working muscles and as result of it - ATP reduction, AMP disamination, rising concentration of ADP, P_i and creatinine where the latter is end-product of creatine phosphate split are observed [J.B. Dossetor, 1966; L. Stryer, 1981].

It is necessary to say that availability of significant correlation ($r = 0.667$) between inorganic phosphate level in blood after the physical exercise and concentration of blood urea, which is end-product of oxidative splitting of amino acids in lever and muscle tissues, seemly means drawing urea cycle into process of oxygen debt compensation during development of tissue hypoxia. Take into consideration a character of distribution ("architecture") of the correlation structures for these biochemical indicators we suppose as a working hypothesis that glucose-alanine cycle is one of important bioenergetic mechanisms supporting homeostasis during combined action of physical exercise and high altitude, so as it includes mobilization of blood glucose and increasing of its metabolic exchange between blood and tissues, and its interconnection with metabolites of other cycles, in particular with urea cycle. This cycle supplies working muscles of glucose from lever where for its produce is used carbon structure of alanine and transfers aminogroups to lever from skeleton muscles where the ones are converted into urea [A.L. Lehniger, 1982].

Summarizing results mentioned above we can conclude that combined effect of maximal physical exercises and high altitude hypoxia causes interconnective activation of the above showed bioenergetic metabolic cycles in human organism which is directed both to

liquidation of energetic debt in muscle and other tissues, and to metabolic formation of human adaptive resistance and his physical tolerance.

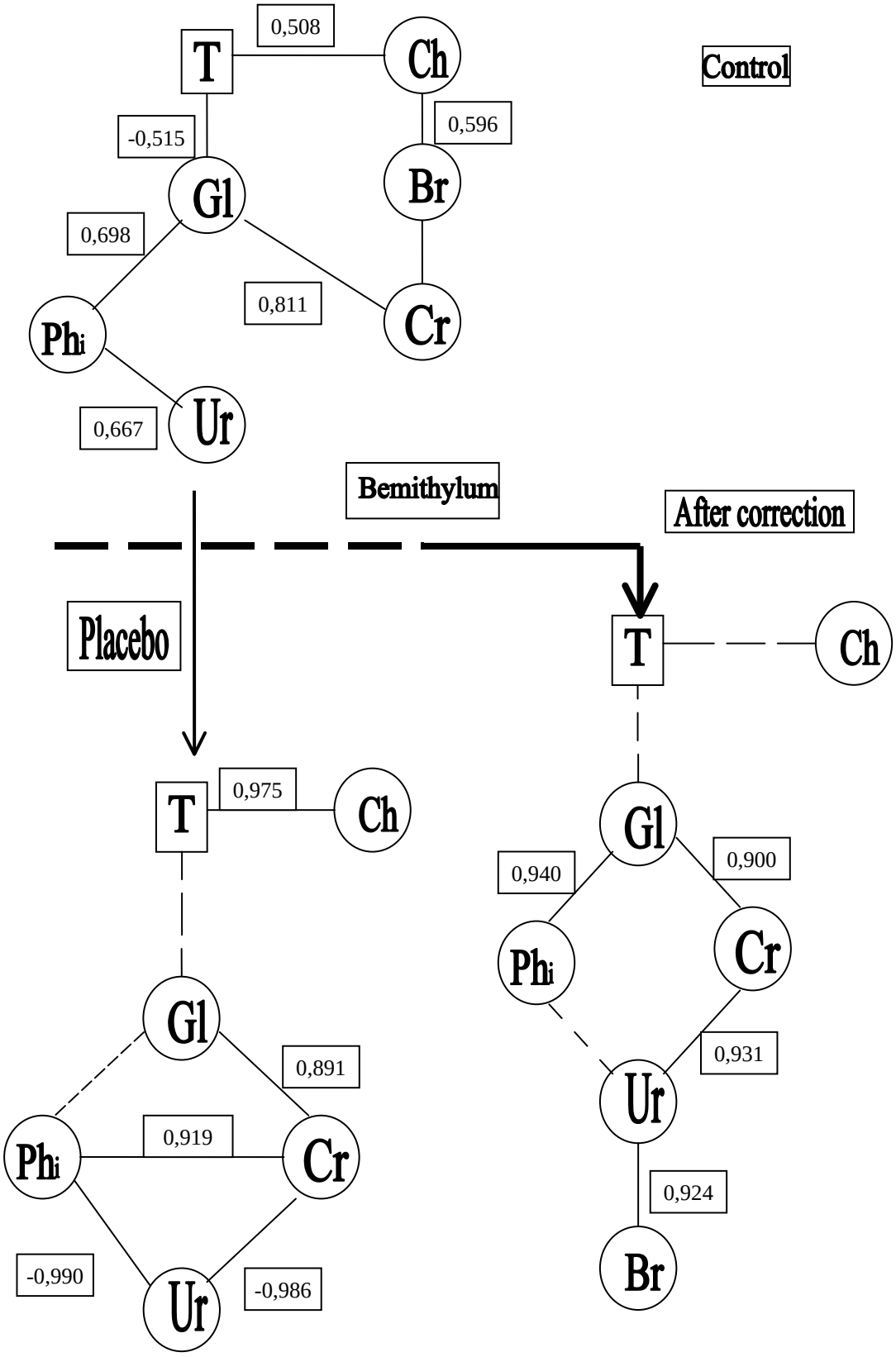
As scheme 1 shows correlation structure has continuation. So creatinine level correlates both with bilirubin level after physical exercise (r = 0.688) and with rate of its concentration change in blood (r = 0.599). In one's turn rate of bilirubun exchange correlates with rate value of cholesterol concentration change in blood (r = 0.596) that reflects equal-directed increase of bilirubin and cholesterol circulations between tissues and blood during control maximal physical exercise. Thereby, value of cholesterol increase in blood has significant positive correlation with individual time of the distance overcoming by the subjects (r = 0.508) which means that increase of time on making physical exercises is caused by essential rise of cholesterol concentration in blood. According to observations of a number of scientists a cholesterol produce increases both in mountain conditions and during physical activities [R.K. McDonald and V.C. Kelly, 1947; R. Bason and Ch.E. Billings, 1969; R. Silvester et al., 1977; A.R.P. Walker et al., 1982]. However, excessive increase of cholesterol concentration in blood under action of stress environmental factors are regarded by these authors as one of signs of functional tension of nonspecific adaptive mechanisms that causes decreased physical workability.

Use of 5-day procedure with *bimethylum* in acute period of high altitude adaptation caused significant effect on metabolic indicators' changes (Table 1). So persons who took *bimethylum* had lesser increase in blood levels of glucose, inorganic phosphate and creatinine in comparison with the data registered in the group of subjects who took *placebo*. These subjects had increase of mentioned indicators for 46.8%, 45.9% and 18.6% accordingly. Our results compared with the results of studies of *bemithylum* effect on energetic metabolism of S.S. Boiko et al. [1987] and G.V. Morozov et al. [1987] who found reducing consumption of creatine phosphate and lesser accumulation of lactic acid during physical exercises as result of this compound action.

The *bemithylum* caused also marked effect onto metabolic exchanges of cholesterol and bilirubin. Concentration of cholesterol and bilirubin significantly increased on the 6^{th} day of mountain adaptation of subjects who took *placebo* (for 156.5% and 48.5% accordingly, $P<0.01$). At the same time persons taken *bemithylum* have non-significant changes in concentrations of these indicators before and after physical exercise.

Thereby, separate elements (links: *Gl–Cr* and *Phi–Ur*) in "architecture" of glucose-depending links of subjects taken *placebo* have maintained as in control research. However specific character of these correlations' forces and polarity is different (see scheme 1). So, correlative forces between rate of inorganic phosphate concentration change in blood and urea level registered after physical exercise significantly increased, and initial polarity of this connection changed (r = –0.990). The initial correlative forces between rate of glucose concentration change in blood and individual time of the distance overcoming by the subjects is significantly decreased (r = –0.053). New strong links have formed between creatinine increase and urea level in blood after physical exercise (r = –0.986), and also between creatinine level and inorganic phosphate (r = –0.919). Nevertheless, the change of polarity in link between inorganic phosphate and urea can indicate on essential changes in work of bioenergetic cycles.

At the same time, direct correlation between blood cholesterol increase and individual time of the distance overcoming increased approximately by two times in this group (r = 0.975). It corroborates once more that excessive rise of blood cholesterol influences negatively to human organism and reduces his workability during physical exercises in conditions of acute period of adaptation to high altitude hypoxia.



Scheme 1. Correlation structures of metabolic indicators in control and post-period of pharmacological correction after maximal physical exercises at altitude of 2800 m over sear level.

Analysis of correlation structures of biochemical indicators showed that "architecture" of glucose-depending links of subjects taken *bemithylum* is similar to the one of control research. But forces of correlation between indicators essentially increased in comparison to control and formed new significant interconnections as follows: *Cr–Ur* (r = 0.931) and *Ur–Br* (r = 0.924); there occure brake of links *Cr–Br* and *Ch–Br*. And correlation between blood cholesterol and individual time of the distance overcoming is statistically non-significant (r = 0.496). It is necessary to mention that glucose increase in blood in these persons during physical exercise was really decreasing in comparison with the data of control physical exercise, which is caused by economizing of glucose produce and also more effective use of glucose substrate by muscle tissues, so that glucose metabolic exchange between blood and tissues increased by 1.5 times ($P<0.01$).

Increase of glucose metabolic exchange rate between blood and tissues during physical exercise in comparison with the control data also occurs in group of subjects with *placebo*-effect. If we take into account that cellular oxygen utilization is directly proportional to the intensity of accumulated substrate transfer through membranes [H.Yost, 1975] we may state that these changes reflect sharply increased need of cells in energetic substrates in conditions of acute oxygen deficiency, connected with high energetic consumption of working muscles when oxygen utilization rate is increased.

Essential increase of correlative dependence between glucose and other metabolic indicators, and statistically significant lesser increase of their level after physical exercise confirm overall economizing and antioxidative (in case of bilirubin) effect of *bimethylum* on metabolic processes. When comparing these results with corresponding antihypoxic and rehabilitative effects of *bimethylum* we see that in conditions of combined effects of hypoxia and physical exercises at 2800m altitude the activity of this compound connected with decrease of energetic resources consumption, particularly with economizing glucose produce and its more effective use by muscle tissues. *Bemithylum* blocks substantial accumulation of blood cholesterol and thereby increases human physical fitness for work in high altitudes.

Table 2 shows that time of the distance (T) covered by the subjects who took *bemithylum* decreased more than by two times in comparison with the data received in group with *placebo*-effect. Besides, increase (Δ) of heart rate and systolic blood pressure decreased in these persons by 1.85 and 2 times accordingly. According to S.A.Kryzhanovsky et al. [1994] it can be explained that overall target of this actoprotector is optimization of activity of all organism physiological systems and decrease of physiological "value" of work unit.

Group	Time of adaptation	Phase of research		Heart rate (beats/ min) Mean±S.E.	Systolic pressure (mm of Hg) Mean±S.E.	ΔT (sec)
I	Day 1	Control	Rest	82,2±4,42	120±5,17	79,2
			Exercise	118,5±3,31	126±3,1	
			P	<0,05	>0,5	
	Day 6	Bemithylum	Rest	81,0±60,07	116,3±2,63	
			Exercise	101,7±5,0	128,6±4,46	
			P	>0,5	>0,5	
II	Day 1	Control	Rest	74,0±2,06	111,7±4,01	162
			Exercise	108±3,27	125,2±2,58	
			P	<0,05	<0,05	
	Day 6	Placebo	Rest	64,0±5,19	108,3±2,47	
			Exercise	109,0±5,23	134,2±1,54	
			P	<0,05	<0,05	

Table 2. The hemodynamic indicators and difference between meantime (ΔT) of the marsh distance overcoming by the 1st and 2nd groups before and after pharmacological correction at the altitude of 2,800m.

It is necessary to specially emphasize the inhibitory effect of *bemithylum* on excessive bilirubin accumulation, whose increased concentration can be examined as combined effect of high altitude and physical exercises to the level of hemogroups disintegration in hemoglobin [V.P.Mahnovsky et al., 1988].

Data of special literature shows that unconjugated bilirubin has pro-oxidative properties, and with excessive concentrations is capable to penetrate through blood-brain barrier [M.Perlman and J.W.Frank, 1988], to bound with tissues and damage cellular structures, especially CNS cells [S.T.Nilsen et al., 1984; T.W.R.Hansen and D.Bratlid, 1986]. There was established direct correlation between decrease of brain mitochondrial enzymatic activity (NADH cytochrome-c-reductase, ATP-ase) and accumulation of total and unconjugated bilirubin in the blood serum [V.A.S.Almeida and L.Rezende, 1981]. It is well known that bilirubin can be bounded with human erythrocyte membrane structures [F.A.Oski and J.L.Naiman, 1963; D.Bratlid, 1972; H.Sato and S.Kashiwamata, 1983], making bilirubin-erythrocyte complexes whose formation is a criteria sign of bilirubin encephalopathy origin risk [N.A.Kaufman at al., 1967; D.Bratlid, 1972]. It appears that bilirubin toxicity is accompanied by its direct relation with certain proteins or certain components of mitochondrial membranes.

It is necessary to emphasize that bilirubin is a product of hemoglobin hemogroup disintegration, whose main site binds with serum albumin and then transferred to lever. Human albumin has paramount high bounding site for bilirubin and also one or several low bounding sites [J.Jacobsen and R.P.Wennberg, 1974; K.S.Lee et al., 1975; N.P.Shabalov, 1982]. When direct (paramount) bounding site of albumin is saturated then prompt increase of unconjugated bilirubin amount in plasma occurs [R.Brodersen, 1980]. This is toxic bilirubin which is capable to interact with membranes of nervous cells, erythrocytes and to decrease activity of some membrane-bounded enzymes as a result of complex combination with phospholipids [R.Brodersen, 1979, 1980; S.Kashiwamata et al., 1981]. If we take into account that acute hypoxia significantly hinders bilirubin clearance from blood [J.Shorey et al., 1969] then its possibility to react with quite big number of cellular compounds significantly increases. This leads to aggravation of compensation process of hypoxic stress in organism, to decrease of his total resistance and adaptability, to changes in processes connected with consentration and thinking that are both supported by our previous research results [A.S.Shanazarov, V.P.Mahnovsky et al., 1989] and by data given in this paper.

In particular, in the first day of residence at 2800m altitude significant correlation between a number of mistaken solutions according to test of "Disarranged lines " and bilirubin level in blood ($r = 0.900$) in group with *placebo*-effect was founded. It continued to be the same and on the 6^{th} day of mountain research ($r = 0.833$). Time of solving the tasks and a number of mistaken solutions were lesser in group of subjects with *bemithylum*-effect for 26.5% and 22% accordingly in comparison with control data, and the correlation between a number of mistaken solutions and bilirubin level was non-significant. The exposed protective effect of *bemithylum* on mental workability during climatic pressure chamber experiences was founded by other researchers. It was shown that use of this actoprotector in the dose of 500 mg decreased a number of mistakes in compensatory tracking and in addition of numbers in the regime of time deficit [L.I. Voronin et al., 1988]. In the conditions of pressure chamber hypoxia ("altitude" of 4500 m) *bemithylum* increased mental workability for 10% according to the re-encoding test [A.V. Smirnov et al., 1990]. It seems here the effectiveness of this compound is caused by its drooping psychostimulating and antiasthenic actions, and also by its possibility to accumulate selectively in cerebral structures, making psychoenergizing effect on cerebral metabolism [S.S. Boiko et al., 1987a] and neutralizing toxic effect of bilirubin.

Thus, application of 5-day procedure of *bemithylum* correction in acute period of adaptation to high altitudes makes activating influence on human physical and mental workability through restructuring of activity of metabolic cycles to economizing regime and providing more economic use of energetic substrates (glucose in particular) by tissues, as well as preventing excessive formation of cholesterol and bilirubin, and preserving sufficiently normal level of concentration.

Interesting data on *bemithylum* prescription to correct hypoxic resistance of military personnel and increase of their high altitude adaptability were received by us in the initial period of their residence at 3600m altitude in Pamir region.

Treatment of two 5-day procedures with *bemithylum* correction for persons with low hypoxic resistance allowed mainly to influence the process of their high altitude metabolic adaptation. So, already after one 5-day procedure with *bemithylum* significantly decreases lactic acid accumulation (for 72.3%, P<0.01), (Fig.1) and value of excess lactate (for 76.9%, P<0.01), (Fig.2) in blood in comparison with group of low resistant persons who took *placebo*. Increase of creatinine, cholesterol, uric acid and especially urea was also lowered for 22.5% (P<0.01), 27.1% (P<0.01), 59.8% (P<0.01) and 122.1% (P<0.01) in these persons accordingly (Fig.1).

At the same time essential increase of glucose in blood (for 45-55% in average) was observed in all subjects in groups with *placebo*- and *bemithylum*-effect , which can be explained by metabolic adaptation character of low resistant individuals in severe climatic conditions of Pamir. Nevertheless, further after two 5-day procedures with *bemithylum* (15th day of research) even in so called high altitude "desert" with specific climatic conditions of this region (i.e. with combination of hypoxia and very low humidity, high solar radiation and extremely poor range of colours of environment), this actoprotector made more economizing effect on concentration of above mentioned metabolites in blood, having reduced increase of glucose for 17.6%, lactic acid for 33.8%, uric acid for 19.3%, creatinie for 21.2%, urea for 179.3% and cholesterol for 74.3% in comparison with subjects with *placebo*-effect (Fig. 1).

As seen from Fig.1 and 2, on 25th day of adaptation to 3600m altitude recovering changes of the majority of these metabolic indicators occured in persons with *bemithylum*-effect. At the same time in persons with *placebo*-effect "excess" amount of lactate as well as concentration of uric acid, creatinine and especially glucose in blood appeared to be significantly increased (P<0.01) in comparison with group with *bemithylum*-effect.

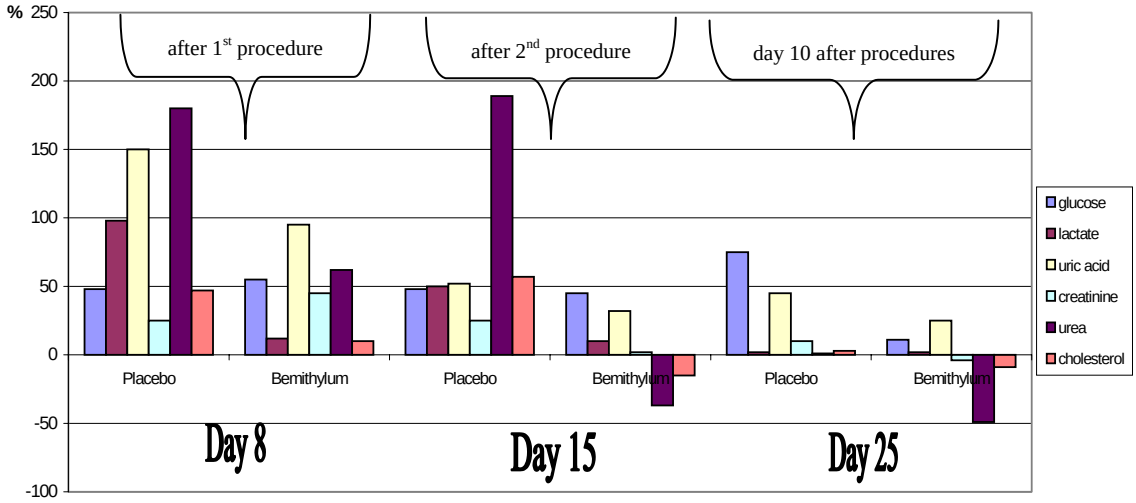


Figure 1. Effect of one and two 5-day procedures with bemithylum and placebo on metabolites' changes in blood of subjects with low hypoxic resistance during adaptation at 3600m altitude.

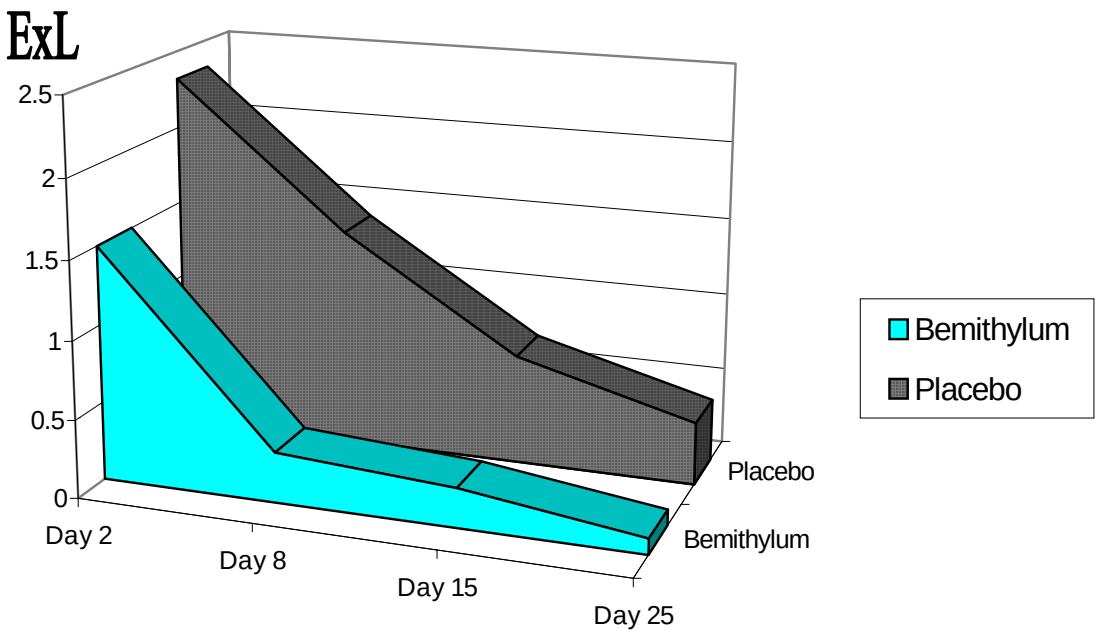


Figure 2. Change of excess lactate value in subjects with placebo- and bemithylum-effect at 3600m altitude.

CONCLUSIONS.

Analyzing the above mentioned research results we may make the following conclusions:

1. Treatment of one or two 5-day procedures with *bemithylum* (in the dose of 750 mg per day) in acute period of high altitude acclimatization allows to reorganize positively metabolism, mainly for the sake of rational decrease of energetic resources consumption, particularly economizing of glucose produce and its more effective use by muscle tissues.

2. *Bemithylum* makes essential psychoenergizing and stimulating effects on the processes of concentration and mental workability in conditions of high altitude hypoxia by means of its ability to be accumulated selectively in cerebral structures and to activate increase of macroergs (high energetic compounds) in nervous cells and also for the sake of direct influence on hemoprotein catabolism, i.e. preventing increase in bilirubin formation to the levels promoting its penetration through blood-brain barrier and following inhibition of activity of cerebral mitochondrial enzymes, including also ATP-ases.

3. Excessive increase of blood cholesterol during physical exercises in conditions of acute period of adaptation to high altitude hypoxia causes negative influence on human organism and significantly decreases his workability. *Bemithylum* prevents significant cholesterol accumulation in blood and simultaneously increases human physical work capacity in conditions of high altitudes. In persons treated with pharmacological correction with *bemithylum*, time of making maximal physical exercise decreased more than by twice in comparison with the data received in subjects with *placebo*-effect.

4. The scheme of one 5-day treatment with *bemithylum* seems to be the most effective both for reducing of terms in achieving urgent adaptation to acute phase of high altitude hypoxia and for transfer of passive form of adaptation into active one. It is necessary to increase treatment with *bemithylum* to two 5-day procedures with obligatory one-day interval between procedures to rise adaptability and resistance of human organism to long-term residence in high altitude conditions.

5. We may conclude that *bemithylum* treatment promotes in significant degree metabolism recovering processes, prevents exhaustion of functional reserves and adaptation breakdown, increases total organism hypoxic resistance and so accelerates human adaptability

to high altitude hypoxia and allows to widen limits of his urgent adaptation to complex of extreme high altitude factors.

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Prognozing of the Resistance to Hypoxia in Military Pilots by Cardiovascular and Respiratory Parameters

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SUMMARY

The effect of hypoxic hypoxia on the autonomic cardiovascular response pattern and the prognosis of resistance to hypoxia were determined after exposure to hypoxic hypoxia in barochamber at simulated altitude 5000 m in 21 military pilots. Cardiovascular: heart rate variability (HRV) measures, heart rate, systolic and diastolic blood pressure, and respiratory parameters: arterial oxygen saturation were examined in pre-hypoxic and post-hypoxic exposure. Although mean values of cardiovascular and respiratory parameters corresponded to referents, hypoxia caused significant effect on HRV measures, diastolic blood pressure, and arterial oxygen saturation. Military pilots were tolerant to hypoxia and did not reveal symptoms of cardiovascular collapse. Hypoxic exposure induced integrated reflex response revealed by significant dependences of the arterial oxygen saturation on spectral power of the R-R intervals in the Respiratory Sinus Arrhythmia band (vagally mediated), and of the diastolic blood pressure on spectral power of the R-R intervals in the Traube - Hering - Mayer band (sympathetically and parasympathetically mediated). In post-hypoxic exposure we observed a pattern of increased both sympathetic and parasympathetic activities with prevailing relative dominance of the vagal cardiac activity over sympathetic one on the control of heart rate variations revealed by significant increase of the mean value of R-R intervals. Prognostic significance for determining of resistance to hypoxia possessed spectral power of the R-R intervals in the Temperature band (sympathetically mediated), and the level of physical training assessed by HRV index - PS. Post-hypoxic sympathetic activity evaluated by P_T could be predicted by pre-hypoxic level of the percent arterial oxygen saturation and diastolic BP; predictor of the post-hypoxic level of the physical training was pre-hypoxic level of P_T and systolic BP.

INTRODUCTION

Physiological stress of the high altitude flight has been the subject of intensive human factors research in aviation medicine. The high altitude exposure characterizes with different from pilot's habitual environment physical and physiological features. During military operations while flying or during physiological training these specific features can lead to hypoxia or risk from Decompression Illness, Mountain Sickness, Pulmonary Barotrauma and Cerebral Arterial Gas Embolism.

Tolerance to hypoxic hypoxia is used to control the physiological training of military pilots and to define their flight performance. During high altitude exposure physiological adjustments that improve pilot's hypoxic tolerance can be evaluated, and alternatively the early symptoms of hypoxic intolerance, resp. pilots predisposed to Barotrauma or Decompression Illness can be detected.

Hypoxic hypoxia is caused by the reduced oxygen partial pressure in inspired air. Exposure to hypoxic hypoxia induces a process of immediate physiologic responses to maintain an adequate tissues oxygen supply: respiratory, cardiovascular, cerebrovascular and visual responses (1; 13; 39; 41; 56; 66). Regardless of permanent studies the response pattern of the autonomic cardiovascular control to hypoxic hypoxia, and its dependence on the arterial oxygen saturation, heart rate, and systolic and diastolic blood pressure for prognozing of the pilot's resistance to hypoxia is not fully determined.

EFFECT OF HYPOXIA ON AUTONOMIC CARDIOVASCULAR CONTROL ASSESSED BY HEART RATE VARIABILITY

Changes in the oxygen partial pressure in the arterial blood perfusing the brain and the peripheral chemoreceptors affect the heart through autonomic nervous control. These indirect effects of hypoxia are dominant and determine response of cardiovascular parameters. Results of available studies will be reported below. Noninvasive mode to study the autonomic cardiovascular control: sympathetic and parasympathetic activity is to analyze components of Heart Rate Variability (HRV): Temperature component of heart rate fluctuations in the frequency band 0.01 - 0.05 Hz, mediated by sympathetic activity (2; 32); Traube-Hering-Mayer (T-H-M) wave component of heart rate fluctuations in the frequency band 0.06 - 0.14 Hz, mediated by sympathetic and parasympathetic activity (2; 42; 50), and Respiratory Sinus Arrhythmia (RSA) component of heart rate fluctuations in the frequency band 0.15 - 0.50 Hz, mediated by parasympathetic activity (2; 31; 50).

Acute hypoxia modulates the sympathetic and parasympathetic cardiac activity (24; 56; 57; 74; 78) but the pattern of changes in both autonomic activities under altitude-induced exposure at rest is not fully defined. To our knowledge there are a few studies of the effect of altitude hypoxia on autonomic cardiovascular control in healthy subjects. Prevailing part of the studies of the effect of hypoxia on autonomic cardiac activity in healthy subjects revealed increase of the sympathetic stimulation accompanied with parasympathetic withdrawal or no effect of hypoxia on

autonomic cardiac control whereas in animal studies co-activation of the activities of both autonomic branches is observed.

Comparing the effect of an exposure to hypoxia at 5050 m on HRV components, with their sea level values by postural manipulations demonstrated high values of the sympathetically/parasympathetically mediated T-H-M-/RSA spectral ratio which could be attributed to a shift of the sympathovagal interaction at rest towards sympathetic dominance (48). 24 h effect of the hypoxic hypoxia in barochamber at the simulated altitude of 4500 m decreased the spectral power in the RSA band and reduced the values of the time-domain HRV measures: standard deviation of the R-R intervals, percentage of differences between successive R-R intervals larger than 50 msec and mean R-R intervals compared with normobaric conditions (78). Reduction of the HRV, assessed by interpolated R-R intervals using cubic splines was attributed to hypoxia caused by the impact of breathing gas mixtures with less than 99.5 % oxygen content during rapid decompression in hypobaric chamber from simulated altitude of 6096 to 15239 m (9).

Contrary to these results other studies revealed that the chemoreceptors modulation caused by hypobaric hypoxia in barochamber did not affect significantly spectral powers in the HRV components, the spectral power in the RSA-band/total spectral power ratio (considered the spectral marker of the parasympathetic activity), the spectral powers in the frequency bands 0.00-0.15 Hz/RSA-band ratio (considered the spectral marker of the sympathetic activity), and heart rate at rest whereas during exercise hypoxia the induced responses were modified: decrease of the spectral power in the RSA-band/total spectral power ratio and increase of the spectral power in the frequency band 0.00-0.15 Hz/RSA-band ratio and heart rate (75). Similar results examining Gamma scaling properties of long-term HRV revealed preserved intrinsic dynamic property of heart function as a result of exposure to hypoxia at 5050 m (43).

In animal studies activation of the chemoreflex in response to decreased oxygen partial pressure under hypoxia caused activation of both sympathetic and parasympathetic cardiac activity (27; 28). Stimulation of the chemoreceptors elicited a simultaneous increase in vagal and sympathetic activity to the heart but activity of which autonomic branch dominated was not determined; the suggestion was vagal origin of activity as cardiac responses were little affected by beta-adrenoreceptor blockade (14; 39). The influence of the respiratory activity upon the magnitude of the excitatory sympathetic reflex was less than upon the cardiovagal chemoreceptor reflex (14).

The effect of an acclimatization process was associated with physiological responses of different character: immediate and long-term adjustments to altitude that improve human's tolerance to altitude hypoxia (41) . Studying of the autonomic cardiovascular responses to acclimatization with pharmaceuticals in different altitude phases revealed immediate compensatory responses: increasing of the spectral powers of the cardiointervals (R-R intervals) in the temperature and the T-H-M band, and decreasing of/in: the spectral power of R-R intervals in the RSA band, the total spectral power, the mean value of the R-R intervals and their standard deviation indicating sympathetic stimulation together with parasympathetic withdrawal whereas long-term adaptations characterized with opposite changes in the HRV components indicating reduction of the adrenergic activity and increased parasympathetic activity (56). Similar results were reported on exposure to acute hypobaric hypoxia at 6000 m (24). Reduced cardiac sensitivity to adrenergic stimulation investigated by postural manipulations was observed under chronic hypoxia (one month stay at 5050 m): evidence for decreased vagal tone was declining of the spectral power of the R-R intervals in the RSA component with little or no change in sympathetic activity examined by the spectral power of the R-R intervals in the T-H-M component (40). Adaptive response to high altitude hypoxia characterized with preserved or enhanced vagal tone evidenced by higher value of the spectral power in the RSA component and lower value of the T-H-M-/RSA-band ratio in high-altitude residents at 4800 m compared to acclimatized low-landers (44; 47).

EFFECT OF HYPOXIA ON SYMPATHETIC AND PARASYMPATHETIC CONTROL ASSESSED BY CARDIOVASCULAR AND RESPIRATORY PARAMETERS

Related to specific changes in autonomic cardiovascular control examined by HRV are adjustments in the cardiovascular and respiratory parameters as their response activation was caused also by stimulation of the chemoreceptors. Chemoreceptors activation induces changes in the autonomic function. Reduction in arterial oxygen partial pressure (PaO2) in the arterial blood stimulates the peripheral chemoreceptors in the carotid and aortic bodies. The resultant increase in the frequency of impulses in the afferent nerve fibres from the chemoreceptors stimulates the vasoconstrictor regions. Parallelly with chemoreflex activation, changes in the PaO2 modulate ventilation, heart rate, arterial pressure, vascular resistance, cardiac output and myocardial contractility via autonomic function.

Resting tachycardiac response to acute hypoxia in healthy subjects was discussed as due to increased activity in the medullary sympathetic centers occuring after stimulation of the peripheral chemoreceptors (5; 22; 24; 64; 67; 71) and/or parasympathetic withdrawal (24; 34). The underlying sympathetic stimulation, inducing cardiac acceleration, increased with acute exposure to hypoxia (15; 40; 53; 60) followed by progressive blunting of the sympathetic response with prolonged hypoxic exposure (57; 58). These alterations affected heart rate: heart rate was maximal after a few days at altitude and then decreased due to declining of the cardiac response to adrenergic activation (56) but did not always return to its basal normoxic value (25; 33; 72). Hypoxic tachycardiac response was not found to be a result from impaired baroreceptor reflex cardiac function (14). Hypoxia did not affect the baroreceptors when the arterial blood pressure did not alter (14; 39). Contrary to sympathetic, parasympathetic heart rate response to acute hypoxia continued

to be controversial, some studies revealed vagal withdrawal (24; 34), other - vagal dominance (21; 23). In animals heart rate response to hypoxia was bradycardiac (30; 35; 39; 45; 61; 65).

Differential response of heart rate was observed at exercise in hypoxic conditions. Exercise at altitude was a predisposing factor for Decompression Sickness (DCS) (36; 49; 54; 62) due to probability of gas emboli formation related to work load levels. Prior exercise at anaerobic threshold was found to have protective: increased blood flow to muscles and tissues facilitated gas elimination, and adverse effects: increased microbubbles formation in critical tissues influencing the incidence of DCS (10; 37). Medical issues associated with the effect of low barometric pressure on pilots (hypoxia and symptoms of Decompression Sickness), and technical aspects of oxygen system, and cabin pressurization inducing oxygen pressure disturbances were discussed extensively (3; 6; 7; 46; 59; 66; 68; 69; 70). During exercise heart rate was increased in hypoxia for low and moderate workloads, and was decreased for near maximal and maximal workloads (16; 55; 73). Alterations in cardiovascular parameters: heart rate and mean blood pressure were apparent only after exercise load occured at approximately 3000 m (63). Short-term exposure to hypoxia in hypobaric chamber at 4000 to 5000 m induced acclimatization to altitude and improved aerobic endurance affecting mainly the adaptive respiratory and circulatory responses (8; 77).

Peripheral chemoreceptors are related to the respiratory control causing increased depth of breathing, increased respiratory rate and pronounced hyperventilation when arterial oxygen saturation (SaO_2) decreased to 93 % at an altitude of 2400 m (66). Arterial oxygen saturation depends on the oxygen partial pressure of the arterial blood (PaO2). SaO_2 was a reliable parameter for studying of the effect of hypoxia and for the acute hypoxic tolerance (76). Declining of SaO_2 to 87 % indicated a status when hypoxic symptoms were obvious; further declining to 65 % was considered as critical for aircrews (66). Under hypoxia oxyhemoglobin dissociation curve was shifted slight to the right that decreased the oxygen affinity of hemoglobin and facilitated the release of available oxygen to the tissues.

In aircrews, reflex cardiovascular response to hypoxia induced increase of heart rate and moderate increase of systolic blood pressure (BP) (66). In military pilots under hypoxic esposure at 5000 m could be observed except tachycardia, moderate increase of systolic BP with 3-18 mm Hg, and decrease or increase of diastolic BP with no more than 10 mm Hg; however in most of the cases hypoxia caused no effect on systolic and diastolic BP (13). Breathing hypoxic mixtures revealed either maintaining or increasing of BP (38). In healthy untrained subjects of a wide age range (6-83 yr) moderate altitude of 2950 m induced small but significant increase of BP (71). Alterations in cardiovascular parameters: icreased BP and heart rate, and acute reduction in cerebral regional oxygen saturation were found to occur only after exercise load at approximately 3000 m altitude in unacclimatized subjects (63).

Adaptation to high altitude hypoxia at 4800 m induced no effect on systolic BP (71). Chronic hypoxia at 5050 m resulted in higher resting systolic and diastolic BP that could be related to increased activity of the Sympathetic Nervous System (SNS) (25).

Reported results focussed on the effect of hypoxia in military pilots and healthy subjects indicated that cardiovascular and respiratory parameters are reliable and significant indicators for studying of the effect of hypoxia and for the determination of the acute hypoxic tolerance. Acute hypoxic exposure at 5000 m at rest affects the sympathetic and parasympathetic cardiac control but results showed that the response pattern is not fully determined. To our knowledge the research on the effect of hypoxic exposure on autonomic cardiovascular function in healthy subjects is not extensive as the research sources on that topic is relatively insufficient. The observed trends of changes in hypoxic response of the autonomic cardiac control are: sympathetic dominance with parasympathetic withdrawal; vagal withdrawal; preserved sympatho-vagal interaction. Contrary to these results Koizumi, Terui., Kollai (1983) and Koizumi, McBrooks (1984) revealed in response to chemoreflex activation induced by the decreased PaO2 in animals, non-reciprocal pattern of autonomic cardiovascular control of co-activation of both sympathetic and vagal activities, followed by reciprocal response with prevailing vagal control over sympathetic concerning the sinus node. Hypoxic tachycardiac response and increased BP in humans are considered to be modulated by the autonomic function and present similar pattern of change as autonomic cardiac control: increased activity in the medullary sympathetic centers and/or parasympathetic withdrawal. Vagal dominance over sympathetic one on heart rate response to hypoxia was also observed (21; 23). Examination of the autonomic cardiac activity by HRV components under hypoxic exposure would elucidate the response pattern of autonomic control, and its causality for predisposition of cardiovascular collapse. Determination of the influence of hypoxia on the HRV components, resp. autonomic cardiac activity and clarifying of the dependence of SaO_2 and BP on HRV would promote for prognozing of the pilot's resistance to hypoxia. Effect of hypoxia on the ANS cardiac function is important to diagnoze the early symptoms of cardiovascular pre-collapse and collapse, and to detect subjects predisposed to Decompression Illness, and to determine pilot's resistance to hypoxia based on autonomic cardiovascular response pattern examined by HRV.

The aim of the present study is to examine the effect of the hypoxic hypoxia on the autonomic cardiovascular response pattern and to determine the prognosis of resistance to hypoxia in military pilots.

METHOD

Subjects

21 male military pilots employed by the Bulgarian Military Air Force whose age ranged from 21 to 42 years (mean age, X±SD: 39.85±9.12) were examined.

Criteria for exclusion included: systolic BP>130 mm Hg; diastolic BP>85 mm HG; body mass index>25 kg/m2; smoking; using medications; cholesterolaemia; diabetes; and a history or evidence of cardioavascular, respiratory, renal, hepatic, gastrointestinal or systemic disease.

Procedure

Military pilots were exposed to hypoxia in hypobaric chamber.Tolerance to hypoxic hypoxia is one of the flying physical examinations for controlling of the physiological training and performance of military pilots. Simulated altitude of 5000 m was accomplished by vertical speed ascent of 20 m/sec. The parameters of the pressure in barochamber were: barometric pressure at an altitude of 5000 m - 405.4 mm Hg, an oxygen partial pressure in inspired air - 84.8 mmHg. Hypoxic exposure was maintained during 30 minutes. Water vapour saturation partial pressure - 47 mm Hg, and carbon dioxide partial pressure - 40 mm Hg were constant during exposure.

Cardiovascular: heart rate variability measures, heart rate, systolic and diastolic blood pressure (BP), and respiratoty parameters: SaO_2 were examined from 10 min periods in sitting position before (pre-hypoxic) and after (post-hypoxic) exposure to hypoxic hypoxia. HRV data were obtained from I bipolar standard ECG lead. Heart rate was computed by continuous recording of II standard ECG lead (Nehb). Systolic and diastolic BP was recorded continuously by sphygmomanometer. Arterial oxygen saturation was recoreded continuously by plethysmographic signal from the left finger.

Heart Rate Variability

Computerized method for analyzing of HRV was applied (11; 45). A portable electronic device was used to transform ECG signal into R-R intervals and to transmit R-R intervals to IBM compatible PC for on-line processing. ECG signal was transformed to R-R intervals by AC convertor (QRS detector and timer, resolution time 2224 samples per second). This sampling rate gives a variation of 0.48 msec in locating the peak of R-wave and results in a minimum accuracy of 99.55 % in computing heart rate up to 140 beats/min.Time-domain and frequency-domain HRV measures, and HRV derived indices were analyzed:

1. Time-domain HRV measures:

X (mean R-R interval) (msec), resp. mean heart rate (beats/min); Short-Term Variability (STV) (msec) (reflecting respiratory oscillations in heart rate variations); Long-Term Variability (LTV) (msec) (reflecting baroreceptory- and thermoregulatory influences on heart rate variations); Time-Domain Index (TDI) (arb. un.) (assessing sympathetic/parasympathetic influences on histogram R-R intervals distribution).

2. Frequency-domain HRV measures:

Spectral power of the R-R intervals in the Temperature band (0.01-0.05 Hz) (P_T) (ms^2) (sympathetically mediated); spectral power of the R-R intervals in the Traube-Hering-Mayer band (0.06-0.14 Hz) (P_{THM}) (ms^2) (sympathetically and parasympathetically mediated); spectral power of the R-R intervals in the Respiratory Sinus Arrhythmia (RSA) band (0.15-0.5 Hz) (P_{RSA}) (ms^2) (parasympathetically mediated); Frequency-Domain Index (FDI) (P_T/P_{RSA}) (arb. un.) (reflecting sympathetic/parasympathetic ratio). Spectral powers of the R-R intervals in the respective frequency bands were calculated using Fast Fourier Transform.

3. HRV-derived indices:

Physical Stress (PS) (arb. un.) (mathematical algorithm based on difference between measured and age-referent values derived from the time-domain HRV measures); Mental Stress (MS) (arb. un.) (mathematical algorithm based on difference between measured and age-referent values derived from the frequency-domain HRV measures); Functional Age (FA) (yr) (mathematical algorithm computing difference beween measured and age-referent values of autonomic activity derived from the frequency-domain HRV measures); Health Risk (%) (mathematical algorithm derived from PS, MS-coefficients and number of premature heart beats).

Computerized system Schiller AG - type Cardioswiss CM - 8 was used to monitor heart rate (beats/min), systolic and diastolic BP (mm Hg) and arterial oxygen saturation (SaO_2) (%) before, during and after hypoxic exposure.

To be comparable to HRV values mean values of heart rate, SaO_2, and systolic and diastolic BP were computed in pre-hypoxic and post-hypoxic exposure.

Analysis of Data

HRV measures, HRV-derived indices, heart rate, SaO_2 and systolic and diastolic BP are expressed as means standard deviations. Means of HRV measures, HRV-derived indices, heart rate, SaO_2,and systolic and diastolic BP in pre- and post-hypoxic exposure were compared by paired-samples t-test. To determine correlations between SaO_2, heart rate, systolic and diastolic BP, and HRV measures correlation analysis was applied. Step-wise method of multiple linear regression analysis (using SaO_2, heart rate, systolic and diastolic BP as independent variables, and the HRV measures

as dependent variables) was performed for determining the dependence of SaO_2, systolic and diastolic BP, heart rate on HRV measures and for defining the resistance to hypoxia. A p value lesser than 0.05 was considered statistically significant.

RESULTS

I. Effect of Hypoxic Hypoxia on: Autonomic Cardiovascular Control Examined by HRV measures; Heart Rate; SaO_2; Systolic and Diastolic BP

To examine the effect of hypoxic hypoxia on cardiac and respiratory function, HRV, SaO_2, heart rate, systolic and diastolic BP parameters were compared between pre- and post-hypoxic exposure by paired-samples t-test. Mean values of cardiovascular and respiratory parameters are presented in Table 1.

Table 1. Means (X ± SD) and p-values of time- and frequency-domain HRV measures, HRV-derived indices, heart rate, systolic and diastolic blood pressure and arterial oxygen saturation in pre-hypoxic and post-hypoxic exposure

Variables	Pre-hypoxic exposure X ± SD	Post-hypoxic exposure X ± SD	p-value
Heart rate (beats/min)	83.10 ± 9.73	81.60 ± 13.62	n.s.
STV (msec)	42.11 ± 1.91	49.39 ± 1.63	0.026
LTV (msec)	33.11 ± 1.96	39.06 ± 1.19	0.038
TDI (arb.un.)	36.67 ± 1.95	42.11 ± 1.46	0.048
mean -R-R (X) (msec)	789.94 ± 99.02	818.89 ± 117. 65	0.05
$P_{(T)}$ (ms^2)	6.04 ± 0.67	10.74 ± 1.34	n.s.
$P_{(THM)}$ (ms^2)	8.54 ± 0.18	11.45 ± 0.82	0.003
$P_{(RSA)}$ (ms^2)	6.34 ± 0.14	9.16 ± 0.59	0.03
FDI (arb.un.)	27.34 ± 1.51	33.69 ± 1.08	0.008
PS (arb.un.)	0.71 ± 0.09	0.14 ± 0.01	n.s.
MS (arb.un.)	0.38 ± 0.03	0.57 ± 0.05	n.s.
HR (%)	52.83 ± 8.20	45.72 ± 6.94	n.s.
FA (yr)	41.94 ± 1.72	42.61 ± 1.82	n.s.
systolic BP (mmHg)	127.45 ± 10.54	122.30 ±13.33	n.s.
diastolic BP (mmHg)	78.75 ± 10.12	74.60 ± 9.93	0.033
SaO_2 (%)	97.10 ± 1.07	94.05 ± 4.96	0.009

Significant effect of hypoxic exposure was observed for HRV measures, SaO_2 and diastolic BP. Hypoxia induced significant decrease of diastolic BP and SaO_2. Hypoxia resulted also in significant increase of mean values of the mean R-R interval (X), STV, P_{RSA}, P_{THM}, LTV,TDI ad FDI. Fig. 1, Fig. 2, Fig. 3 and Fig. 4 illustrate differences in mean values of: mean R-R interval (X), STV and LTV; P_{RSA} and P_{THM}; diastolic BP; SaO_2 in pre-hypoxic and post-hypoxic exposure.

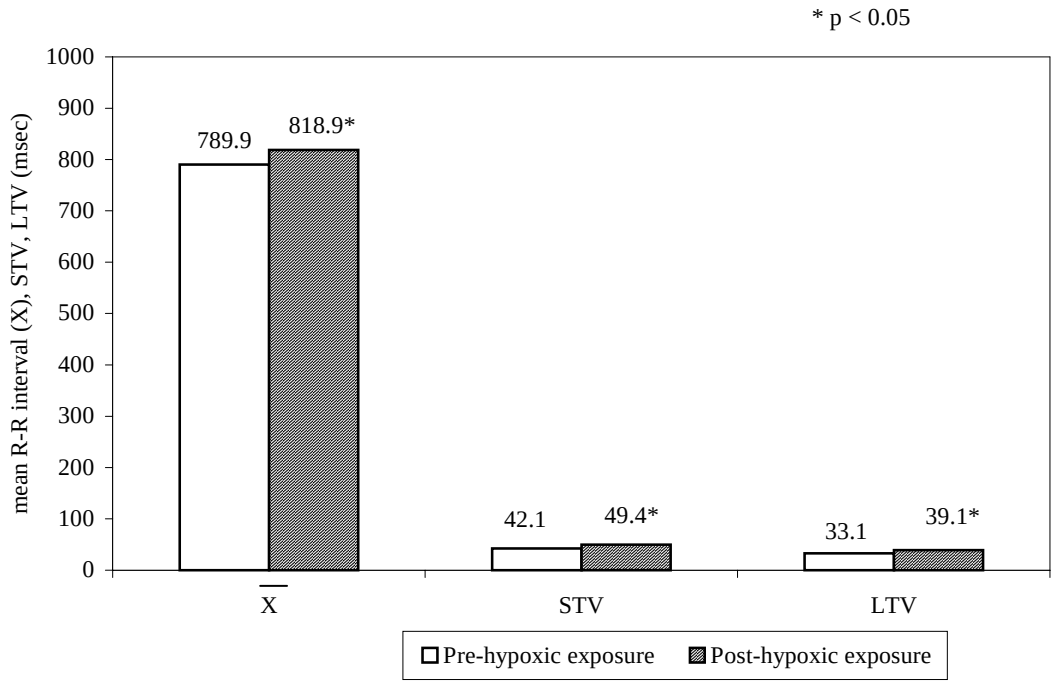

Fig. 1. Mean values of the mean R-R interval (X) (msec), STV (msec) and LTV (msec) in pre-hypoxic and post-hypoxic exposure

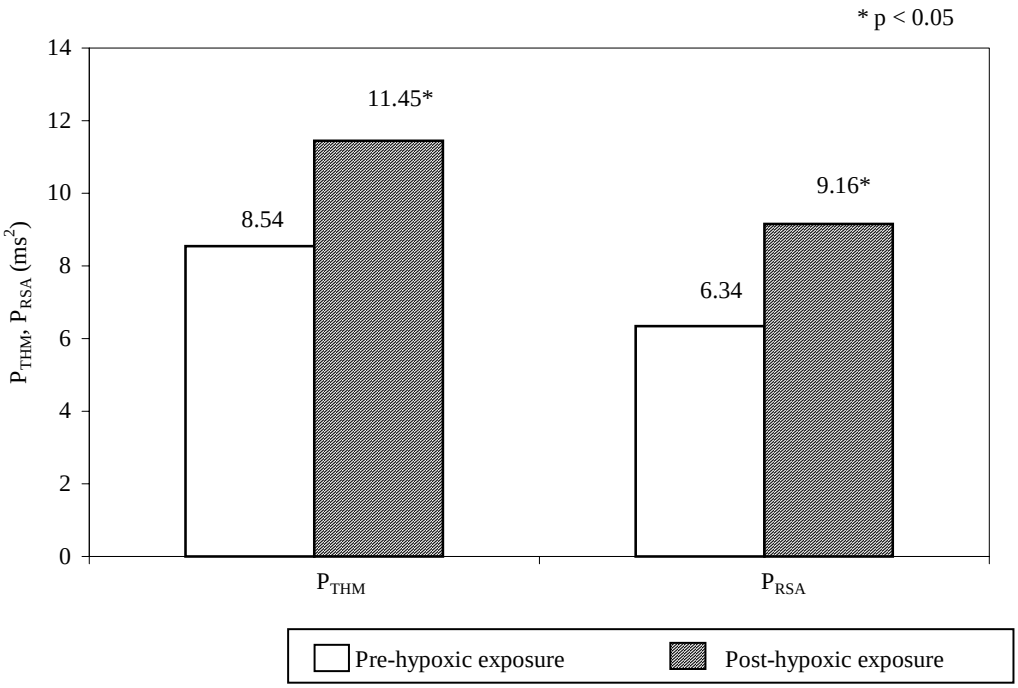

Fig. 2 Mean values of the P_{THM} and P_{RSA} (ms^2) in pre-hypoxic and post-hypoxic exposure

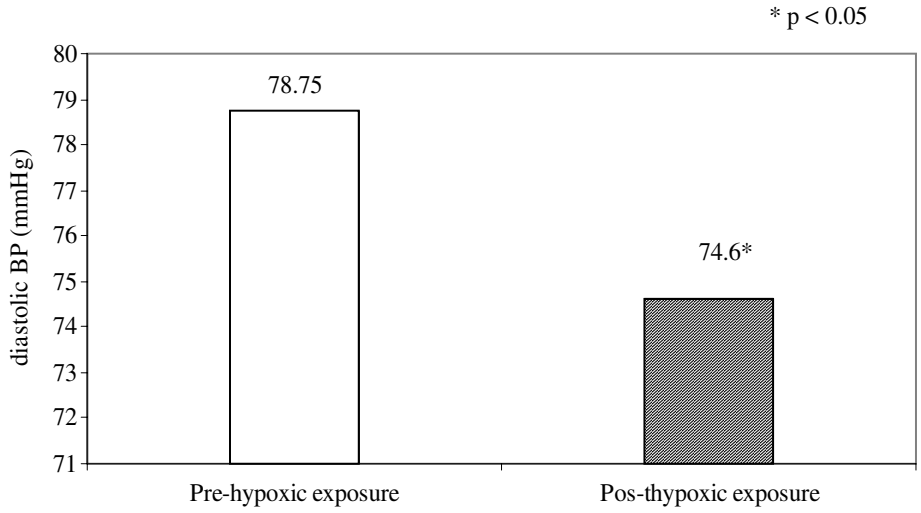

Fig. 3 Mean values of the diastolic BP (mmHg) in pre-hypoxic and post-hypoxic exposure

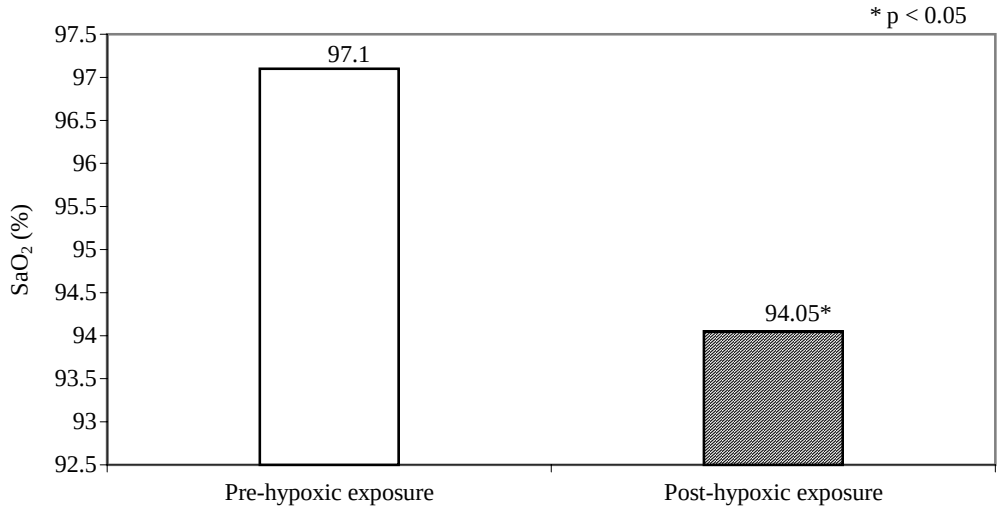

Fig. 4 Mean values of the SaO_2 (%) in pre-hypoxic and post-hypoxic exposure

II. Effect of Hypoxic Hypoxia on Association between Autonomic Cardiovascular Control Examined by HRV, and SaO_2 and diastolic BP

Effect of the response to hypoxia on the association between autonomic cardiovascular control examined by HRV, and heart rate, SaO_2, and systolic and diastolic BP parameters was determined differentially by correlation and step-wise method for multiple linear regression analysis. Results of both analyses revealed dependence only of SaO_2 and diastolic BP on the autonomic cardiovascular control.

1. Correlations of SaO_2 with HRV

1.1. Prehypoxic correlations:

- Significant positive correlations of SaO_2 with time-domain HRV measures: Mean R-R interval (X) ($r = 0.63$, $p < 0.005$); STV ($r = 0.49$, $p < 0.05$); LTV ($r= 0.55$, $p < 0.01$); TDI ($r = 0.55$, $p < 0.01$)

- Significant negative correlations of SaO_2 with HRV-derived indices: FA ($r = -0.58$, $p < 0.01$); HR ($r = 0.51$, $p < 0.05$)
- Significant negative correlation of SaO_2 with heart rate ($r = -0.59$, $p < 0.01$)

1.2. Posthypoxic correlations:

- Significant negative correlation of SaO_2 with P_{RSA} ($r = -0.54$, $p < 0.01$).

2. Correlations of diastolic BP with HRV

Significant correlations of diastolic BP with HRV were observed only in posthypoxic exposure.

- Significant negative correlation of diastolic BP with frequency-domain HRV measure: P_{THM} ($r = -0.46$, $p < 0.05$); FDI ($r = -0.51$, $p < 0.05$).
- Significant negative correlations of diastolic BP with time-domain HRV measures: STV ($r = -0.50$, $p < 0.05$); TDI ($r = -0.50$, $p < 0.05$).
- Significant positive correlation of diastolic BP with HRV-derived index: HR ($r = 0.56$; $p < 0.01$)

Correlation coefficients of SaO_2 and diastolic BP with HRV measures in pre- and post-hypoxic exposure are presented in Fig. 5 and Fig. 6.

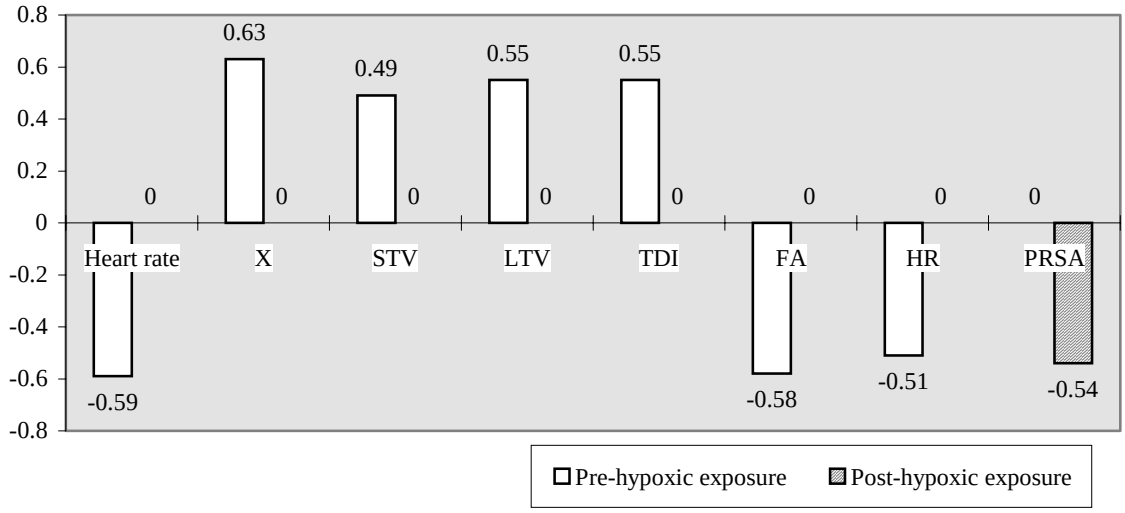

Fig. 5 Correlation coefficients of the SaO_2 with HRV measures in pre-hypoxic and post-hypoxic exposure

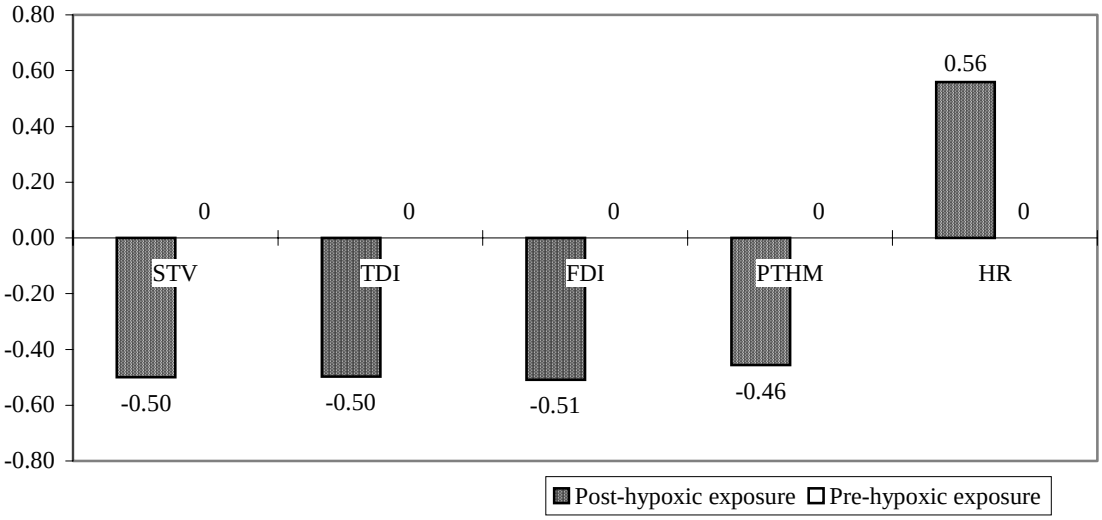

Fig. 6 Correlation coefficients of diastolic BP with HRV measures in pre-hypoxic and post-hypoxic exposure

Correlation of some paired identical measures in pre- and post-hypoxic exposure did not show statistical significance although is normally expected to present high correlation:

- Time-domain HRV measures: STV ($r = 0.43$, $p = 0.07$); LTV ($r = 0.15$, $p = 0.54$); TDI ($r = 0.44$, $p = 0.07$)
- Frequency-domain HRV measure: P_T ($r = - 0.03$, $p = 0.90$)
- HRV-derived index: HR ($r = 0.27$, $p = 0.27$)
- SaO_2: ($r = 0.34$, $p = 0.15$).

The rest of correlations between paired identical measures were significant.

3. Dependences of SaO_2 and diastolic BP on HRV

Dependences of SaO_2 and diastolic BP on HRV were observed only in posthypoxic exposure. The following dependences were observed:

- Slow extent of increasing of the spectral power of R-R intervals in the Traube - Hering - Mayer band with declining of the diastolic BP
- Moderate increasing of the spectral power of the R-R intervals in the Respiratory Sinus Arrhythmia band with declining of SaO_2.

Regression equations describing dependences of SaO_2 and diastolic BP on HRV are presented in Table 2.

Table 2. Regression equations of dependence of SaO_2 and diastolic BP on HRV measures in post-hypoxic exposure

$\mathbf{P_{THM}}$ = 23,927 - 0,171* x diastolic BP
$\mathbf{P_{RSA}}$ = 42,336 - 0,376* x SaO_2

*p < 0.05

III. Prognozing of the Resistance to Hypoxic Hypoxia by Cardiovascular and Respiratory Parameters

Prognozing of the resistance to hypoxia by cardiovascular and respiratory parameters was performed in post-hypoxic level based on definite values of the same variables in pre-hypoxic condition. Our results revealed that prognosis of resistance to hypoxia could be determined by P_T and PS:

- Post-hypoxic value of the spectral power of the R-R intervals in the Temperature band considered to be sympathetically mediated defined resistance to hypoxia by pre-hypoxic level of SaO_2 and diastolic BP
- Post-hypoxic level of the physical stress, resp. physical training predicted the resistance to hypoxia by pre-hypoxic level of P_T and systolic BP

Regression equations determining the prognosis of the resistance to hypoxia are presented in Table 3.

Table 3. Regression equations for prognozing of the resistance to hypoxia

$\mathbf{P_T}$ (post-hypoxic exposure) = -705.92 + 7.82* x $\mathbf{SaO_2}$ (pre-hypoxic exposure) - 0.54* x **diastolic BP** (pre-hypoxic exposure)
PS (post-hypoxic exposure) = -3.05 - 0.362* x $\mathbf{P_T}$ (pre-hypoxic exposure)+ 0.04* x **systolic BP** (pre-hypoxic exposure)

* p < 0.05

DISCUSSION

Hypoxic Tolerance

Our results of exposure to moderate hypoxia in comparing of pre-hypoxic and post-hypoxic exposure demonstrated that military pilots were tolerant to hypoxia. Mean values of the heart rate, systolic and diastolic BP in pre- and post-hypoxic exposure corresponded to referents computed by the method of percentiles for both exposures (26). Hypoxic tolerance was supported by the evidence that in post-hypoxic exposure pilots did not reveal symptoms of cardiovascular pre-collapse or collapse.

Effect of Hypoxia on Autonomic Cardiovascular Control

We investigated the effect of hypoxic hypoxia caused by decreased partial oxygen pressure in inspired air (PaO2). Decreased PaO2 is a stimulus for activation of the peripheral chemoreceptors. In our study more likely mechanism for the integrated reflex cardiovascular and respiratory responses was chemoreceptors activation. Chemoreflex responses on cardiovascular and respiratory function were considered to be mediated via autonomic function (14; 39).

In post-hypoxic exposure we observed a pattern towards increased both sympathetic and parasympathetic activities with prevailing relative dominance of the vagal cardiac activity over sympathetic one on the control of heart rate variations revealed by significant increase of the mean value of R-R intervals. Vagally mediated P_{RSA} and STV measures both reflecting rhythmic heart rate variations associated with the respiratoty phases were increased after exposure to hypoxia. RSA is considered as a measure of cardiac vagal tone (31; 51). Our evidence of increased vagal cardiac control in post-hypoxic exposure was supported also by significant dependence of the SaO_2 on P_{RSA} observed only after exposure to hypoxia. Increased vagal activity reflected by the P_{RSA} could be predicted by minimal declining of the SaO_2.

Studies of Simon, Taha, Dempsey, Skatrud, Iber (1995) of respiratory modulation of hypoxic tachycardiac response, and of Grossman and Wientjes (1986) of association between respiration, RSA and cardiac vagal control suggested the centrally acting mediated brainstem rhythm to be responsible for the respiratory modulation of the parasympathetic efferent traffic to the sinus node. This model could be referred to the observed by us result of an association between vagally mediated P_{RSA} and SaO_2 with a certain approximation as we examined indirect measure of the respiratory function: SaO_2.

In post-hypoxic exposure also we observed parallelly to elevated vagal activity slight indirect trend for increased sympathetic cardiac activity. After exposure to hypoxia mean values of the considered sympathetically and vagally mediated P_{THM}, LTV, FDI and TDI were increased. Evidence for significant effect of hypoxia on autonomic cardiac activities were lack of correlations between some paired identical measures of HRV: sympathetically mediated P_T; sympathico-vagally mediated LTV, TDI, HR, and of SaO_2 in pre- and post-hypoxic conditions which in normal conditions are characterized with high significant correlation. Relatively most affected by hypoxic exposure was the sympathetic activity reflected by the P_T ($r = - 0.03$; $p = 0.90$).

To a certain degree indirect evidence for relatively increased sympathetic cardiac activity was the dependence of diastolic BP on P_{THM}. We hypothesized relative sympathetic increase as this band of the HRV spectra (P_{THM}-band) was considered sympathetically and vagally mediated (2; 42; 50). In post-hypoxic exposure decreased values of diastolic BP were associated with an increased P_{THM} response. Our study revealed an association between rhythmical fluctuations of arterial BP due to vasomotor variations synchronous with the respiration: Traube-Hering waves, and due to rhythmical variations in the activity of the vasomotor center: Mayer waves that were observed in other studies (39; 52). Increased discharge from chemoreceptors might contribute for the specific Mayer waves (19). Mayer waves were slow oscillations in the arterial pressure. When arterial pressure shows even a slight trend to decline hypoxia stimulates chemoreceptors. Arterial pressure increases as a response to stimulation which improves oxygen supplying of chemoreceptors. Specific 0.1 Hz rhythm of HRV spectra was considered sympathetically mediated, and activated from alterations of blood pressure and oxygen saturation (29). This sympathetically mediated rhythm was to a certain degree responsible for the observed by us dependence of diastolic BP on P_{THM}. Sympathetically mediated 0.1 Hz rhythm was not subject of our study. Further investigation could be performed to reveal response of the 0.1 Hz rhythm to hypoxia to determine the association of the 0.1 Hz rhythm with SaO_2 changes.

We observed activation of both sympathetic and parasympathetic cardiac activities caused by exposure to hypoxic hypoxia but the response pattern was relative dominance of vagal activity over sympathetic one on the control of heart rate variations. Studies investigating the change of the autonomic cardiac control under hypoxia are scarced and results are controversial. Our result is consistent with the results of Koizumi and McBrooks (1984) and Koizumi, Terui, Kollai (1983) evidencing that the activation of the chemoreflex in response to changes in PaO2 or PaCO2 induced non-reciprocal pattern of co-activation of sympathetic and parasympathetic cardiac activity followed by reciprocal response with prevailed vagal control over sympathetic on the sinus node. As the studies of Koizumi and McBrooks (1984) and Koizumi, Terui, Kollai (1983) were performed on animals and as there are to our knowledge only two studies of increased parasympathetic heart rate response to hypoxia (21; 23), the result of our study of pattern of co-activation of sympathetic and vagal cardiac activities with prevailing relative dominance of the vagal activity over sympathetic on

heart rate variations, induced by 30 minutes continuous exposure of hypoxic hypoxia in barochamber, needs further continuation to determine specific effect of hypoxia on autonomic cardiovascular control.

Our study confirmed an integrated response to hypoxia result of the activation of chemoreceptor reflex mechanism modulating the respective cardiovascular and respiratory responses via autonomic function, observed in the studies of Sheffield and Heimbach (1996), and of Berne and Levy (1990).

Prognozing of the Resistance to Hypoxia

Prognosis of the resistance to hypoxia of military pilots was determined by HRV measures: P_T and PS. These measures of the autonomic cardiovascular control possessed pronounced prognostic significance for determining of the resistance to hypoxia. Results indicated clearly that post-hypoxic sympathetic activity (P_T) could be predicted by pre-hypoxic level of the percent arterial oxygen saturation and diastolic BP. Strong predictor for the post-hypoxic level of physical fitness, resp. physical stress (PS) was pre-hypoxic level of the sympathetic activity (P_T) and systolic BP. Regression equations for determining of the resistance to hypoxia are valid only for the definite intervals of changes of the independent variables. To our knowledge an attempt for prognozing of resistance to hypoxia by these variables up to now is not reported.

In summary our results of acute simulated hypoxic hypoxia in military pilots demonstrated:

1. Military pilots were tolerant to hypoxia. Mean values of the heart rate, systolic and diastolic BP in pre- and post-hypoxic exposure corresponded to referents computed by the method of percentiles for both exposures. Hypoxic tolerance was supported by the evidence that they did not reveal post-hypoxic symptoms of cardiovascular pre-collapse and collapse.
2. In post-hypoxic exposure we observed a pattern towards increased both sympathetic and parasympathetic cardiac activities with prevailing relative dominance of the vagal cardiac activity over sympathetic one on the control of heart rate variations revealed by significant increase of the mean value of R-R intervals. Our result is consistent with the results of Koizumi and McBrooks (1984), and Koizumi, Terui, Kollai (1983) evidencing that the chemoreflex activation in response to reduction of the PaO2 caused non-reciprocal pattern of co-activation of sympathetic and parasympathetic cardiac activity followed by reciprocal response with prevailed vagal control over sympathetic on the sinus node.
3. Our study confirmed an integrated response to hypoxia result of the activation of chemoreceptor reflex mechanism modulating the respective cardiovascular and respiratory responses via autonomic function, observed in the studies of Sheffield and Heimbach (1996), and of Berne and Levy (1990). Our evidence of increased vagal cardiac control in post-hypoxic exposure was supported by significant dependence of the arterial oxygen saturation on P_{RSA} observed only after exposure to hypoxia. To a certain degree indirect evidence for relatively increased sympathetic cardiac activity in post-hypoxic exposure was the dependence of diastolic BP on P_{THM}.
4. Prognosis of resistance to hypoxia of military pilots was determined by P_T and PS. These measures of the autonomic cardiovascular control possessed pronounced prognostic significance for determining of the resistance to hypoxia. Results indicated clearly that post-hypoxic sympathetic activity (P_T) could be predicted by pre-hypoxic level of the percent arterial oxygen saturation and diastolic BP. Strong predictor for the post-hypoxic level of the physical fitness, resp. physical stress (PS) was pre-hypoxic level of the sympathetic activity (P_T) and systolic BP. To our knowledge an attempt for prognozing of resistance to hypoxia by these variables up to now is not reported.

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Alternobaric Vertigo: Incidence in Portuguese Air Force Pilots

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Abstract

Alternobaric Vertigo is a sudden and transient vertigo caused by asymmetrical changes in middle ear pressure (Lündgren – 1965). These changes are directly related to the daily activity of aircraft pilots (and divers). This vertigo strikes often in critical maneuvers (attacks or evasions) causing sudden disorientation. We used an anonymous enquiry, multiple-choice type, preceded by a briefing about alternobaric vertigo. We found 29% of the pilots with 1 or more episodes of alternobaric vertigo, all being caused directly by rapid ascents and/or brisk Valsalva maneuvers.

Introduction

Alternobaric Vertigo is a sudden and transient vertigo caused by asymmetrical changes in middle ear pressure (Lündgren – 1965). These changes are directly related to the daily activity of aircraft pilots (and divers), which implies variation of altitude (or depth). This vertigo typically lasts few seconds, with prompt *restitutio ad integrum*, and no organ damage is observed. The precise physiopathologic mechanism is not known, even though several studies have been made searching for circulatory, thermal or pressure changes in internal ear, as well as anatomical variations.

Its importance derives from the fact that it strikes often in critical maneuvers (attacks or evasions) causing sudden disorientation.

Known in divers since 1896, and observed in pilots since 1937, was first coined "Alternobaric Vertigo" by Lündgren in 1965. Probably (predictably) fairly common in high-performance aircrafts, as well as in divers:

RAF pilots 10% - Jones, 1956 [3]
Swedish Air Force Pilots 17% - Lündgren 1966 [4]
Divers 26% Lündgren 1965 [4]

It is assumable that pilots are reluctant to report such symptoms and so these data are most likely underestimated…

The importance of this situation drove our Aeronautical Medical Center to enquire our high performance pilots, to get *au pair* of our numbers, as well as to learn more about how to prevent and deal with it.

Materials and Methods

It was used an anonymous enquiry, multiple-choice type, preceded by a *briefing* about alternobaric vertigo. We included questions about specific details of the episode, as well as risk and precipitating factors.

This quiz was filled by 12 Alphajet and 12 F16 pilots (about 2/3 of our pilots flying each of these aircrafts)

Results

More than predicted by previous studies, we found 7 pilots with 1 or more episodes of alternobaric vertigo (29%): 3 in F16, 2 in Alphajet, 1 in Epsilon and 1 on the floor prior to flying. In 5 cases there were more than 1 episode. We were unable to determine a relation between the number of episodes and the total flown hours; even though, 5 pilots have more than 1000h. No incidents were officially reported.

Characteristics:

In most cases, the vertigo was rotary horizontal, with 2 episodes of sagital vertigo. All but 1 episode were not accompanied by other symptoms, the exception being tinnitus.

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Precipitating factors

All the episodes were precipitated either by rapid ascent or by Valsalva maneuver.

Risk factors

About 71% (5) of the episodes were connected with recent or contemporary upper respiratory tract infection. 1 pilot has history allergy with predominant terrain in the upper respiratory tract. 59% (4) of the referred pilots are smokers (14% light smoker, 28% moderate and 14% heavy). 28% (2) mentioned chronic recurrent upper respiratory tract afflictions (sinusitis, rhinitis…). Only 1 pilot had no identified risk factors. None of our study pilots had had adenoidectomy.

Discussion

Even though we had few pilots to enquiry (24), the numbers were impressive in two ways: the problem seems more common than expected, probably because of the increased performance of the aircrafts since the studies presented, in spite of the fact the selection methods are more careful nowadays. The second striking aspect was the role clearly present for the precipitating factors, having all the episodes being caused directly by rapid ascents and/or brisk Valsalva maneuvers, demonstrating the critical role of pressure changes in this type of vertigo. Confirming this datum are the risk factors that were almost omnipresent.

As this vertigo is typically brief and self-limited, one can only prevent it and limit its consequences:

- -Learn to promptly recognize it and deal with it properly – leveling the flight, limiting the pressure changes.
- -Avoid flying with active risk factors – UTI, active allergy…
- -Avoid smoking and other respiratory irritants.
- -Avoid precipitating factors – make frequent and progressive Valsalva maneuvers, especially when flying low level or 100% O_2.
- -Pilots should pay frequent visits to the flight surgeon, to rule out any Eustachian tube dysfunction
- -Flight surgeons should also keep pilots on continuous formation, including this subject in physiology refreshment courses.

Finally we remind that Alternobaric Vertigo is (as we've seen) an important cause of sudden spatial disorientation, leading to sudden incapacity in flight that cannot be omitted when investigating causes for aircraft accidents.

It is also obvious that it is also important to divers, for the same mechanism(s) inflicts the same pressure changes in the middle ear.

The fact of being brief and self-limited should not minimize it's importance in our minds. It can occur at any critical time!

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Neuropsychometric Test in Royal Netherlands Navy Mine-Clearance Divers

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Background: In recent years, there has been growing concern within the diving community that divers may be suffering long-term neurological damage [1-4]. Neurological changes may exist either as clinical manifestations or as silent asymptomatic abnormalities only demonstrated by neurological and neuropsychological techniques [5]. The aim of this study was to investigate possible neuropsychometric effects in Netherlands Navy mine-clearance divers without any previous neurological decompression sickness.

Methods: Forty-three Navy mine-clearance divers were selected based on a career of at least 15 years of military diving. The average age of the divers was 42 (range 37-50) years. Their mean diving experience was 1767 (range 734 - 2800) dives (Table 1).

Table 1 Data on exposure for the Navy divers

	Divers (N=43)		
	Mean	SD	Range
Exposure			
– Years of diving	18.7	7.1	15-29
– Number of dives last year (<30 meter)	44.0	45.2	4-130
– Number of dives last year (>30 meter)	24.4	19.3	1-75
– Total dives to 30 meter [a]	1272	699	300-3000
– Total dives deeper than 30 meter [b]	495	334	20-1500
– Mean divetime (min) to 30 meter [c]	50.5	15.0	18-100
– Mean divetime (min) deeper than 30 meter [d]	45.2	25.0	8-80
– Dive index [a*c/60+b*d/60] (hours)	1464	839	177-4000

A computerized neuropsychological test battery, the Neurobehavioral Evaluation System (NES2) was applied [6]. The battery consists of tests in the domains of Attention (Simple Reaction Time Test, Switching Attention Test), Motor performance (Finger Tapping Test, Hand-Eye Coordination Test), Learning and memory (Verbal Memory Test, Digit Memory Span Test-Forwards/Backwards), Perceptual coding (Symbol-Digit Substitution Test) and Verbal ability (Vocabulary Test) (Table 2).

Table 2 Computer Administered Neurobehavioral Tests

Test	Abbreviation	Function
Vocabulary	VT	Verbal ability
Finger Tapping Test	FTT	Motor performance
Simple Reaction Time Test	SRTT	Attention
Verbal Memory Test (1)	VMT-1	Learning/memory
Switching Attention Test	SWAT	Attention
Symbol-Digit Substitution Test	SDST	Perceptual coding
Hand-Eye Coordination Test	HECT	Motor performance
Verbal Memory Test (2)	VMT-2	Learning/memory
Digit Memory Span Test (F/B)	DMST-F/B	Learning/memory

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In addition, questionnaires for neurotoxic symptoms (Neurotoxic Symtom Checklist-60, NCS-60) and mood states (Profile of Mood Scales, POMS) were used. The tests in the domains were evaluated using Hotellings T^2 test, individual tests were analysed with T-tests or Mann Whitney tests were appropriate. A group of Navy corpsmen (n=68) matched for age, education and vocabulary score was recruited to serve as the control population (Table 3).

Table 3 Demograhics

	Divers	Control group
– **Number** of persons	43	68
Gender		
– All males	43	68
Age		
– Mean (years)	42.2	42.3
– SD	4.3	3.5
– Range	37-50	36-50
Education		
– Level (Groninger Scale)	4.3	4.2
– SD	1.1	0.9
– Range	2-6	3-7
– School years (N=)	11.6	11.0
– SD	3.3	2.0
– Range	8-23	8-18
Vocabulary score		
– Correct (N=)	13.1	13.2
– SD	2.5	3.1

Results: The Navy clearance divers showed no abnormal neuropsychometric test results compared to the Navy control population. The divers had significantly better scores for the DMST and FTT ($p<0.05$) (Table 4).
There were no differences in NSC-60 and POMS scores between the divers and control group (data not shown). Subjects of both groups had normal values compared with the reference values for the test. No relationship was found between the effect parameters and diving exposure in our naval diving population.

Discussion: In this study on mine-clearance divers we found no clear evidence of neuropsychometric deficits due to extensive diving exposure. This is in contrast to results of other studies, although most of these latter studies involved saturation divers [7-9]. In the Royal Netherlands Navy, the extensive initial medical and psychological screening, the yearly medical control and the use of conservative decompression procedures are the factors which most likely contribute to the healthy neuropsychometric status of our divers.

Table 4 Results of neuropsychometric performance

	Divers (n=43)		**Control group (n=68)**		**t-test**	
	Mean	SD	Mean	SD	t-value	p-value
Attention/speed					8.73[a]	0.32
Simple Reaction Time Test						
– Latency (ms)	217.3	21.8	220.8	34.4	-0.59	0.55
Color Word Vigilance Test						
– Latency (ms)	588.1	60.3	594.6	66.8	-0.52	0.60
– # false positive	0.56	0.73	1.12	1.57	1152[b]	**0.043**[c]
– # omissions	0.49	0.67	0.76	1.04	1320[b]	0.33
Switching Attention Test						
– latency “side” (ms)	253.5	38.0	259.0	37.4	-0.75	0.45
– latency “direction” (ms)	414.1	65.8	411.8	57.9	0.19	0,85
– latency “switching” (ms)	617.1	192.6	638.0	164.3	-0.61	0,54
Perceptual coding					-0.16	0.87
Symbol-Digit Substitution Test						
– latency “symbol- figure” (sec)	2.57	0.33	2.58	0.30	-0.16	0.87
Learning/memory					16.7[a]	**0.036**[c]
Verbal Memory Test						
– # correct trial 1/5	43.6	10.7	43.4	9.8	0.09	0.93
– # correct “short delay free recall”	8.7	3.2	8.6	3.2	0.22	0.83
– # correct “long delay free recall”	9.1	3.0	9.4	2.9	-0.49	0.63
– # correct recognition– list	14.3	1.6	13.8	2.1	1.31	0.19
– semantic clustering	2.1	0.9	2.1	0.7	-0.05	0.96
Digit Memory Span Test						
– mean span length forwards	6.65	0.95	6.18	0.92	2.63	**0.0098**[c]
– mean span length backwards	5.93	1.12	5.42	1.10	2.39	**0.019**[c]
Motor performance					11.02[a]	0.068
Hand-Eye Coordination Test						
– mean absolute error “sine wave” (pixels)	1.61	0.26	1.63	0.26	-0.39	0.69
– mean absolute error “tooth of saw” (pixels)	1.86	0.21	1.86	0.24	0.03	0.98
Finger Tapping Test						
– # taps dominant hand	168.9	30.7	153.6	28.1	2.69	**0.0082**[c]
– # taps non-dominant hand	161.6	29.2	146.3	21.7	2.97	**0.0041**[c]
– # taps alternative	214.6	60.2	200.0	49.8	1.39	0.17

a: Hotelling T^2 test b: Mann- Whitney test c: significantly better score in divers group compared with control group

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Spanish Navy Up to Date Data in DCS

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Summary:

In this paper we present a short update on Spanish Navy Decompression sickness (DCS) treated at the Spanish Navy Diving Centre (CBA) located on La Algameca Naval Base of Cartagena (Southeast, Mediterranean coast) with special emphasis on diagnosis, clinical types, treatment and results, and hyperbaric facilities.

Key words :

Decompression sickness, hyperbaric, diving accidents.

Spanish Navy (SPN) has been diving from the first new world ship wrecks, however modern diving started with CBA (SPN Diving Centre) during 1970, with a 150 m. Draëguer hyperbaric complex.

Today SPN carry out SCUBA air diving until 50 meters, surface supplied diving with air (60 m.) or heliox (90 m.), and close bell diving with heliox until 110 m.

In CBA from 1970 were trained and formed 8177 people, including civilian, military, security forces, firemen, etc., and up to date we have 715 navy active duty divers.

Main diving units are located on navy bases : Ferrol (north), Cádiz (south), Canary Islands, and Cartagena (east).

Hyperbaric treatment facilities are : 5 transportable compression chambers, 8 built into ships, 6 permanently sited ashore (one of this is a 20 multiplace seated patients located in a Naval Hospital). All of them have NATO ring

SPN diving Centre of Cartagena (CBA) is where most DCS patients were treated, and it is also where protocol DCS sheets of other patients treated in another Spanish Navy chambers are databased.

The most frequently cause of DCS it is partial or completed omission of decompression during diving. From 1969 until to 2000 we have treated 234 cases of DCS and 36 cases of lung overpressure. Annual rate of DCS was between 2 and 14 patients per year, civilian and military. Civilian DCS patients usually had serious DCS with a typical high elapsed time to the hyperbaric chamber, and lesser for military ones. On 1990 and 1997 two civilian hyperbaric chambers were opened on our area, and by this reason DCS treated patients rate decreased clearly. So during 1999 we have not any treatment and during 2000 until June only one.

Diagnosis was based on clinical signs and symptoms, following de London Decompression Panel of Medical Research Council of London by Golding et als (1960) whom described DCS in Type 1 DCS (“mild”) Type 2 DCS (“ serious). Only in few cases we use also bubble doppler detection when the ill diver arrived to the chamber to confirm bubbles level, or – along experimental dives- during decompression phase or just when they get surface to prevent DCS.

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DCS develops after the diver has commenced decompression or ascent or in the next hours. Onset of symptoms are very close to other world navies, so 209 patients (89%) develop their clinic within first 6 hrs after diving , and only had 25 cases (11%) later than 6 hrs.

From DCS 234 cases, 119 (50,8%) were minor or DCS Type 1, and the rest 115 (49,2%) serious cases or DCS Type 2

Minor forms or DCS Type 1 were : pain only (69 %), skin bends (13 %) and rest (18%) mixed.

Serious cases or DCS Type 2 distribution were : central nervous system (58%), lungs clinic (with or without "chokes") 4%, inner ear (16%) and mixed cases (22 %).

About treatment tables results it is necessary try to explain some conclusions about it: first until 1985 we use mainly the Air Tables, and after Oxygen tables; second we must realize that tables choice it is a function of gas availability, clinical type and medical choice, evacuation method, elapsed time until recompression, diving profile and other factors. So this tables are applied on different therapeutic protocols, with quite separated gravity index, by those important reasons it is incorrect to make a direct comparison between tables and final results.

Tables 1, 1A and 5 do not have sequelae because if they are unsuccessful we change to another Tables, and we only register the last one

It is clearly important use supportive and drug therapy as an adjunct to recompression therapy.

Total recovery after recompression treatment for all DCS types was 80%. Minor sequelae (chronic pain) was observed after 14% of DCS type I cases. For DCS type II we only had 6% of sequelae (paresia, paralysis). We have noticed that when the elapsed time until patients started recompression therapy was more than 6 hrs. Sequelae rate increase clearly.

Conclusions:

DCS is a low frequency disease find during military diving. In our statistics from 1969 until now we have seen and treated 234 patients. Civilian cases usually are serious cases and military ones minor types. One quickly and clear diagnosis and recompression treatment on hyperbaric facilities it is mandatory, following by drugs and other therapeutic measures. Final results are similar to another world navies diving centres

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Hypobaric Training for Royal Air Force Aircrew – An Update

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INTRODUCTION

Until 1998, the Aviation Medicine Training Centre (AMTC) carried out most aviation medicine training for Royal Air Force aircrew at RAF North Luffenham. With the closure of its parent station, AMTC relocated to RAF Henlow in Bedfordshire. At RAF Henlow, it combined with the School of Aviation Medicine from RAF Farnborough, to form the RAF Centre of Aviation Medicine (RAF CAM). The subsequent relocation and refurbishment of the hypobaric chambers, together with the loss of experienced staff, resulted in many challenges for the restoration of hypobaric training at this new unit. This paper states the training requirement, describes the hypobaric chambers, highlights aspects of safety and outlines the hypobaric training profiles and details the results so far.

TRAINING REQUIREMENT

Hypobaric training is conducted to meet the requirements of STANAG 3114 (1). RAF aircrew undergo hypobaric training before initial flying training, on changing of aircraft type, on returning to flying duties after an absence, and after an interval of 5 years from their last attendance at a formal aeromedical training course. All training is conducted in accordance with the standard operating procedures detailed in the RAF Aviation Medicine Training Memorandum 33 (2)

HYPOBARIC CHAMBER COMPLEX

Four hypobaric chambers were refurbished and installed at RAF CAM by Aeroform Ltd. Each chamber has seating for up to 10 aircrew and one instructor. There is a large compartment with a total of 9 seats and a separable small compartment with 2 seats. Oxygen is supplied to the chambers at a pressure of 1800 lb/in^2. This supply is then reduced in pressure to provide 2 separate oxygen circuits capable of supplying a variety of regulator types at each seat position. However, in the future, it is planned to dedicate each chamber to a particular type of oxygen system. Therefore, 2 chambers will be dedicated to fast jet and 1 chamber to transport aircraft oxygen systems. This will leave one chamber for research and specialised high altitude chamber profiles.

Each hypobaric chamber is under manual control. The main valves are pneumatic with interlocks to limit the rates of ascent and descent. For research or other purposes not involving aircrew training these interlocks can be disengaged to permit much faster rates of pressure change. In addition, two, 2 inch valves which may be under either automatic or manual control, provide height hold and cross venting when the chamber is occupied. There is a digital display of the altitude in feet and mmHg, as well as an analogue display of altitude and its rate of change. To accomplish rapid decompressions, an electrically operated isolation valve (which controls the rate of pressure change) and an electrically controlled, but pneumatically operated, butterfly type, rapid decompression valve are utilised. The chambers main electrical supply is supplemented by a battery back up that will last a minimum of 1 hour in the event of a power failure.

A computer monitoring system provides the pressure chamber operator (PCO) with a variety of display screens. These are as follows: initial details, pre-climb checks, recording screen, pre-rapid decompression

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checks and the duration of individual hypoxia experiences. All procedures are checked by another PCO on the central console of the chamber complex. The hypoxia run is monitored and recorded by video cameras, which provide a continuous 4-channel display. These show the operating PCO, the small chamber and 2 views of the occupants of the large chamber. A digital tape of each hypobaric training profile is also recorded.

Each hypobaric chamber can be connected to a combination of up to 4 vacuum reservoirs and 4 vacuum pumps. To initiate a climb, the ascent valve, which connects the chamber to the vacuum pumps, is opened. To carry out a rapid decompression, the reservoir tanks are evacuated by the vacuum pumps to the required pressure and the isolation valve is set to control the rate of the decompression. The rapid decompression is subsequently initiated by opening the rapid decompression valve, which connects the chamber to the reservoir tanks.

SAFETY

Since many of the staff had departed during the relocation of the unit, it was necessary to arrange a programme to train new PCOs and inexperienced medical officers. Aviation medicine specialists, experienced PCOs, and engineering and Aeroform personnel contributed to the training course. The syllabus included lectures, practical instruction and multiple training runs. All the medical officers had completed the Diploma in Aviation Medicine and updated their advanced life support skills. As PCOs gained experience, they moved on to be accredited for rapid decompressions and higher altitude profiles. Staff performance is regularly assessed and any chamber incidents are subject to review by the whole team. Each hypobaric chamber training profile requires one operating PCO, one console PCO, one medical officer and an engineering technician. Additional personnel comprising 2 medical officers, one PCO, one survival equipment fitter and one engineering technician are also readily available, if required.

Adjacent to the hypobaric chambers is an Admiralty Compression chamber Mk1. This provides an emergency facility for the treatment of decompression sickness and other dysbaric illnesses that might result from exposure to altitude in the hypobaric chambers. The compression chamber is capable of a simulated depth of 80 metres and is tested to 18 metres before each episode of hypobaric training. All the medical officers have completed the Navy Underwater Medicine Course, and the PCOs have also been trained in the use of the compression chamber by the Royal Navy. Full emergency treatment facilities are located beside the compression chamber.

AVIATION MEDICINE INSTRUCTION

As required by STANAG 3114, prior to hypobaric exposure, RAF aircrew receive appropriate instruction in aviation medicine. This includes basic physiological responses to altitude exposure, hypoxia, hyperventilation, hazards of pressure change and decompression sickness. This is followed by a chamber brief on equipment to be used, pre-climb checks, pre-rapid decompression checks, verbal and non-verbal communication, and safety issues. In particular, aircrew are advised of the procedures for the individual hypoxia demonstrations and the need for ear clearing on descent. They then complete a medical questionnaire and have their Eustachian tube function assessed.

HYPOBARIC CHAMBER TRAINING PROFILES

Hypobaric chamber training profiles are designed to match the aircraft flown. They are as follows:

a. Initial flying training. Climb to 25 000 feet at 4000 feet/minute.

b. Fast jet low level. Climb to 8000 feet at 4000 feet/minute, followed by a rapid decompression from 8000 to 25 000 feet in 3 seconds.

c. Fast jet high level. Climb to 18 000 feet at 4000 feet/minute, followed by a rapid decompression from 18 000 to 45 000 feet in 3 seconds. Then descend to 25 000 feet at 10 000 feet/minute. Students are given experience in pressure breathing at least 16 hours prior to this training profile.

d. Transport aircraft. Climb to 8000 feet at 4000 feet/minute, followed by a rapid decompression from 8000 to 25 000 feet in 12 seconds.

e. High altitude training profiles for Canberra and Eurofighter aircrew will be discussed by Wg Cdr Gradwell.

f. High altitude training profiles are also provided for parachutists and other special groups, as required.

All individual hypoxia demonstrations are conducted, in pairs, at 25 000 feet. The medical officer instructs aircrew to remove their masks and presents them with various tasks. During the hypoxia experience they record their symptoms and continue air breathing until they have experienced their particular initial signs of hypoxia and demonstrated deterioration in their abilities. Each trainee is then instructed to replace his mask and the medical officer inside the chamber may give assistance, as needed. The average duration of exposure to hypoxia is between 2.5 and 3 minutes. Following the hypoxia demonstrations, the chamber altitude descends from 25 000 feet to ground level at 4000 feet/minute. After hypobaric chamber training, aircrew are debriefed on their individual hypoxia demonstrations and advised again of the symptoms of decompression sickness. To limit the risk of decompression sickness chamber time above 18 000 feet is kept to a minimum, and for exposures above 45 000 feet all chamber occupants are required to pre-oxygenate (denitrogenate) by breathing 100% oxygen for 30 minutes before the ascent. In addition, to limit the risk for the training staff, medical officers do no more than one chamber training profile per day.

RESULTS

In the 3 month period, between June and August this year, 98 courses were held at RAF CAM. 497 aircrew received hypobaric chamber training with individual hypoxia demonstrations. 17 aircrew were unfit for training. No major problems were recorded during this period and no chamber training profile was aborted. There were 13 minor holds of chamber altitude on descent, due to aircrew suffering ear discomfort. These all resolved with the use of otrivine and further attempts at ear clearing. No significant otitic barotrauma was noted on the ground. However, in the last year there has been 1 case of decompression sickness. This occurred in a 30 year old male who complained of left elbow pain and developed a rash on his chest. Of relevance, he was overweight and had previously fractured his left elbow. His symptoms quickly resolved on compression therapy at 18 metres following the Royal Navy Table 61 (intermittent oxygen regime). This gives a rate of 1 per 1000 exposures. During the 5-year period 1983 to 1987 there were 5 cases of DCS giving a rate of 0.4 per 1000 exposures (3).

CONCLUSION

Hypobaric chambers provide a safe environment in which aircrew may be exposed to hypoxia, pressure changes and rapid decompressions. This provides aircrew with practical experience and engenders confidence in their equipment. Appropriate supporting facilities and fully trained staff are prerequisites. With careful planning and well-motivated staff, new units can be quickly created where staff have the necessary skills to provide hypobaric training for aircrew in as safe an environment as possible.

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Hypobaric Training Issues for High Altitude Agile Aircraft

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Introduction

Over the next few years the inventory of many western air forces will change with the introduction into front line service of new high performance aircraft. Such so-called fourth generation combat jets offer enhanced capabilities in terms of speed, agility and altitude, and in particular the potential for these attributes to be combined on a single platform. In Sweden the JAS Grippen has entered service, the development of the F22 Raptor proceeds rapidly in USA and in at least four European countries the introduction of Eurofighter is awaited eagerly. The introduction of these aircraft must be matched by training of the aircrew destined to fly them. Appropriate aeromedical training will, of necessity, be based on the capabilities of the aircraft and thus it will result in a sudden increase in the requirement for more advanced, and more complex hypobaric training.

Aircraft performance

Whilst elements of the capabilities of specific aircraft may remain classified the fundamental performance of this group of aircraft is well known. Indeed the broad requirements for high altitude flight, high agility and survivability are common to all of the aircraft of the next generation. Thus we can expect that the man or woman flying this aircraft will be achieving altitudes of 60,000 ft, fly at speeds up to mach 2 and be exposed to accelerations of up to $+9G_z$. The onset rate of the G loading will be high, perhaps 15G/s, and having achieved peak G it will be sustainable for relatively prolonged periods.

The further complexities of performances include the potential for the application of G in more than one axis and the interaction of elements of the aircraft performance. For example, the aircraft will be capable of very high rates of ascent, and having achieved high altitude will retain much of its high G capability. This will inevitably have consequences for the operation of life support systems and, in the event of a breaching of the integrity of the cockpit, to a potentially significant additional hazard to the pilot.

Life support systems

Taking Eurofighter as an example of these new aircraft types, the primary source of breathing gas for the pilot will be a molecular sieve oxygen concentrator, controlled in such a manner as to deliver to the pilot's mask a gas containing an adequate fractional concentration of oxygen to prevent hypoxia. To avoid the risk of acceleration atelectasis the sieve will operate well below its maximum concentrating capacity, unless higher oxygen content is necessary to prevent hypoxia. However, with high rates of ascent the response of the MSOC control system must be rapid to ensure that it maintains an appropriate FiO_2 in the face of rapidly falling cabin altitudes.

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The requirements for altitude protection up to at least 55,000-60,000 ft were identified early in the development programme for the Eurofighter. At such aircraft altitudes, with an intact cabin, the pilot would be exposed to an altitude no more than 22,500 ft (300 mm Hg). Loss of cabin pressurisation, however, would result in the aviator being exposed to an ambient pressure of perhaps as little as 54 mm Hg. To afford protection against the worst consequences of hypoxia positive pressure breathing is provided, with mask cavity pressures of approximately 70 mm Hg (9.3 kPa). This short duration protection against hypoxia is not, of course, without its own adverse physiological consequences, making it essential that an efficient counter-pressure assembly is worn. In the case of Eurofighter that counter-pressure assembly consists of a chest counter-pressure waistcoat, incorporated in to the aircrew Flight Jacket, and full coverage anti-G trousers.

With pressure breathing used as an element of the G protection system (PBG) it is desirable that the two components of physiological protection operate in a complementary fashion (1). In the case of Eurofighter the roles of the breathing regulator and the anti-G valve are integrated elements of the aircrew services package (ASP), which also serves as the route for the connections between aircraft services, the ejection seat and the man. The inter-linkage between the breathing regulator and the G valve allows the use of anti-G trouser inflation as a part of the altitude counter-pressure assembly. The inflation of the anti-G trousers is performed in accordance with a ratioed relationship with breathing pressure, to provide enhanced lower body counter-pressure. The ASP has therefore two gas supplies, one bringing MSOC product gas to provide the pilot's breathing gas, and the other delivering compressed air for anti-G trouser inflation.

Current high altitude training

The Royal Air Force has operated aircraft at altitudes in excess of 55,000 feet over many years. These aircraft included the Lightning interceptors and the V-force bombers such as Vulcan and Victor. Although these types are no longer in service there is a continuing need to train crews to operate very high altitude reconnaissance aircraft. It has been the established philosophy of RAF aeromedical training that all aircrew should first experience potential physiological challenges such as high altitude under the controlled conditions of hypobaric training in a suitable chamber.

Although the details of the training given to these crews has been described in detail elsewhere (2) it is worth outlining current practice. Aircrew selected to operate high altitude photo-reconnaissance Canberras have previously received aeromedical training which will have included exposure to positive pressure breathing, up to 30 mm Hg (4 kPa), and a rapid decompression to 45,000 ft. Prior to flying the Canberra they are required to experience decompression in a hypobaric chamber, over 3 seconds, from 25,000 ft to 56,000 ft. To prevent severe hypoxia at this altitude they are provided with 100% oxygen at a breathing pressure of 70 mm Hg (9.3 kPa) above ambient.

To prepare the crew for this type of chamber training they are given an intensive, individual course in the use of their specific counter-pressure assembly. This assembly consists of a partial pressure jerkin, covering the whole of the trunk, including the hernial orifices, and a pair of anti-G trousers. Since the bladders of the garments are supplied with gas from the panel mounted pressure demand breathing regulator in the aircraft the mask cavity pressure will be mirrored equally by the pressure in the garments.

To be able to tolerate breathing pressures of this order, however, it is essential that the aircrew are given training in the breathing technique to be adopted. Theoretical training on pressure breathing and the use of counter-pressure garments, appropriate ground level pressure breathing training and physiological assessments are all conducted on the first day of a two-day course. At the end of that first day the crew must be able to tolerate 70 mm Hg PPB for a period of 30 seconds, followed by a progressive decay in the mask cavity pressure to 0 mm Hg over the next 90 seconds.

The following day, after a medical examination, they dress in their normal Aircrew Equipment Assembly (AEA), including counter-pressure garments, helmet and mask, before carrying out a 30 minute period of preoxygenation to reduce the risk of decompression illness at altitude. They are then decompressed breathing 100% oxygen, at a rate of 4,000 $ft.min^{-1}$ to a base altitude of 25,000 ft. When all necessary safety precautions and monitoring are satisfactory they are rapidly decompressed, in 3 seconds, to an altitude of 56,000 ft.

The chamber is held at that altitude, during which time the aircrew subject maintains pressure breathing at 70 mm Hg (9.3 kPa). Descent of the chamber, at a rate of 10,000 $ft.min^{-1}$ is matched by a progressive reduction in breathing pressure, so that after 90 seconds, when the chamber has descended to an altitude of 40,000 ft, the mask cavity pressure is no more than normal safety pressure. The descent rate is maintained until the chamber has been recompressed to 25,000 ft, at which point descent is slowed to 4,000 $ft.min^{-1}$. On return to ground level the subject leaves the chamber, but subsequently receives a thorough debrief on his performance at altitude. Each subject is decompressed individually and to conduct this training requires the co-ordinated efforts of a team of at least six staff, including specialist medical officers, pressure chamber operators and monitoring technicians.

Subject monitoring

Since high breathing pressures are a physiological challenge in themselves the aircrew undergoing training are medically examined before beginning the ground level training and are monitored both during these positive pressure breathing (PPB) exercises and when undergoing hypobaric exposure to 56,000 ft. For the ground level PPB training the variables observed are: ECG, heart rate, blood pressure, respiratory rate, inspiratory and expiratory flow, and mask tube pressure. A display of inspiratory and expiratory flow is overlaid on a suitable moving sinusoidal trace to assist the subjects to learn to adopt the correct breathing pattern and frequency. This measure is valuable in minimizing the potential for hyperventilation during pressure breathing. Breathing gas pressure is measured from the mask tube, rather than the cavity, to avoid disturbing the subjects own oro-nasal mask.

During the subsequent decompression to high altitude the variables measured are similar, but flow measurements are omitted and haemoglobin saturation added.

Eurofighter hypobaric training

The Director General Medical Services (RAF) established a working party in 1998 to examine the aeromedical aspects of the introduction of Eurofighter into service (3). One of the conclusions of that working group report was that

Eurofighter aircrew should have the benefit of hypobaric training analogous to that given to our existing Canberra aircrew. Therefore it is planned that at least one, and perhaps two hypobaric chambers at RAF CAM will be modified to accept the Eurofighter ASP, mounted on a representative ejection seat.

Cockpit depressurization in agile military aircraft is always possible but the rate at which such an event occurs would depend on the mechanism of its causation. A slow leak of cabin pressure would be detected and can be acted upon by the aircrew in a timely manner but loss of canopy will induce a very rapid decompression. In such an event the rate of decompression can be as fast as 0.1 seconds. Fortunately such events are rare at high altitude, but they do occur. It is not considered necessary, however, to subject aircrew in training to such a fast decompression. Instead they are taught an appropriate, safe breathing pattern to adopt when the countdown to the RD is called. This ensures that their lungs are at end-tidal volume at the time of the decompression. Lung gas expansion will not then result in a significant hazard of pulmonary barotrauma. (4)

To reflect accurately the operation of the normal cabin pressurisation differential, and thus pressure changes in the event of its loss, the base and final altitudes for hypobaric training will be set in accordance with the performance of the environmental control and life support systems. Therefore, as described above, aircrew undergoing training would be decompressed slowly to a base altitude representative of the intact cockpit and then undergo a rapid decompression to a final altitude of, for example 55,000 ft. Although Eurofighter is more manoeuvrable at high altitude than is the Canberra, we anticipate remaining at the final altitude for 30 seconds, before initiating a descent to below the altitude at which pressure breathing is required. Such training would continue to be conducted on an individual basis, with full physiological monitoring. This does, of course, have consequences in terms of the requirement to have available staff trained and experienced in this type of hypobaric exercise.

Further hypobaric considerations

In the training scenario described above the decompression will be conducted as if the aircraft was in straight and level flight. However Eurofighter is an agile aircraft, capable of sustained high G levels at altitude which will be associated with the operation of PBG in the intact cabin. Indeed even if PBG were not used, aircrew would be carrying out anti-G straining manoeuvres which have the effect of raising intra-thoracic pressure. Sudden decompression, in the presence of elevated lung pressure carries a risk of lung barotrauma. Fortunately such events have been rare, to date. However, the more widespread use of high G at higher altitudes must carry an increased risk. Moreover, this risk occurs at any altitude at which cabin pressurisation begins to operate and becomes maximal at the point at which full cabin differential pressures are reached.

Some investigation into this problem has already been conducted (5,6). In two series of experiments subjects were rapidly decompressed whilst already pressure breathing. In the first group decompressions were carried out in 2 seconds between altitudes of 8,000 and 25,000 ft, and in the second group the rapid decompression time was reduced to 1 second. In both groups the subjects tolerated the decompressions well, with no adverse physiological incidents. However, the faster the rate of decompression the greater the risk of an unacceptable increase in intra-thoracic pressure

during the change in ambient pressure. Whilst such decompression profiles are perhaps not a suitable training goal it is an area where further research is needed to determine what degree of risk exists and how it may be mitigated.

Conclusion

When the next generation of high performance aircraft enter service there is a need to ensure that the aircrew destined to fly them have received the best possible training, to allow them to cope with the potential significant physiological hazards that are associated with this type of flying. We believe the RAF is well placed to build on many years experience in high altitude training to apply smoothly the lessons learned to the training of aircrew on Eurofighter. It is important to remember however, that in training some of the hazards of loss of cabin pressurisation are significantly reduced and there are areas that require further physiological study, to ensure that we can continue to give appropriate training and timely advice to our aircrew.

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Designing Efficient and Effective, Operationally Relevant, High Altitude Training Profiles

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Canada experienced a serious case of altitude DCS in Jan 1998 and the author was tasked to review the current high altitude training profiles being conducted by the Canadian Forces (CF) to determine their safety, effectiveness, and to recommend any changes that were deemed necessary. This paper is based on that report (dated 07 July 1999) and focuses on the process that was used to answer these questions.

The initial step was to determine exactly what high altitude training was currently being conducted by Canada and other NATO countries. It became apparent that this training varied widely between countries. An area of concern was the ear and sinus check (a bounce from ground level to 5,000 ft altitude and return to ground level) as some individuals felt the ear and sinus check might be increasing the risk of DCS on the subsequent altitude runs. For the training to be operationally relevant, it had to match the characteristics of the aircraft the students will be flying. Therefore, the characteristics of current aircraft flown in the CF were reviewed.

A few general principles were used to develop the new training profiles and these same principles should be used to refine those profiles as planes and types of flying change. The training must be as realistic as possible. Therefore, the equipment in the altitude chamber should be as similar as possible to the equipment used in the plane the students will be flying (oxygen regulators, face masks, etc.). The rates of ascent and descent in the chamber should match as closely as possible those expected in real situations, while minimizing the risks of DCS/AGE (minimize the time spent above 18,000 ft). The altitudes attained in the chamber should match the altitudes the students will be flying at so that they will have first hand experience with and trust in their life support equipment.

Hypoxia demonstrations must result in signs and symptoms to be effective. If the student does not experience hypoxia, the training has a negative effect (the student thinks they are resistant to hypoxia). Therefore, hypoxia training must be at a high enough altitude for a long enough period of time that virtually all students will experience signs and symptoms. Ground level hypoxia training is not realistic. The students need to relate the experience of hypoxia with altitude. It was also felt that students should experience both the CNS and visual effects of hypoxia. Therefore, hypoxia training was suggested at two altitudes.

Partial pressure breathing is a unique experience for most students. They will experience brief PPB at altitude in the chamber but it was felt that a longer period of time was required for each student to learn how to breath properly against pressure and to communicate while partial pressure breathing. To do this prolonged, individual training at altitude would involve exposures with a very high risk of DCS. Therefore, in addition to the brief altitude PPB experience, ground level PPB training where the student could dial in the PPB according to altitude was felt to be required. The student could be instructed in correct PPB technique and practice communicating on this ground level trainer for as long as was required.

All of these variables were balanced in two new proposed altitude training profiles that could be used for training the crew of all current pressurized aircraft currently used in the Canadian Forces (one profile for aircraft with PPB and one for those without). These profiles could easily be fine tuned for specific aircraft and oxygen regulators. Finally, current altitude training profiles where felt to be irrelevant to the real physiological stresses of aircrew in unpressurized aircraft and helicopters. A profile developed by the Danish Airforce was felt to meet this need and was recommended.

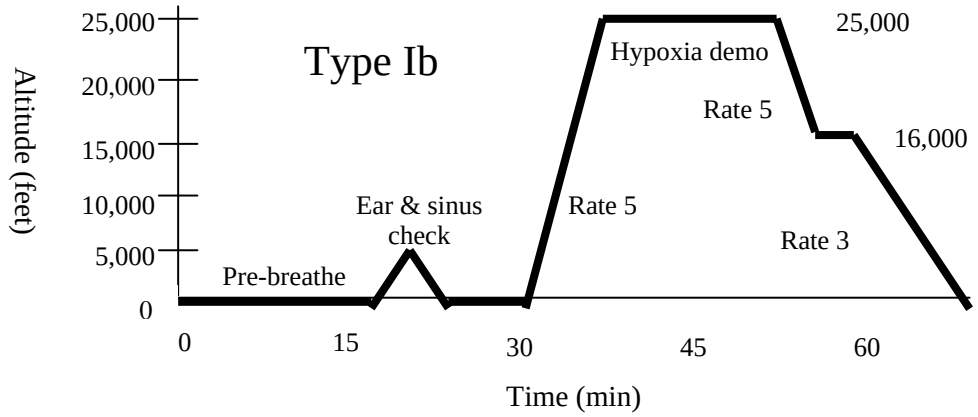
Paper presented at the RTO HFM Symposium on "Operational Medical Issues in Hypo- and Hyperbaric Conditions", held in Toronto, Canada, 16-19 October 2000, and published in RTO MP-062.

CURRENT CANADIAN FORCES HYPOBARIC PROFILES (1999)

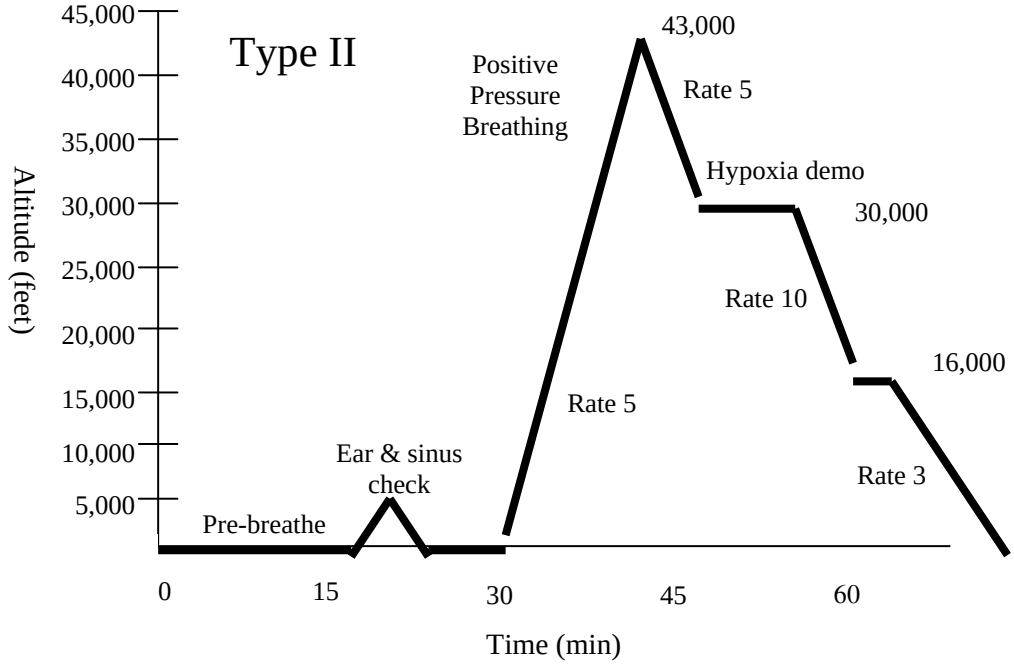
The Canadian Forces aeromedical training currently involves hypobaric chamber exposures as follows:

- Type I Ground to 25,000 ft for hypoxia demonstration and return to ground (three variations)
- Type II Ground to 43,000 ft for positive pressure breathing demonstration, to 30,000 ft for hypoxia demonstration, freefall to 16,000 ft, return to ground
- Type III Rapid decompression from ground to 10,000 ft (one second), return to ground
- Type IV Slow decompression from 4,000 ft to 18,000 ft (10 to 15 seconds), recompression to 9,000 ft and return to ground

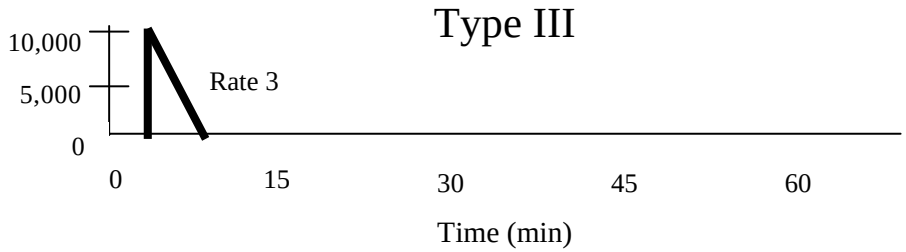
Two additional hypobaric profiles (Types Va and Vb) are conducted as part of HALO (high altitude, low opening parachute jumping) and Sky Hawk (parachute demonstration team) training. These profiles will not be considered in this discussion.



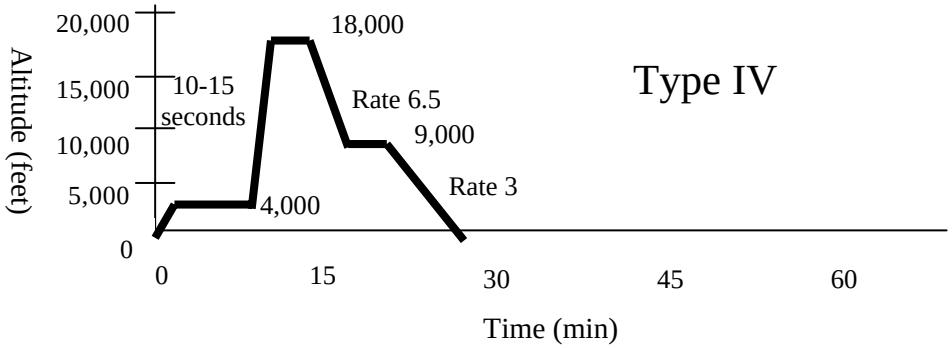
The Type I profile involves hypoxia training at 25,000 ft and has three variations. The most common variation (Type 1b, shown above) is used for all basic aircrew (including pilots and navigators) as well as rotary wing aircrew refresher training. The Type Ia profile differs in that the descent from 25,000 ft to 16,000 ft is at rate 15. It is used for refresher training of ejection seat aircraft crew. Rate refers to the number of feet of altitude change per minute (Rate 15 = 15,000 feet / minute). The Type Ic profile differs in that the descent from 25,000 ft to 9,000 ft is at rate 6.5. It is used for refresher training of non-ejection seat fixed wing aircraft crew. The various descent rates reflect the probable descent rates of the aircrew in an emergency.



The Type II profile involves positive pressure breathing training at 43,000 ft and hypoxia training at 30,000 ft. It is used for all basic pilot training and for pilots flying ejection seat aircraft on refresher training.



The Type III profile involves explosive decompression to 10,000 ft (less than 1 second). The profile is preceded by an ear and sinus check if required. It is used for all basic pilot training and for crew flying ejection seat aircraft on refresher training.



The Type IV profile involves slow decompression (10 to 15 seconds) from 4,000 to 18,000 ft. The profile is preceded by an ear and sinus check if required. It is used for all basic aircrew training, including pilots and navigators.

EAR – SINUS CHECK

Part of the review was to evaluate the requirement for an ear-sinus check (ground to 5,000 ft return to ground) prior to all profiles. It was felt by higher authority that this may be contributing to the development of DCS at higher altitudes and that this was not a common practice in the international aeromedical community. After reviewing the available information, the following observations were made.

The rationale for the ear and sinus check is as follows. Clearing the middle ear on ascent is a passive process as the expanding air in the middle ear forces the eustachian tube open to allow equalization. This process is usually effective even when eustachian tube function is compromised by inflammation due to allergies or infection. Therefore, very few individuals experience difficulty equalizing on ascent.

On descent, the air in the middle ear is compressed, causing a relative vacuum in the middle ear and a further collapse of the normally closed eustachian tube. The person has to actively open the eustachian tube to allow equalization and this process can be extremely difficult or even impossible in the presence of significant inflammation. In addition, if the pressure differential is allowed to become too great, the eustachian tube will “kink” and equalization becomes impossible, even in a normal eustachian tube. Therefore, in a altitude chamber, it is easy to ascend but can be extremely difficult to return to ground level.

The ear and sinus check is to ensure that individuals in the chamber will be able to return to ground level. An altitude of 5,000 ft was chosen so that there would be a great enough volume/pressure change to ensure the person can equalize but not too much to prevent return in case they have difficulty. At 5,000 ft, the atmospheric pressure is approximately 830 mb. Therefore, if the chamber were at sea level, the gas in the

middle ear would expand to 1013/830 = 122% of its original volume. If the person were able to equalize at 5,000 ft but unable to equalize during the return to sea level, the pressure differential that would develop would be at most (1-100/122) * 14.7 = 2.6 psi. In reality, the pressure differential would be less as the tympanic membrane, round and oval windows would move in and take up some of the volume. The relative vacuum would result in fluid being drawn into the middle ear until the pressure was equalized and eventually, the person would be able to clear.

If however, the person was taken straight to 25,000 ft and had the same problem, they could be stuck above 18,000 ft, unable to clear, increasing the risk of developing decompression sickness the longer they stayed at altitude. The chamber operators would have no choice but to return them to ground level, rupturing the ear drum in the process. This is unlikely to result in significant harm, but is extremely painful and easily avoided with a simple 5,000 ft ear and sinus check. In addition, in 1977 Nicholas Davenport (4) reviewed 160 cases of barotrauma which occurred during altitude chamber runs, He found that there were no predictors as to which individuals would have problems. Therefore, the ear and sinus check is critically necessary to identify who is able to equalize and who is having problems.

The statement that the ear and sinus check may be contributing to DCI at higher altitudes is suspect. A reduction of 22% in the ambient pressure is equivalent to ascending from a saturation dive at a depth of 7.26 ft. sea water. There is no evidence in the diving literature that a pressure reduction this small contributes to the development of intravascular bubbles or DCS. In fact, the minimum saturation depth from which any bubbles have been seen is 16 ft sea water and the minimum depth which has resulted in any cases of DCS is 26 ft sea water. Therefore, it is extremely difficult to see how the ear and sinus check could be contributing to the later development of DCS. Most NATO countries use the ear and sinus check prior to exposure to higher altitudes.

Therefore, it was concluded that the ear and sinus check is necessary, that it does not significantly contribute to the risk of DCS, and that it should be retained.

CF AIRCRAFT INVENTORY

The current aircraft flown by the CF were reviewed for their cruise altitude, ceiling altitude, and cockpit altitudes, both at cruise and ceiling altitudes. The aircraft were then grouped according to the kinds of physiological stresses the occupants might be exposed to.

The group with the greatest potential physiological stresses are the pressurized aircraft with cabin altitudes above 10,000 ft where the occupants would be exposed to positive pressure breathing if the cabin lost pressurization at the maximum altitude of the plane. The second group are the pressurized aircraft with maximum cabin altitudes of 10,000 ft or less. The third group comprises the fixed wing unpressurized aircraft. The last group is the unpressurized helicopters.

Pressurized, Cabin above 10,000 ft, PPB

Aircraft	Ceiling Alt.	Cruising Alt.	Cruising – Cabin Altitude
CF-18 Hornet	48K	38-40K	8K – sea level 23K – 8K 35K – 14.5K 50K – 20K
CT-33 Silver Star (2.75 psi differential)	41K		8K – 8K unpressurized 15K – 8K 41K – 25K max (regulations)
CT-114 Tutor (3.00 psi differential)	41K	25-39K	8K – 8K unpressurized 17K – 8K 41K – 25K max (regulations)

Pressurized, Cabin below 10,000 ft

Aircraft	Ceiling Alt.	Cruising Alt.	Cruising – Cabin Altitude
CP-140 Aurora	35K	31K	10K max (regulations)
CP-140a Arcturus	35K	31K	10K max (regulations)
C90A King Air	30K	26K	10K max (regulations)
CC-150 Polaris	41K	33-39K	8K max (regulations)
CC-144A-Challenger	41K	33-37K	8K max (regulations)
CT-142 Dash 8	25K	25K	8K max (regulations)
CC-130 Hercules (15" mercury differential)	35K	22-28K	15K – sea level 20K – 1.5K 25K – 4K 30K – 6K 35K – 8K

Unpressurized, Fixed Wing

Aircraft	Ceiling Alt.	Cruising Alt.	Cruising – Cabin Altitude
CC-15 Buffalo	26K	14-18K	unpressurized
CC-138 Twin Otter	20K	10K or less	unpressurized
T-67C Firefly	10K	10K or less	unpressurized

Unpressurized, Helicopters

Aircraft	Ceiling Alt.	Cruising Alt.	Cruising – Cabin Altitude
CH-113 Labrador	10K	10K or less	unpressurized
CH-124 Sea King	10K	10K or less	unpressurized
CH-146 Griffon	10K	10K or less	unpressurized
CH-139 Jet Ranger	10K	10K or less	unpressurized

PROPOSED NEW HYPOBARIC TRAINING PROFILES

To properly discuss the proposed changes to training hypobaric profiles, it is first necessary to review why altitude exposures are a required part of aeromedical training. The USAF define the purpose of hypobaric chamber flights as, "to demonstrate the hazards associated with changes in barometric pressures and the proper use of protective equipment. These hazards include the symptoms of hypoxia, pressure breathing, mechanical effects of barometric pressure change, and proper use of oxygen equipment". The training should match as closely as possible the real situations the students are being prepared to meet. This includes the rates of ascent and descent as well as the equipment used in the hypobaric chambers. This practical experience will help the students to become familiar with and trust the safety equipment in the aircraft.

The second step in this process is to examine the types of aircraft the CF currently flies to determine the types of AMT required. The first group of aircraft is comprised of those pressurized aircraft that fly with cabin altitudes above 10,000 ft. Aircrew in these aircraft will be exposed to cabin altitudes up to 25,000 ft (limited by CFP-100, Canadian Forces Flying Orders). If they lose cabin pressure or eject, they will be exposed to positive pressure breathing and very rapid decompression (1-3 seconds) up to maximum altitudes of 48,000 ft. Therefore, these aircrew need to be trained in rapid decompression, positive pressure breathing and hypoxia at both low (visual hypoxia) and higher (CNS hypoxia) altitudes.

The second group of aircraft is comprised of those pressurized aircraft that fly with maximum cabin altitudes of 10,000 ft or less. The aircrew in these aircraft will be exposed to maximum altitudes of 41,000 ft

if they lose cabin pressure but they will not experience positive pressure breathing (or at most minimal PPB) and the rate of decompression should be much slower than in the smaller cockpits. Therefore, they need to be trained in a slower rate of decompression (10-15 seconds) and hypoxia at both higher and lower altitudes.

The third group of aircraft is comprised of those that are unpressurized fixed wing. The aircrew in these aircraft will be exposed to maximum altitudes of 26,000 ft but will normally fly much lower. They will never experience decompression or positive pressure breathing but they do require training in hypoxia.

The last group of aircraft is comprised of the unpressurized helicopters. The references state that these aircraft are limited to a maximum altitude of 10,000 ft but several are capable of flying higher. It is suggested that a lower level hypoxia demonstration (e.g. 10,000 – 15,000 ft) would be useful to these aircrew.

Given the above requirements for altitude chamber training, it is necessary to determine the optimal manner in which this training can be performed, remembering that the training should match as closely as possible the actual situations for which the aircrew are training. A second consideration is the risk of the training. Decompression sickness (DCS) is a risk every time a person is exposed to altitudes above 18,000 ft. Cases of DCS have been reported as low as 12,000 ft but this is extremely rare and these few cases have all been extremely mild. At altitudes above 18,000 ft, the risk of DCS is related to the altitude and the time of exposure. Even then, the cases of DCS are usually very easily treated and do not usually result in any permanent problems, especially when hyperbaric treatment is readily available. One additional caution is to ensure that the students have not been exposed to increased pressure (scuba diving) for at least 48 hours before being exposed to altitude. Diving before ascending to altitude dramatically increases the risk of DCS.

The risk of DCS during AMT can be reduced by having the students pre-breathe for 30 minutes on 100% oxygen (most NATO countries do this) before they ascend to altitude. This procedure removes some of the dissolved nitrogen from the tissues of the body. It does not remove all of the nitrogen and therefore the time spent above 18,000 ft is still a consideration and should be kept to a minimum. Therefore, DCS is a definite risk of altitude training but if hyperbaric treatment is immediately available, permanent problems should be exceedingly rare.

Positive Pressure Breathing. The current training in PPB is fairly realistic in that the PPB is proportional to the altitude but there are several shortfalls. First, the F-18 pilots are not being trained on the regulator that they will be using in the aircraft. Second, the maximum altitude of exposure (43,000 ft) and the maximum PPB are less than could be experienced in a real situation (48,000 ft). Third, the time of exposure to maximum PPB is very short and the students have limited opportunity to learn how to breathe effectively under PPB. Finally, the aircrew will have to communicate while breathing under PPB in the real situation and that is not being effectively trained with the present profiles. Therefore, the following changes are proposed for PPB training.

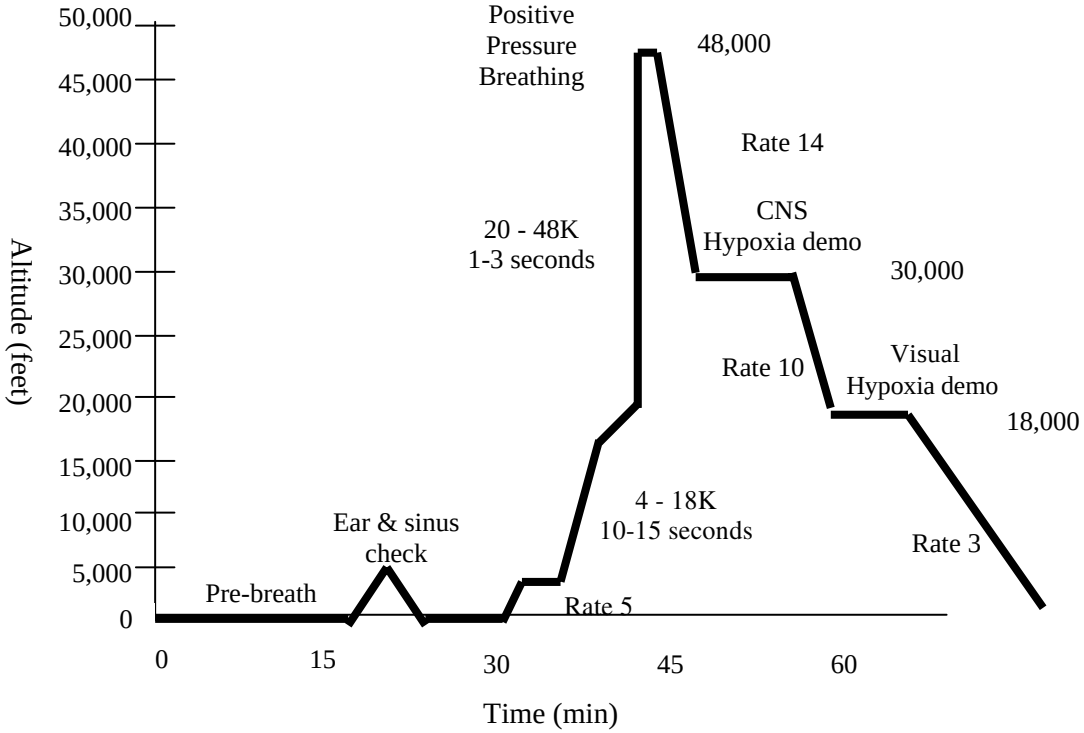
a. A ground-level PPB trainer needs to be built. The Royal Airforce has designed and built such a trainer (low cost). It has the following features and advantages. The students breathe positive pressure for several minutes and during this training they can match their breathing cycle with the ideal (5 seconds in, 5 seconds out), training themselves to breathe properly under PPB. They also can dial up the altitude to experience the same PPB as they will be exposed to in the aircraft, to a maximum altitude of 48,000 ft. Finally, once the students have learned to breathe properly under maximum PPB, they can practice talking and communicating while under PPB.
b. The CF altitude chambers at CFSAT and DCIEM need to be equipped with the oxygen regulator used in the F-18. This is considered an operational necessity.
c. The PPB altitude profile needs to go to 48,000 ft (the operational ceiling of the F-18), and the students need to remain at that altitude for 30 seconds to demonstrate to them that their safety equipment will support them at this altitude. The students will have had extensive ground level PPB training prior to this profile. The increased risk of DCS from going to 48,000 ft instead of the current 43,000 ft is considered small and more than justified by the increased training realism. In addition, other changes to the training profiles should reduce the risk of DCS.

Hypoxia Demonstration. The current training primarily involves hypoxia demonstration at 25,000 ft for a maximum of five minutes off oxygen. Some students also experience a hypoxia demonstration at 30,000 ft for a maximum of 2.5 minutes. The Polish Air Force has demonstrated that many people can go for more

than 10 minutes at a hypoxia level equivalent to 25,000 ft. In addition, it has been the CF experience that many students go the full five minutes at 25,000 ft without experiencing any symptoms of hypoxia, thereby negating the purpose of the training. In addition, current training does not demonstrate the subtle but very real effects of hypoxia at lower altitudes (10,000-20,000 ft, primarily visual). This training would have relevance for many CF aircrew. Therefore, the effectiveness of current CF hypoxia training could be substantially improved. The following changes are proposed for hypoxia training.

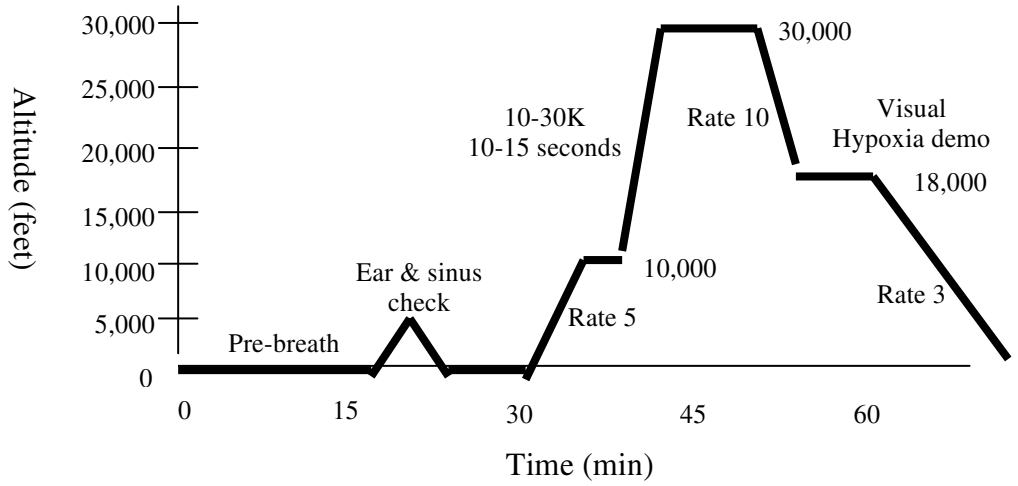
a. CNS hypoxia training should occur at 30,000 ft with no fixed time limit (currently 25,000 ft for a maximum of 5 minutes for most students). It is anticipated that most students should have definite symptoms of hypoxia in two to three minutes and only rarely will more time be required. In addition, it might be of use to fit each student with an oximeter to demonstrate objectively their level of hypoxia. This change should result in all students experiencing definite symptoms of hypoxia and also reduce the risk of DCS by reducing the time spent above 18,000 ft.
b. A new hypoxia demonstration should be included in the training at 18,000 ft. This training should be patterned after the USAF training and would primarily demonstrate the effects of this level of hypoxia on vision.
c. A new low level hypoxia (10,000-13,000 ft) training profile should be created to demonstrate to helicopter and other non-pressurized aircrew the significant visual and psychomotor degradation they can experience at these altitudes. This profile could be patterned after the new Danish profile (their helicopter crews have been extremely pleased with the training).

Rapid and slow decompression training. The current training requires a separate chamber run for each profile. This training could be made much more efficient if it was incorporated into the other profiles. In addition, the current training is unrealistic as the decompressions do not occur at realistic altitudes. Finally, by incorporating the training into the other profiles, the time the students spend above 18,000 ft would be reduced, thereby reducing the risk of DCS.



The above profile is suggested for all aircrew who will be flying in pressurized aircraft that fly with cabin altitudes above 10,000 ft. It should be preceded by ground-level PPB training. The profile starts with a 30 minute pre-breathe on 100% oxygen, during which a 5,000 ft ear and sinus check is done. The chamber can either be decompressed to 20,000 ft (rate 5) or, if the students require it, a decompression from 4,000 ft to 18,000 ft in 10-15 seconds (current Type IV profile) can be conducted during the ascent. They are then

rapidly decompressed (1-3 seconds) from 20,000 ft (maximum cabin altitude in the Hornet) to 48,000 ft (the same pressure change as the current Type III profile and the real altitude change the Hornet pilots would experience). The chamber is then held at 48,000 ft for 30 seconds so that the students can experience maximum PPB and practice communicating. The chamber is then brought to 30,000 ft at the maximum rate of descent of the aircraft/chamber (approximately rate 14) and the CNS hypoxia demonstration is conducted. The chamber is then brought to 18,000 ft at rate 10 and the visual hypoxia demonstration carried out. The time above 18,000 ft should be less than 15 minutes and therefore the risk of DCS should be minimal (current training standards allow 20 minutes and it is often difficult to complete the training in this time).



The above profile is suggested for all other aircrew. It starts with a 30 minute pre-breathe on 100% oxygen, during which a 5,000 ft ear and sinus check is done. The chamber is brought to 10,000 ft and the students remove their masks (they would not be wearing them in the plane). Breathing air at 10,000 ft does not interfere with the oxygen pre-breathe as the students will still be off-gassing nitrogen breathing air at this altitude. The students are exposed to slow decompression from 10,000 ft to 30,000 ft in 10-15 seconds (replaces current Type IV profile and simulates the real decompression likely to be experienced in a large pressurized aircraft). The students can either go straight into the CNS hypoxia demonstration at 30,000 ft or they can all don their oxygen masks and do their safety drills before starting the hypoxia demonstration. Alternatively, ½ the students could don their oxygen masks while the remainder go straight in to the hypoxia demonstration. The rest of the profile is identical to the previous profile and the time above 18,000 ft should be less than 10 minutes.

It is also suggested that the helicopter, and possibly non-pressurized transport (plus CC130) crews be given the 13,000 ft training profile developed by the Danish Air Force (see ref 1).

Finally, as new aircraft are brought into service in the CF, the above training parameters need to be adjusted to reflect the flight characteristics of the new aircraft. In addition, if the new aircraft use a different oxygen regulator, it needs to be installed in the altitude chambers at CFSAT and DCIEM to ensure the continued usefulness of the training.

Subsequent to this report, a review committee determined that the maximum PPB with the oxygen regulator used in the F-18 is attained by 43,000 ft. Therefore, it was decided to limit the first training profile to a maximum altitude of 43,000 ft and to not go to 48,000 ft.

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Military Personnel Selection and Diagnostic Control of Human Functional State in High Altitude Conditions

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Abstract. In the paper the initial attempts and modern approach to the evaluation of individual resistance to high altitude hypoxia in the human organism are reviewed. It is presented a big informative material about using Valsalva maneuver and its modified versions (Burger probe, Flack test, etc.) for a diagnostic estimation of cardiovascular function in the different areas of public medicine and applied human physiology. Specific role is attached use of dosed version of Flack test with 50 sec. duration of strain (DFT) for prognostic evaluation of functional opportunities of the human cardiovascular system, its adaptive potential and regulative functions in high altitude conditions. Clinical observations performed during acute period of adaptation of selected individuals to altitude of 3600 meters demonstrated an 80%-level of verification of the results of this prognosis. Method of military contingent selection and control procedures for healthy service at frontier posts in high mountains of Tien Shan and Pamir are described. It was shown that exemption of people with low resistance to hypoxia (by the results of preliminary selection with the DFT) from military service in mountain regions of Tien-Shan and Pamirs has allowed researches to bring down the morbidity among frontier-guards at high altitude frontier posts by more than 18%; to reduce the number of severe high altitude disadaptations from 70-75 to 35 cases per year; and practically to avoid lethal consequences of severe mountain disease.

Key words: Dosed Flack Test, Straining, Hypoxic Resistance, Adaptation, High Altitude, Cardiovascular System.

I. Background: initial attempts and modern approach to the evaluation of individual resistance to high altitude hypoxia in the human organism.

Development of disadaptive forms of high altitude pathology with military personnel sent to mountains, behavioral and psychological incompatibility among the personnel do great harm to the human health, to his ability to work and cause large social and economic losses. This means that when forming military units including border guards to serve at high altitude, it is extremely important to reveal individuals who have high possibility to get "adaptation" sicknesses.

To diagnose correctly, to predict and, finally to prevent situations which are dangerous to human health is an important problem requiring an immediate solution.

An important component for ensuring the successful resolution of this problem is to select military service personnel by means of a scientific process, in which adaptability to high altitude environments is considered. The qualitative and purposeful selection of the recruits for a service in high mountainous regions largely prevents the development of the disadaptive phenomena, reduces the probability of high mountainous forms of pathology originating. It is necessary to mention that the first attempts to select soldiers resistant to high mountainous hypoxia were undertaken by the Russian doctors at the end of the last century.

When considering the early research on two subjects, the works of Tretyakov, N.N. [1897] should be emphasized. Tretyakov's research noted, that the development of symptoms of mountain illness is exhibited by military service men in different degrees, and that at an altitude of 3000-4000 m, they lose ability to execute any activity. Tretyakov, based on his observations, has raised a question about the necessity of

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individual selection of military service men for service in high altitude regions. He offered method of selection, which envisaged that before dislocation of a military unit in mountains, the special functional test should be conducted as though, permitting to reveal weak and low resistant soldiers unable to serve in high altitude conditions. Tretyakov offered to conduct the tests with considerable physical exercises in conditions of normal barometric pressure, i.e. on the plain. He wrote that a selection conducted by forcing soldiers to run two Russian versts (3500 English feet), chasing each other, and determining who lagged behind, was subject to faint in vomiting etc., or had a pulse so weak, that it could not be counted, were recognized as not being fit. Tretyakov, observing the condition of soldiers after they had been transferred to the mountains, noticed that the soldiers who more likely to be subjected to "attacks of mountain sickness" were those who already were physically weak or elderly. However, such a method of selection still could not prevent the progress of many of the symptoms of mountain sickness and could not ensure the keeping of a rather high level of fighting efficiency of the soldiers, in case of climbing to an altitude of 4000-5000 m.

In military medicine in the Soviet period, great attention was given to ensuring the fighting efficiency of soldiers in high altitude conditions. Complex expeditions to study the progress of mountain sickness were carried out, and measures for preventive maintenance of acute mountain sickness were developed. In particular, research of Solovjev, V.K. [1934] indicated that physically strong soldiers with good cordial activity should be allowed to work and serve. The author highlights, that with all other conditions being equal, humans with small, but so-called, "steel muscle" will have an advantage over humans with large, massive muscles requiring plenty of oxygen. At the same time, research on interrelation between deterioration of oxygen transport in conditions of high altitude hypoxia and physical state of an organism has shown, that even for well trained athletes to endure high altitude can be much greater obstacle than for people who do not go in for sports [J. Dempsey, 1986; R.J. Shephard et al. 1988].

Real scientific development of tests permitting evaluation of human endurance of oxygen deficiency begins in 30s - 40s years of our century in the period of rapid development of aviation and high altitude flights. During these years scientists recognized that a pressure chamber could be used to evaluate individual reactions to hypoxic hypoxia and to increase pilots' resistance to it, especially for those who reacted most poorly to a lack of oxygen [P.I. Egorov, 1937; V.V. Strelcov, 1938, 1945; A.M. Apollonov and V.G. Mirolubov, 1988].

Unlike Soviet researchers who showed the principal possibility to increase quickly the pilots' resistance to high altitude hypoxia during ascent in the low-pressure chamber, Western scientists used pressure chamber tests for the purposes of medical examination to select candidates for flight personnel.

Due to empirical observations and accumulated scientific data, it has become possible to proceed from a simple ascertaining of one or another human functional state to scientifically grounded evaluations of a person's possible state in the future under the influence of unfavorable environmental factors. And, on this prognostic basis, to develop principal concepts and methods of selecting people, who would have a high probability of keeping their working capacity in certain professional or ecological conditions.

Research in the field of personnel selection and forecasting of working capacity are practically impossible without a preliminary evaluation of the functional systems of an organism and its potential ability to adapt to extreme conditions of an environment. In many respects, this research depends on the elaboration of adequate methods of prognosis, permitting, in usual conditions, to determine degree of stability and a probable level of working capacity of the individual when transferred to unusual conditions, for example, under the adaptation in mountains.

The literature on the functioning of the human organism in extreme conditions, and, in particular, the literature on hypobaric hypoxia, shows that the majority of the researchers are inclined to study the physiologic deflections of an organism in dynamics to the influence of the hypoxic loading tests. The specialist's efforts are aimed at clarifying the range of physiologic standards on separate parameters of the organism, defining reactions to different systems, searching for additional signs describing probe endurance. Such an approach allows researchers to judge with a certain degree of reliability, the level of functioning of this or that physiologic system of an organism, to determine the volume of reserve capabilities and, finally, to have a picture about the adaptive capability of the individual to extreme factors. Adaptive capability is the final link leading to prognosis, and its correct and concrete definition will determine whether the prognosis will be long-term or short-term. That is why modern prognostic diagnosis is based on an evaluation of the degree of human adaptive capability which first of all is understood as an adequate level of functioning of physiologic systems in the changed conditions [V.P. Kaznacheev et al., 1980]. Individual human qualities, on the whole, reflected in concepts, such as working capacity, endurance and adaptive capability. According to the opinion of Imangulov, R.G. [1982], these concepts and the human conditions,

expressed by them, are closely interconnected and are a reference point for the fighting capacity of military service men. Through determining the state of the physiologic, psychophysiologic and mental functions of a person, it is possible to estimate the informative and motivate maintenance of learn-fighting activity of the experts, the range of adaptive-compensatory opportunities of the person and to predict fighting capacity of the military men during the learn-fighting preparations.

From the physiologic point of view, the success of adaptation, its completeness and resistance are determined by a range of adaptive and compensatory mechanisms, by the level of physiologic reserves of the person [A.S. Solodkov, 1982; A.A. Aidaraliev et al., 1988]. Use of the reserving opportunities is based on the coordinated reactions of separate bodies and systems, which change in unequal ways, but as a whole, provide optimum functioning for the organism as a single unit. The physiologic reserves, as Brestkin, M. P. [1958] remarked, are provided with certain anatomical, physiologic and functional features of structure and activity of the organism, significant intensification of heart activity, increase of the general intensity of blood flow, pulmonary ventilation, high resistance of cells and tissues to various external influences and internal changes in the conditions of their functioning.

Though the physiologic reserves of an organism are individual and are largely determined by hereditary features, they can, in a sufficient degree, be changed under the influence of external environmental conditions. So, during the development of condition of acquired adaptation reserve abilities of an organism can rise both at the expense of increasing contours of the maximal intensification of functional activity of physiologic systems, and at the expense of contours reducing the basal level of activity [G. M. Yakovlev et al., 1990]. The authors note that in the first case the adaptive ability of an organism to achieve a marginal level is caused by both its inborn and gained features.

A specific method of revealing of human individual resistance to hypoxic hypoxia is a pressure chamber test. Along with that, the faster and more expressive mechanisms of protection from hypoxia are in a human, the higher is his ability to adapt [V.I. Medvedev, 1982]. The prognosis is usually based on distinctions in the condition of a number of systems, mainly vegetative, immediately after climbing and after one-hour stay at the higher altitude. According to the opinion of Asyamolova, N. and Malkin, V.B. [1968], a test in a pressure chamber at an altitude of 5000 m. reveals the individual features of adaptive reactions of blood circulation. The USA and Germany, on the other hand, use ascent in a pressure chamber to 7500 m to test individual reactions to hypoxia.

It is necessary to emphasize that there is no direct correlation between resistance to acute hypoxic hypoxia (ascent in the pressure chamber) and chronic high mountainous hypoxia. So, the research of Malkin, V. B. [1968] shows that people who have extremely low sensitivity to acute hypoxia and who have experienced conditions of collapse, sharp bradycardia during the ascent in a barometric camera, and who preserved for a long time (up to 30 days) high mountainous resistance to the chronic influence of alpine environmental factors during transfer to mountains and climbing.

In sport activities dosed standard exercises are used for evaluation of physiologic reserve (Letunov tests, step tests modifications, velo-ergometria, treadmill and treadbane), [V.P. Zagryadski and Z.K. Sulimo-Samuillo, 1976; A.S. Mozjuhin, 1982; V.L. Karpman et al., 1988], moreover the level of reserve capabilities may be judged first of all by parameters of the function of cardiovascular and respiratory systems, and the volume of gas exchange [A.S. Solodkov, 1982].

The research of Mirrahimov, M.M. et al. [1983] showed that during the study of organism's response reactions to various exercises (Harvard's step-test, standard veloergometric exercise with the power of 900 kgm/min during 6 minutes, running to various distances) for a large group of the examinees the best kind of exercises for evaluation of a person's functional state is a method of standard veloergometria.

The choice of an optimum exercises was conducted at sea level where the examinees were asked to do exercises listed above: the volunteers were subdivided into groups of "strong" or "weak", depending on their performance on these tests. Then the volunteers were moved to high mountains at 2900 m., from this height they climbed to the altitude of 3870 m. where they made various kinds of activities. During the research it turned out that part of the examinees were not able to complete physical activities. Based on the results of endurance of climbing to an altitude of 3870 m, on endurance of veloergometric exercises, on research of the objective status (along with attention to clinical symptoms and to complaints of the examinees), a group of persons who endured very badly the transfer to mountains was chosen. It is interesting that the considered group, in conditions of foothills, had shown the worst results of the loads endurance. Only three persons referred by the author in foothills to the "weak" group satisfactorily endured exercises at altitude. From 17 persons who were chosen in this group, on the third day of adaptation to high altitude conditions there remained 13, as the four were sent to foothills. From the rest, the three persons were dismissed from

exercises right up to the 45th day of stay in mountains, as on an electrocardiogram they revealed symptoms of hypoxia of the myocardium, overload of right ventricle and sinus tachycardia. As the authors determined, under such a submaximum veloergometric load, the most expressed mobilization of physiologic functions happens: it is rather great to mobilize reserve, and, at the same time, not so hard to take out an adaptive mechanisms of organism within physiologic limits.

On the basis of clinical parameters and the change of parameters of the cardiovascular and respiratory systems during the execution of a standard veloergometric load, the authors developed a prognostic method of selecting the examinees in groups with a different level of resistance to hypoxia, conventionally called "strong", "average" and "weak".

The most informative parameters were the heart and breathing rate at exercise climax, the index of trends, the sum of pulse activity and its recovery. The index of trends in the strong group was higher than in the weak group by 0.5 points. The sum of pulse activity in the "strong" group in average made 747 + 27.4 strokes per a minute, where in the "weak" group it was 1001 + 6.9 strokes per a minute, the pulse sum of recovery in the same groups - 679+ 22.9 and 831+ 27.9 strokes per a minute accordingly. For persons attributed to the "weak" group a large surplus of heart and breathing rate was marked in execution time of exercises. To the important indications permitting the subdivision of the examinees into groups, apart from physiologic parameters, the authors also attribute clinical manifestations arising during standard exercises (the 2nd tone accent, it's splitting at the pulmonary arteries etc. The criteria for placing someone in a "weak" group include: a low vital capacity of lungs (less than 3000 ml), the volume of forced inhalation – attributed VFI (less than 1000 ml), tests of Tiffno (less than 70%), heart rate (more than 75 strokes per a minute), breathing rate (more than 28 strokes per a minute), the test of Shtanger (less than 45 sec.), the test of Genchi (less than 25 sec.).

The analysis of electro cardiograms made at sea level and in the mountains, shows that the changes in electrocardiograms were registered the most frequently in the weak group.

Emergence of disadaptive phenomena during the performance of physical exercises in the mountains in individuals with minor changes of electrocardiograms at sea level points out to the necessity of more careful selection of people to work in high altitude conditions. Registration of electrocardiograms is mandatory for all those being inspected and for this, implementation of various probes (hypoxic ones, tests with physical load, etc.) during electrocardiogram is deemed quite useful.

The range of organism's capabilities or its physiologic reserves is revealed also through various functional probes (probes of Shtanger, Genchi, Valsalva, etc.; probe with breathing of hypoxic gas mixture and re-respiration probe), [A.G. Dembo et al., 1975; V.P. Zagryadski and Z.K. Sulimo-Samuillo, 1976; P.V. Buyanov and P.V. Pisarenko, 1977; A.B. Gandelsman et al., 1984; V.V. Goranchuk et. al., 1997, K.S. Drugova, 1997]. Implementation of these probes is much simpler in comparison with testing in pressure chambers, and it does not require expensive and unique equipment, and can provide their application in field trips. Probes of straining under impaled breathing and re-respiration characterize the compensatory processes on the part of the respiratory system and blood circulation, the ability of an organism to maintain the acid-alkali balance and the reserve capabilities of an organism [G.M. Pokalev, 1976].

One of such test which has been widely used in aviation and space medicine, is the so called "Flack's test" and some other modifications of Valsalva's probe [P.I. Egorov, 1925; V.E. Danilov, 1948; G. Armstrong, 1954; M.M. Link et al., 1975; L.G. Maksimov et al., 1975]. They are widely used for diagnosing of cardiovascular diseases in various fields of medicine and human applied physiology.

A breathing test with straining was offered by the Italian scientist Antonio Maria Valsalva (1666-1723) in 1704 for use in diagnosing ear diseases [A.M. Valsalva, 1717]. In the first half of the 20th century Flack, and then also Burger, modified Valsalva's test and developed a new technique for estimating the functional state of the cardiovascular system on the basis of that test.

In 1917 Martin Flack, a lieutenant colonel of British Air Force, while studying the influence of straining using Valsalva's experiment on the human organism, measured the heart rate right before the probe and every five seconds during the straining. Applying this method for selection of candidates to military aviation, the author used the manometric systems for dosed straining force, connected to a mouthpiece, in which the examinee executed an exhalation. The test consists of the examinee making a deep inhalation and then an exhalation in the mouthpiece for pressure maintenance in the pressure gauge equal to 40 mm of the mercury pole. The examinee should continue the dosed straining «till refusal».

The author considered it as a good indication, when at this time a cordial rhythm would speed up just moderately or remain unchanged, and straining would proceed, at least for 50 seconds. He considered slowed down or noticeably speeded up cordial activity and also, increase of blood pressure, as indications

of shortage of blood circulation functions [M. Flack and B.S. Oxon, 1921; M. Flack and B.S. Burton, 1922].

More than a half-century ago, Anderson, G. [citation by P.I. Egorov, 1925] wrote that the Flack's test with straining was a valuable method to use to find out the condition of the lungs, heart, and brains of good and poor pilots; thus, "eligibility models" for air flights could be established. Anderson's research showed that, those pilots, who suffered at high altitudes, couldn't hold back breathing unlike those, who were not influenced by altitude.

Afterwards, a program of tests for medical examination of the pilots was confirmed at the Ministry of Aviation of Britain. One of the tests has been used up until present time and is the one with a 4 millimeter U-tube with mercury (Flack's test). According to Dawson, P.M. [1943] the original modification of the test with straining had been very successfully used to determine functional conditions of British Air Force pilots, and proved itself as the most reliable test. However, some authors in their researches have obtained the results which denied the significance of Flack's test as one determining physical eligibility in aviation [A.W. Lapin, 1943; T.J. Powell and F.A. Sunahara, 1958; M. Vlasak, 1963]. Obviously, differences in methodology related to the dosage and the time of straining may have made the above-mentioned researchers have a negative opinion about the use of Flack's test in a pilot examination.

Confirmation of the suitability of Flack's test, as an indicator of the emotional and physical characteristics of candidates for flight, was given in 1944 by Anon [quotation on T.J. Powell and F.A. Sunahara, 1958] after examination of 9573 pilots of Canadian Air Force, when the author obtained a large percent (57,6%) of the coincidence by test's results. Then the efficiency of the respiratory test with straining was proved for selection of the astronauts and aviators in the USA [N.M. Link et al., 1975]. In the opinion of the authors, except for an evaluation of the reflex regulation of vascular systems, the test is of interest for revealing the violations of a cordial rhythm by the data of an electrocardiogram and arterial pressure.

In particular, Asiamolov, B.F. et al. [1979], studying the resistance of the human to strain on "head-pelvis", have determined the exact correlation between the expressed violation of a cordial rhythm during the execution by the examinees of Valsalva's test and the endurance of strains. In their work, the prognostic value of the performed test is accentuated, as the expressed violations of a cordial rhythm revealed by the Valsalva's probe, were observed in individuals with reduced resistance to strains. The dosed probe with straining became highly useful under the evaluation of compensatory reactions of the human cardiovascular system [L.G. Maksimov et al., 1975]. The original prognostic criteria, as the authors consider, may be the biggest deflections of the investigated indicators during the execution of the test (Amax), after test (Amax"), and also sum of these deflections (Amax + Amax"). Thus, for example, under the violations of heart activity regulation the systolic pressure is increasing considerably immediately after the execution of test and in a period of recovery. Under the normal state of heart activity the changes of arterial pressure (AP) are insignificant [V.P. Zagryadski and Z.K. Sulimo-Samuillo, 1976].

From the changes of systolic and diastolic pressures before and after the execution of the test Zagryadski, B.D. and Sulimo-Samuillo, Z.K. [1976] have offered an informative parameter (PQR – parameter of quality of a reaction), permitting us to evaluate the response of the cardiovascular system to an additional stimulating effect.

The authors consider that if the meaning of PQR exceeds 0.10-0.25, then the cardiovascular system of the examinee is in a condition of stress. At the degree of increase of the pulse for 5 sec., in relation to an initial level during the execution of the Flack's test the following three types of reactions are distinguished:

- No more than 7 strokes – good
- No more than 9 strokes - satisfactory
- 10 strokes and more - unsatisfactory

It is also an estimated criteria of the state of cardiovascular system.

Through the research of Sergeev, V.N. [1959] it is established that a limit of allowable displacement («norm») under the Valsalva's test (15-20 sec.) using the data of oscillometry are:

a) an increase of diastolic and mean arterial pressure AP no more than 10-15 mm of mercury pole (Hg);
b) changing of systolic pressure AP (increase or decrease) for 10-20 mm of Hg;
c) decreasing of pulse pressure no more than 15-20 mm of Hg;
d) decrease of oscillometric index no more than 5-8 mm of Hg.

According to the author's data, patients with "pulmonary heart", even in the latent period of violation of compensation, the increase of diastolic more than 20 mm of Hg is a distinctive sign. During the decrease

of contractile function of the myocardium, an expressed decrease of pulse pressure (more than 30 mm of Hg) and oscillometric index is observed.

The functional test of heart by Valsalva/Burger [M. Burger, 1921, 1925] gave the beginning to the diagnostics of many cardiovascular diseases, and it is recommended to apply the test under latent violations of hemadynamics and the clarification of character of the functional violations with "pulmonary heart", myocardiodystrophy, compensated valvular disease of heart, and hypertonic illness of heart of the 1st degree [W.C. Little et al., 1985; R.A. Nishimura and A. Jamil Tajik, 1986].

This method was successfully applied under the aortography and coronarography [H. Ludin, 1962], during a study of the large vein and the "right heart" [P. Amundsen, 1953; A. Celis et al., 1956], and the kidney's arteries [J.M. Riby, 1965; A.W. Templeton, 1965]. It had been shown that the application of the test with a simultaneous record of the vector-, ballisto- and electrocardiograms, to a greater degree reflects the changes in the functional state of heart [I.N. Vasiliev, 1978; A.F. Zarine and E.Y. Gaile, 1982]. Valsalva's test is often used for study of peripheral hemacirculation and arterial pressure [R.H. Johnson et al., 1969; B.D. Zabudski and S.V. Gadiatov, 1970; J.L. Reid et al., 1971], vein pressure and tonus [E. Wick and R. Knebel, 1961], changes in hemadynamics of visceral organs [B. Gforer, 1951], the state of vascular baroreceptors [J. Szachowski et al., 1968; L. Stejskal, 1969; H.A. Palmero et al., 1981; D.S. Goldstein et al., 1982; B.Trimarco et al., 1983; K. Shimada et al., 1986; S.A. Smith et al., 1986], the state of electromyographic activity [P. Tornow and C., Durst 1969] and the dynamics of blood circulation through the brain [H. Lechner et al., 1968; A.I. Martynov et al., 1968; V.G. Spirin and E.I. Savchenko, 1974].

It is recommended to apply the test or determining the degree of blood circulation deficiency in liver with rheography [T. Posteli and G.C. Garbini, 1968], as well as for evaluating the functional state of heart of patients with chronic pulmonary diseases [F.V. Arsentiev et al., 1975; A.A. Penkovich,1966]. The specific characteristics of heart's response to the Valsalva's test provide an opportunity to get a picture of the functional state of the vegetative nervous system [R.U. Looga, 1970], the response is one of the indicators of the effectiveness of sanatorium and climate treatment, especially of the functional therapy results.

Valsalva's test in Burger and Flack's modifications is of significant interest in sports and medical researches [M. Burger et al., 1929; H. Reindell et al., 1954; G.K. Birzin, 1958; A.G. Dembo et al., 1975; V.A. Zinochkin, 1985; V.L. Karpman et al., 1988].

It serves as a tool of medical control in physical culture education practice, in solving the problem of the acceptability of dosing, of static efforts connected with straining, in particular; and has large significance for the whole range of sports, in which straining is the integral part of sport activity. This includes, for instance, heavy athletics, shot-put and hammer-throw. Along with these sports, in which the role of exertion is particularly large, the increase of internal pulmonary and internal abdominal pressure is observed during wrestling contests, gymnastic exercises and a whole range of other kinds of sports, in which breathing can also be detained [M. Burger and D. Michel, 1957; A.B. Kozlov et al., 1985]. As studies conducted by Reidell H. et al., [1954] was shown, Burger's pressure test is especially valuable when combined with X-ray kymography of the heart for selecting individuals inclined to collapse, during examination of persons practicing in diving, rock-climbing and weight-lifting.

According to the opinion of Chaillet-Bert P. [1956], it is better to use Flack's "endurance" test in a combination with Pashone-Martine's test (i.e. an orthostatic test before and after knees-bends performed during 40 seconds). He supposes that if these tests are sequentially applied one after another, they mutually supplement each other, characterizing the functional state of the "right heart" in the first case, and the "left heart" in the second case.

From the studies of functional states of highly qualified sportsmen performing underwater diving, who performed Valsalva's test before and after the standard veloergometric exercise, it was found that along with frequency of heart rate, it is worthwhile to use indicators of a cardiac output: systolic volume and blood volume per minute, for evaluating an endurance test [V.A. Zinochkin, 1985].

Dembo, A.G. and co-authors [1975] recommend conducting such respiratory tests strictly in a combination with oxyhematometry to control changes in oxygenation of the arterial blood, because the maximum detention of breathing sometimes results in a significant fall of HbOO in blood. These data confirm studies of other authors which revealed that oxyhematometric indicators can be an adequate reflection of compensatory capabilities of the respiratory and heart vascular systems [E.M. Kreps, 1959; N.V. Belyaeva, 1967], and the oxyhematometric method itself can be useful for understanding of hypoxic effects [N.A. Saunders et al., 1976; R.J. Smyth et al., 1986].

The results of the conducted research give us a basis to consider that it is worthwhile to conduct Flack's test with simultaneous registration of the oxyhematometric indicators that allow us to more fully determine the functional state of the human both in rest, and after the physical efforts.

At the same time, special attention should be paid to the separate prognostic approaches to the analysis of testing results with the purpose of selecting the persons suitable for the pilots' profession, for determination of training level of sportsmen, etc. This also could be used for an evaluation of the functional state of people in conditions of mountain hypoxia. As Armstrong, G. [1954] has noted, in an analysis of the test's results for selecting people suitable for the pilots' profession, it is necessary to take into account that in a healthy person the heart rate remains practically constant, or increases within the limits of 72-96 strokes per minute, depending on duration of straining (usually 50-60 sec.). If the pulse becomes much more frequent, for example, within the limits of 72-132 or 144 strokes per minute, then the results of the test are considered unsatisfactory. By results of such test it is possible to judge both about steadiness of nervous centers managing the breathing and blood circulation, and about the potential degree of endurance of this person. Applying so-called dosed tests when, for diagnostic purposes, the time of straining is limited from 20 up to 50 sec., some authors have detected that in normal conditions the increasing of pulse frequency, in comparison with the basic data, proceeds for approximately 15-20 sec., and then the frequency of heart rates is stabilized [V.L. Karpman et al., 1988]. With an insufficient quality of regulation of the heart's activity in individuals with an increased reactivity, the frequency of heart palpitations can be increased during the test. If the initial increase of pulse is replaced by its consequent decrease, that is an indication of a negative response to the test. On the other hand, for well-trained sportsmen the response to the increase of internal pulmonary pressure is expressed only insignificantly. So, the increase of pulse frequency for each 5 sec. at 1-2 strokes, in relation to basic data, is evaluated as an excellent response to the straining. Along with that, the duration of straining is 45-55 sec. If the acceleration of pulse achieves 3-4 strokes for each 5 sec. of straining, then the response is evaluated as "good". The higher speed of pulse (5-7 strokes) is satisfactory for sportsmen, and for untrained people is indicative of a good physical state of the organism.

According to the data of Zinochkin, V.A. [1985], for individuals with reduced physical efficiency, the apparent tachycardia is marked during a Valsalva's test, even prior to the initiation of exertion.

When evaluating the state of the heart muscle by the reaction of maximum arterial pressure to a pressure sample, Burger [M. Burger, 1956] has considered three types of reactions. The normal type of reaction is that the systolic pressure almost never changes during the straining. The increase of arterial blood pressure during straining and the restoration to an initial value in 20-30 seconds after the experiment is stopped (the second type) is typical for trained sportsmen. A negative reaction to the sample (the third type of reaction) is expressed by a significant decrease of AP during straining.

According to the opinion of Burger, M., the increase of the arterial pressure during the test is connected with the fact that the trained heart is capable of pushing large volumes of blood through narrowed lung capillaries. For an untrained heart, this ability is less, owing to how the blood pressure falls in comparison with the initial test [M. Burger, 1925, 1926]. With an "astenic" heart a severe fall in the blood pressure takes place, which can result in collapse, as the regulation of the tone of the vessels is broken. As the research of Reindell, H. et al. [1954] have shown that this test is especially valuable for revealing sportsmen most inclined to collapses.

Trimarco, B. et al. [1983] recommend the use of an analysis of changes in cardiorhythm and systolic pressure in the end of straining during Valsalva's test for estimating the individual state of the examinees. In their opinion, the greatest deviation of heart rate and the least increase of systolic pressure in this period, by comparison with norm, are an attribute of hypertension in the surveyed persons.

The functional meaning of the test is explained by the fact that strong contraction of the exhalating respiratory muscles with closed upper respiratory ducts (i.e. a glottis or a mouth and a nose) results in increase of pressure inside the lungs, to the stagnation of the veins, and to an increasing resistance to the blood flow in the vessels in the small circle of blood circulation. Due to this, there is a decrease of the systolic volume of blood circulation [R.U. Looga, 1970; V.G. Spirin and E.I. Savchenko, 1974; I.N. Vasiliev, 1978; V.L. Karpman et al., 1988]. The decrease of blood circulation volume per minute is accompanied by a change in the tone of the vessels, infringement of blood circulation to the brain, and a change in the quality of the regulation of heart activity.

Straining with a closed mouth and nose leads not only to an increase of internal pulmonary pressure and reorganizations connected with it in the system of cardiopulmonary blood circulation, but also to alveolar hypoxia [A.A. Penkovich, 1966] and to cerebral hypoxia [R.W. Alman and J.F. Fazekas, 1962; J.S. Meyer et al., 1966] as a result of the infringement of blood flow. The last effect, according to the data of the authors, in its turn, caused, on one hand, by the fall of volume of blood per minute, and on the other hand -

by the constriction of blood vessels in the brain, and lung capillaries. As with Valsalva's test, the pressure of COO in the arterial bloods falls. The data of Duke, H.N. [1954], Bergofsky, E.H. et al. [1968], Viles, P.H. and Shepherd, J.T. [1968], Hauge, A. [1969], and Bergofsky, E.H. [1969] specify that fact, the development of alveolar hypoxia is exactly one of necessary components of a pressure reaction of an organism.

From the above stated evidence it follows that respiratory tests with straining, such as Valsalva's test and its modifications, along with the above-described effects to the cardiopulmonary blood circulation, have expressed hypoxic influence on the human organism. The development of alveolar hypoxia and cerebral hypoxia, as the consequence of infringements of blood supply, causes an immediate compensatory-pressure reaction of the cardiovascular system which is displayed in increased frequency of heart reductions and arterial pressure [R.U. Looga, 1970, 1973]. According to the data of Strohl, K.P. et al. [1984], from the degree of compensation of hypoxic stress by the cardiovascular system, when a person is undergoing a respiratory test, one can get an idea about the resistance level of any individual to oxygen deficiency.

The effectiveness of Valsalva's test, used as a hypoxic functional test, is explained by the following: the straining, when parts of the upper respiratory ducts of a human are closed during testing, results in static tension of the lung vessels, vein stagnation and changes in heart regulation [P.E. Paulev et al., 1988). This is well known as "the reflectory preservation of oxygen" phenomenon, which greatly depends upon the continuous supply of oxygenated blood in the organism [R. Elsner and P.F. Scholander, 1965]. Consequently, the extended utilization of oxygen reserves by organs specifically initiates such extreme situations as cerebral and alveolar hypoxia.

II. The Dosed Flack test as a method of diagnostic control of the human functional state in the extreme environmental conditions of high altitudes.

The Valsalva maneuver, and its modified versions (Burger probe, Flack test, etc.) as was mentioned above have widely been used for a diagnostic estimation of cardiovascular function in different areas of public medicine and applied human physiology. In mountain conditions we used a dosed version of Flack test with 50 sec.' duration of strain. According to the results of our studies [V.P. Mahnovsky et al., 1984, 1985, 1986, 1988, 1989], applied to 820 young and healthy military servicemen during adaptation to different altitudes of Tien-Shan and Pamir (800, 1800, 2800, 3600 and 3800 meters), there are some solid preconditions for applying this modification of Flack test to high altitude medico-biological studies in order to estimate the functional state of a human during adaptation to hypoxia. We have found that application of a dosed Flack test is an effective method of estimating the functional state of the human cardiovascular system, particularly of its adaptive potential and regulative functions in conditions of short-term as well as long-term effects of high altitude hypoxia. Table# 1 includes short descriptions of the main areas and directions of using the versions of the Valsalva maneuver.

Basing on the dosed Flack test, we have developed and implemented an express-method of prognostic estimation of the human organism's resistance capacity to the effect of the hypoxic factor into military medicine practice (implementation actions: register No171944 dated 12.01.86 and register No. 85 dated 16.01.98). This method has demonstrated a high effectiveness both for operative medical control of functional state of vital human systems under the influence of stress factors of environment and activities, and for evaluation of general adaptability of organism and the prognosis of acquired adaptability. The great significance of using the dosed Flack test as a prognosis probe was determined by mass selection of military servicemen for high altitude service. Clinical observations performed during acute period of adaptation of selected individuals to altitude of 3600 meters demonstrated an 80%-level of verification of the results of this prognosis [V.P. Makhnovski and R.V. Bolshedvorov, 1986]. Exemption of people with low resistance to hypoxia (by the results of preliminary selection) from military service in mountain regions of Tien-Shan and Pamirs has allowed researches to bring down the morbidity among frontier-guards at high altitude frontier posts by more than 18%; to reduce the number of severe high altitude disadaptations from 70-75 to 35 cases per year; and practically to avoid lethal consequences of severe mountain disease (document No181350 dated 20.01.87).

Therefore, the studied and approved procedures of prognostic estimation and selection mentioned above can be assumed as a basis of a suggested method to control or correct the human functional state in high altitude conditions.

Below we describe our method with necessary procedures on control of the human functional state in the extreme environmental conditions of high altitudes**.**

Table #1

Main Areas and Directions of Using the Versions of the Valsalva Manoeuver

Area	Version	Directions	References
Aviation and Space Medicine	Flack test, 20-30 sec.- dosed Valsalva maneuver	selection of pilots and cosmonauts	Danilov, 1948; Armstrong,1954; Link et al.,1975
Naval Medicine	50 sec.-dosed Flack test	estimation and control of cardiovascular function of navy contingent during long-term autonomous navigation	Aidaraliev et al., 1988; Makhnovski,'1991
Sports Medicine	Burger Pressdruckprobe	estimation of physiologic possibilities and control of coaching levels	Birzin, 1958; Karpman et al., 1988
Mountain and Military Medicine	50 sec.-dosed Flack test with registration of electrocardiogram, arterial blood pressure, and arterial blood oxygenations	estimation and prediction of human functional states during short- and long-term adaptation at high altitude; estimation of level of human hypoxic resistence; selection of military contingents for serving in high altitude conditions	Makhnovski et al., 1985, 1985a; Makhnovski and Bolshedvorov, 1986; Makhnovski et al., 1988; Makhnovski, 1991; Makhnovski et al., 1998
Public Health	Valsalva manoeuver	medical diagnostics and control of cardiovascular diseases	Posteli and Garbini, 1968; Little et al., 1985; Nishimura and Jamil Tajik, 1986
Human Physiology	Valsalva manoeuver, Burger Pressdruckprobe	estimation of the functional state of different organs of the blood circulation system and its vegetative nervous regulation	Gforer, 1951;Celis et al., 1956; Wick and Knebel, 1961; Ludin, 1962; Takagi and Magasaka, 1964; Sharpey-Shafer, 1965; Riby, 1965; Lechner et al., 1968; Tornow and Durst, 1969; Reid at al., 1971; Looga, 1973; Zarine and Gaile, 1982; Trimarco et al., 1983; Smith et al., 1986

Description of the Method

The method includes pre- and high-mountain phases of measures using the dosed Flack test (DFT) described below:

Pre-mountain phase

Selection: using the DFT with the criteria of Table #2 to identify an individual level of hypoxic resistance, i.e. high hypoxic resistance (HHR), average hypoxic resistance (AHR) and low hypoxic resistance (LHR).

High-mountain phase

Control: using the DFT with the criteria of Table #2 to identify, in proper time, the cases of illnesses due to disadaptive disorders in the AHR and HHR persons.

The Dosed Flack Test:

For the test, a person is asked to take a deep breath and then slowly breath out the air into a tube connected with a manometer, in order to lift up and maintain a level of airway pressure of 40 mm of Hg for 50 seconds against a closed mouth and a nose. The electrocardiogram and arterial oxygen saturation are monitored before, during, and after (for 3 min.) the straining. Arterial pressure is measured before, at the end (i.e. at 45-50 sec.), and after (i.e. at 1, 2 and 3 min.) the straining. The integral rheocardiogram is monitored before and after the straining.

The Selection Procedure:

To determine a level of individual hypoxic resistance of a person, it is necessary to conduct a comparative analysis of the DFT results with the use of the value's range of critical physiologic indicators and coefficients and with due regard to the "weight" (significance) of the integral coefficients devised on the basis of our investigations [V.P. Makhnovski, 1991] as mentioned in Table #2. The highest number of coincidences for the measured values of the person's physiologic indicators with the table's data (in the 1st step of the analysis) and the final confirmation of it by the integral coefficients (in the 2nd step of the analysis) allow the division of the subjects into 3 groups, according to their hypoxic resistance type (HHR, AHR and LHR) and so to select the necessary contingent for work at high altitude conditions.

Data Treatment:

Heart rate (HR): HR is calculated on the basis of the electrocardiogram.

Systolic and diastolic pressures is measured by sphygmomanometry.

Mean arterial blood pressure: from the systolic and diastolic arterial pressures, the MAP is calculated as the sum of 1/3 of the pulse pressure and the diastolic pressure.

Types of cardiovascular self-regulation are determined by the express-method of integral evaluation of blood circulation [Arinchin N.I., 1978] on the basis of calculation and percent comparison of the following cardiovascular indexes: (1) fact and proper means of cardiac index (CI = cardiac output/body weight) and (2) fact and proper means of index of total peripheral resistance (TPR = (1333 x 60 x MAP)/CI):

$$C = 100\% \times \text{fact CI / proper CI;}$$

$$P = 100\% \times \text{fact TPR / proper TPR}$$

If in the post-test period there is C > P - a prevalence of cardiac type reactivity of self-regulation; and if there is C < P - a prevalence of vascular type reactivity of self-regulation.

Type of vegetal reactivity: determination of type of vegetal reactivity during the DFT is made on the basis of comparison of indicators of heart rate (HRc - control, HRt - in the end of testing) and arterial pressure (*Am*AP0 - control amplitude, *Am*APt- amplitude in the end of testing) by Grotte's formula [A.V.Vein et al., 1981].

$$A = 100\% \times (A_mAP_t - A_mAP_0) / A_mAP_0;$$

$$B = 100\% \times (HR_t - HR_0) / HR_0$$

Table #2

The Criteria of Human Selection for Work at High Altitude

Indicator	Method	Type of Human Hypoxic Resistance		
		HHR	**AHR**	**LHR**
Heart rate (HR)	Electrocardiography	increase of HR frequency by 1-4 beats per minute for every 5 sec. during 15 sec. at onset of the straining, then relatively stable heart rate	increase or decrease of HR during the straining by no more than 20 beats per minute	initial increase of HR, then its sharp decrease during the straining (i.e. more than by 20 beats per minute)
Systolic arterial pressure (SAP)	Sphygmomanometry	insignificant increase of SAP (i.e. no more than 20 mm of Hg), then its fast restitution (i.e. in 30-50 sec.) after the end of the straining	increase or decrease of SAP, but level of decrease of SAP during the straining must be no more than 20 mm of Hg with its fast restitution after the end of the straining	significant increase or decrease of SAP (i.e. more than by 20 beats per minute) with its relative long-term restitution after the end of the straining
Mean arterial pressure (MAP)	Calculation according Zagryadski and Sulimo-Samuillo [1976]	insignificant change of MAP during the straining (i.e. no more than 4-5 mm of Hg)	change of MAP during the straining is 5-6 mm of Hg	change of MAP during the straining is more than 6 mm of Hg
Index of type of vegetative nervous reactivity	Calculation with use of cardiovascular indicators according Vein et al. [1981]	a parasymphatetic against increasing or relatively stable value of systolic pressure during the straining	a normotonic during the straining	an expressed symphatetic against increasing systolic pressure during the straining

Table #2 (continue)

The Criteria of Human Selection for Work at High Altitude

Indicator	Method	Type of Human Hypoxic Resistance		
		HHR	AHR	LHR
Index of type of cardiovascular self-regulation reactivity	Calculation with use of cardiovascular indicators according Arinchin [1978]	cardiovascular regulation during the straining	cardiovascular regulation during the straining	expressed cardiac or vascular regulation during the straining
Rate of reducing oxygen saturation	Oxyhemametry	insignificant rate of HbO_2% reduction during the straining	insignificant rate of HbO_2% reduction during the straining	high rate of HbO_2% reduction during the straining
Index of compensatory reactivity rate (CRR)	Calculation with use of oxyhemametric indicators according Makhnovski et al. [1989]	CRR = more than 1,20	CRR = 1,00 - 1,20	CRR = less than 1,00
Index of economizing efficiency of oxygen utilization (E)	Calculation with use of oxyhemametric indicators according Makhnovski et al. [1989]	E = 0,32 and more	E = 0,25 - 0,31	E = less than 0,25
Test's tolerance coefficient (TTC)	Calculation with use of cardiovascular indicators according Makhnovski [1984]	TTC = 0,20 - 0,99	TTC = 0,99 - 3,12	TTC = more than 3,12
Functional reserve coefficient (FRC)	Calculation with use of cardiovascular indicators according Makhnovski [1984]	FRC = positive value: 2,00 and more	FRC = positive value: 0,20 - 2,00	FRC = negative value: less than - 0,50

In norm there is A > B, and the regulation is basically conducted by means of arterial pressure, but not by heart rate's changes. If means of A and B increase significantly during DFT there is a prevalence of symphatetic type of vegetal reactivity.

Oxyhemametric indexes: On the basis of a degree of oxygen saturation (HbO2%) changes in arterial blood accordingly the phases of oxyhemagraphic curve [Tichvinsky S.B., 1960] which characterizes the separate time periods of HbO2% during the DTF a rate of reducing oxygen saturation (VHbO2%), an economizing efficiency of oxygen utilization (E) and a compensatory reactivity rate (CRR) are calculated according the following formulas [V.P.Mahnovsky, E.I.Kuzuta, 1989]:

$$V_{HbO_2\%} = \Delta HbO_2\% / \Delta t \ ;$$

$$E = 0{,}02 \times t_{AB}$$

$$CRR = \int_{D}^{E} V_{HbO_2\%} \, \Delta t \ / \int_{E}^{F} V_{HbO_2\%} \, \Delta t$$

These indexes characterize indirectly rate of oxidative processes in blood and its compensatory functions.

Integral evaluation of physiological reserve and quality of the DFT individual tolerance are made on the basis of our designed and verified [V.P.Mahnovsky, 1991] the following coefficients: test's tolerance coefficient (TTC) and functional reserve coefficient (FRC). These coefficients are our modification of an indicator of biosystem adaptability of prof. Melnikov N.P. [1977]. Calculation of the coefficients is based on integrative comparison of fact means of heart rate, systolic and mean arterial pressures (for TTC) or diapasons of its variability (for FRC) which are monitored (1) in rest conditions, (2) in the end of the DFT and (3) in post-testing period. The coefficients are calculated by the following formulas:

$$TTC = \sum_{i=1}^{n} Ki \left(\frac{| P_{p_i} - P_{c_i} |}{| P_{p_i} - P_{t_i} |} - \frac{| P_{t_i} - P_{c_i} |}{P_{c_i}} \right),$$

P – absolute mean of monitoring or calculated parameter, P_c – control mean of the parameter, P_t – a mean of the parameter in the end of strain, P_p – mean of the parameter at 3rd min. of post-testing period, K – coefficient of Djukov V.G. [1970] which characterizes informative and vital importance of every parameter in evaluation of organism's adaptable level.

$$K_i = 1 - (\sigma_i / M_i)$$

σ – standard deviation and M – average mathematical mean of variation of mentioned parameters for most majority of healthy people in normal conditions.

If a subject has good level of the DFT tolerance a value of TTC must have a tendency to minimum mean.

$$FRC = \sum_{i=1}^{n} Ki \left(\frac{| D_{\delta_i} - D_{c_i} |}{| D_{p_i} - D_{t_i} |} - \frac{| D_{t_i} - D_{c_i} |}{D_{c_i}} \right)$$

D – a dispersion of monitoring or calculated parameter, D_c – a control mean of dispersion of the parameter, P_t – a dispersion of the parameter in the end of strain, P_p – a dispersion of the parameter at 3rd min. of post-testing period, K – a coefficient of Djukov V.G. [1970] which characterizes informative and vital importance of every parameter in evaluation of organism's adaptable level.

A value of FRC is in direct dependence from diapason of the monitoring indicators variability, especially during the DFT and post-testing period. When a human organism is reaching an adaptable state the value of FRC must have a tendency to maximum mean, so as the physiological indicators in period of functional exercise get new diapason of its variability which increases mainly and also continues as "a marking reaction" to save in post-testing period on the same level (i.e. Dp ≈ Dt).

Note: a difference of indicators means in these formulas is absolute.

The Control Procedure:

The DFT should be conducted periodically, especially on the third, seventh, fifteenth and twenty fifth days of high altitude adaptation, to find out the disadaptive disorders in the AHR and HHR persons.

Thus, by using the method mentioned above, two important goals could be achieved: the control of human cardiovascular functional activity in high altitude conditions and reducing the cases of mountain illness.

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Some Psycho-Physiological and Cognitive Implications of Hypobaric Exposure during Selection of Slovak Astronaut Candidates

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Abstract

During September and October of 1997, the Military Aviation Hospital in Kosice was entrusted by the Head of the Slovak Air force to select appropriate astronaut candidates for space flight and stay at the Russian Space Station "MIR" from 26 applicants (experienced elite fighter pilots of the Slovak Air Force) to be placed in a mixed international crew (Slovak, Russian and French). A resulting seven-day mission of the first Slovak astronaut in February 1999 was successfully completed. Part of the medical-psycho-physiological selection of applicants was exposure to hypobaric chamber conditions. During a 20-minute exposure to 7,600m (25,000 ft.) of altitude their cognitive capacity was tested (by simplified mathematical tasks) and correlated with other tests of mental capability. The behavioural and mood changes were continuously observed and recorded. Achieved findings were used for the assessment of hypobaric mental work ability of the astronaut candidates. Before and after the hypobaric exposure we took applicants blood samples in order to estimate blood oxygen saturation.

Fig. 1

Keywords: *hypoxia, personality and cognitive processes.*

Introduction

Several studies on hypobaric exposure and extreme hypoxia describe the changes in cognitive performance and psychic states (2, 6, 9, 10).

The most typical changes in psychological states during hypoxia are elation, euphoria, overconfidence and lack of discipline, risky behaviour, higher level of aggression through loss of control, irresponsibility and senselessness. Concerning the effects of hypoxia on cognitive functions, there is a typical performance decrement, difficulty in concentrating and faulty judgement (5, 6, 7, 10). It is well recognised that performance in an hypoxic state does not suddenly change from normal functioning to uselessness, but rather that there exists a progressive performance deterioration, reflecting the arterial blood oxygen saturation. Various aspects of human perception including vision and hearing are sensitive to hypoxia. Another well-known characteristic of hypoxia is that it slows the responding and prolongs the reaction time (4, 5).

Temporary impairments in cognitive functioning found at high altitude include deterioration of the ability to learn, remember and express information verbally, impaired concentration and cognitive flexibility, decline in feeling of knowing, and mild impairment in either short-term memory or conceptual tasks. Other studies reported impairments in grammatical reasoning and in pattern comparison during a slow, multi-day, simulated ascent in the hypobaric chamber. Some cognitive deficits found after high altitude expeditions include decreased memory performance, mild impairment in concentration, verbal learning and memory, and cognitive flexibility. In general many authors agree that high altitude hypoxia is stressful. During acute hypoxia, psychological processes (affective and cognitive) and in particular intellectual abilities appear to be altered. During the second period the subject begins to adapt and should improve. To

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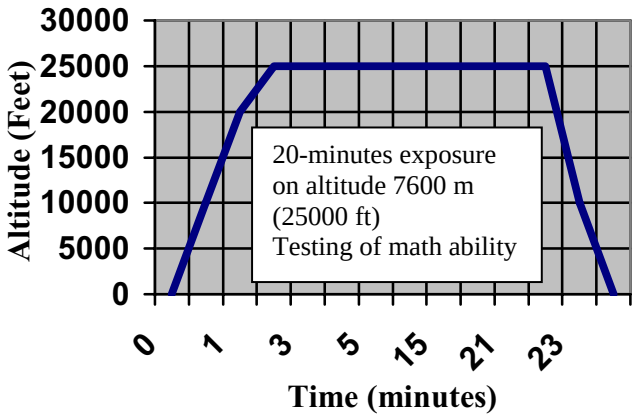
compensate for this decline, the subject may implement conscious and unconscious strategies that allow them to cope and adapt (2).
In our study we suppose that there exists psycho-physiological and cognitive qualities that may be specific predictors of psychological changes during hypoxia.

Fig. 2 HYPOBARIC CHAMBER EXPOSURE PROFILE



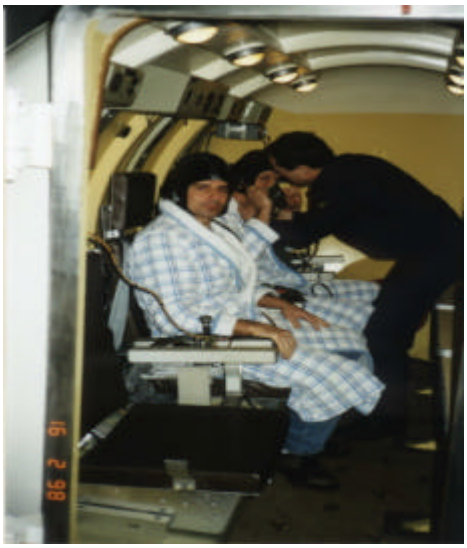


Fig. 3 Hypobaric chamber exposure

Methods

Subjects: 26 male volunteers, experienced jet fighter pilots, age range of 23-42 years and a military aviation academy education.
Procedure: All subjects were tested during medical-psychological pre-selection of candidates in the Military Aviation Hospital in Košice. An examination under hypobaric conditions was performed in the hypobaric chamber instaled at the Military Aviation Academy in Košice.
Cognitive tests: With the view of this study, achieved results selected from sub-tests of Intelligence Structure Test by Amthauer (1) - (ME) memory, (AR) arithmetic and (NU) numerical reasoning and Co-ordination Precision Analyser (AKP) - complex reaction time and error rate, spatial orientation test (OR1, OR 3) were used. The test of simple math ability (summation, subtraction, multiplication and division - MATH) during hypobaric exposure was applied. We scored a number of correct results and errors.
Motivation: Supplementary performance motivation was measured by the performance motivation questionnaire (11).
Personality: Personality traits were tested by the SPIDO questionnaire (8). Four basic factors KO (cognitive variability), EM (emotional variability), RG (self-regulative variability) and AD (adaptative variability) were correlated with the math performance results in hypobaric conditions (Tab. 1.).

Tab. 1 Meanings of the SPIDO basic factors

Factors	**(+) high score**	**(-) low score**
KO - cognitive variability concerning the ability to perceive and process the situational environment variables	+ tendency to search for a change, quality and variability of intensive external stimulation in their perception and complex processing	- tendency to search for more stable interactions with more stable environment
EM - emotional variability concerning emotional response in interaction to environment and situational variables	+ high emotional excitability, tendency to feel situational tension	- emotional stability, very low emotionality
RG - regulative variability concerned with regulation of behavioural function and self-control	+ low self-control, self-regulation, low anticipation of possible consequences in behaviour	- very high anticipation and regulation of own decision making and behaviour
AD - adaptive variability concerning the tendency to adaptive behaviour into new environment and life events	+ high tendency to adaptive behaviour in dynamic environment	- very low adaptability,

Testing in hypobaric chamber conditions: 26 applicants were tested in the hypobaric conditions of chamber PBK-53 during a two week period. The number of examined persons in the hypobaric chamber at the same time was 3 or 4, as well as an aviation physician who monitored health and psycho-physiological conditions and administered the form of the math tests. The Ascent speed from normobaric to hypobaric condition (7,600m) was 3m/sec ad the descent from hypobaria to normobaria was 5m/sec. The total examination time in hypobaric conditions was about 25 minutes and exposure to 7,600m of altitude took 20 minutes. Within 20 minutes of hypoxia a simple math test was administered (see Fig.2). Before and immediately after hypobaric exposure blood samples were taken in order to estimate blood oxygen saturation (Tab. 3).

Direct observation and checking: all subjects were observed and checked by the aviation physician and the aviation psychologist, who carried out all examinations during hypobaric exposure. An aviation physician was inside the chamber with oxygen supply and the aviation psychologist monitored behavioural changes from outside through sights and intercom. Possible significant behavioural changes have been recorded (Tab. 5).

Results

Statistical comparison of mean SaO_2 in normobaric and post-hypobaric conditions (Tab 2.) Based on laboratory analyse of capillar blood flow shows high significance ($p>0.0001$) between normobaria and hypobaria.

Tab. 2

Blood oxygen saturation SaO_2 n=26	**Normobaric aO_2**	**Post-hypobaric SaO_2**
Mean	92,1 %	88,0 %
Minimum - Maximum	86,4 % - 95,8 %	66,8 % - 93,7 %
T-test (level of significance)	p > 0.0001	

Significant effect of hypobaria ($F=4.45$, $p=0.037$) on math performance have indicated statistical comparison between those subjects with different SaO_2 (Table 3.)

Tab. 3

Variable MATH in hypobaria	**Number of cases**	**Mean**	**SD**	**Statistic significance level**
Group 1 SaO_2 66.8 % - 89.4 %	14	55.5714	25.542	F = 4.868 P = 0. 037*
Group 2 SaO_2 90 % - 93.7 %	12	67.5833	17.474	

As aforesaid we supposed a statistically significant effect of general cognitive abilities in normobaria on math performance during hypoxia. Statistically significant relations were found between parameters AKP 1 E - errors in normobaria and MATH 1 - errors in hypobaria ($p=0.009$), AKP 1 R- reaction time and MATH 1 - errors ($p=0.04$), AKP 2 - errors in complex reactions and MATH 1 - errors ($p=0.05$) and AKP 2 R- complex reaction time and MATH 2 - math performance accuracy.

Considerable findings were found by statistically significant relations between MV - performance motivation and MATH 2 - hypobaric math performance accuracy ($p=0.05$), between AB - performance braking activities and MATH 1 - hypobaric math error rate ($p=0.046$) and between KO - cognitive variability and MATH 2 - hypobaric math performance accuracy ($p=0.038$). Correlation coefficients of cognitive and personality tests and the math performance test carried out in hypobaric conditions (see Tab. 4).

Tab. 4

Tests of cognitive ability and personality traits (normobaric conditions)	**MATH 1 Math performance Errors (hypobaric conditions)**	**MATH 2 Math performance Accuracy (hypobaric conditions)**
AKP 1 E (error rate)	0.4594 **p=0.009*** **	0.1631 p=0.213
AKP 1R (reaction time)	0.3503 **p=0.04** **	0.1631 p=0.213
AKP 2 E (error rate)	0.3155 **p=0.05***	-0.1405 p=0.247
AKP 2R (complex reaction time)	0.1855 p=0.182	0.3775 **p=0.029** **
IST ME (memory)	0.1532 p=0.227	0.2320 p=0.127
IST AR (arithmetic ability)	0.1020 p=0.31	0.0626 p=0.381
IST NU (numeric ability)	0.1229 p=0.275	-0.1642 p=0.211
OR 1 (spatial orientation ability)	0.1641 p=0.212	0.2198 p=0.140
OR 3 (spatial orientation ability)	0.1429 p=0.243	0.1645 p=0.211
MV (performance motivation)	-0.0412 p=0.421	0.3181 **p=0.05***
AP (performance supporting activities)	-0.0556 p=0.394	0.1291 p=0.265
AB (performance braking activities)	-0.3381 **p=0.046***	-0.1569 p=0.222
KO Cognitive variability	-0.1380 p=0.251	0.3536 **p=0.038** **
EM Emotional variability	-0.396 p=0.424	0,0034 p=0.493
RG Regulative variability	-0.0709 p=0.365	-0.2118 p=0.149
AD Adaptive variability	0.0362 p=0.430	0.303 p=0.442

During hypobaric exposure we observed and checked all 26 subjects and remarkable behavioural symptoms were recorded:

Tab. 5

Behavioural symptoms of hypoxia	**Within 10-min of hypobaric exposure Number of subjects**	**Until the end of hypobaric exposure Number of subjects**
Hyperventilation	2	10
Sweating	4	5
Deceleration of reactions	5	15
Feeling of well being or euphoria	3	10
Loss of control	1	1
Sleepiness	1	1
Cyanosis	1	1
Loss of consciousness	-	-

The altitude chamber gives the opportunity to experience and observe symptoms of hypoxia under controlled conditions. In the event of the last four symptoms occurring (e.g. cyanosis, sleepiness, loss of control or consciousness) math testing in hypobaric conditions would have been stopped and oxygen

supply immediately recovered. Subjects with manifestation of these serious symptoms during hypobaric exposure were rejected. During the hypoxia exposure, nobody lost consciousness.

Conclusion

On the basis of these findings it can be stated that the error rate as a cognitive aspect in normobaria has a statistically significant effect on operational error rate in hypobaric conditions and could be used as a psychological predictor of operational aptitudes in time of useful consciousness. Similar findings could be stated for reaction time in relation to math performance accuracy. There are also personality traits - cognitive variability and performance motivation, that have significant influence on cognitive performance in general and consequently on cognitive processes in hypobaric conditions. However, we acknowledge that hypobaric conditions and hypoxia have significant influence on the reduction of cognitive aptitudes. Higher levels of operational cognitive aptitudes and performance motivation in general has positive influence on operational performance in time of useful consciousness.

We understand our findings are also supporting the idea, that time of useful consciousness and mental operational performance could be increased by means of quality and demanding personality assessment and systematic training in coping with hypobaric conditions.

We appreciate the necessity of further application and comparing the identical mental performance tests in normobaria and hypobaria, which could give us a more exact answer on formulated hypothesis. In the possible event of the ability to simulate the effect of hypoxia in an operational environment (e.g. the cockpit of an aircraft simulator), this could be a challenge for the next pilot selection programme, also for the research and development of training equipment in aviation.

Acknowledgement

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The Role of PWC in Declaring a Diver Fit

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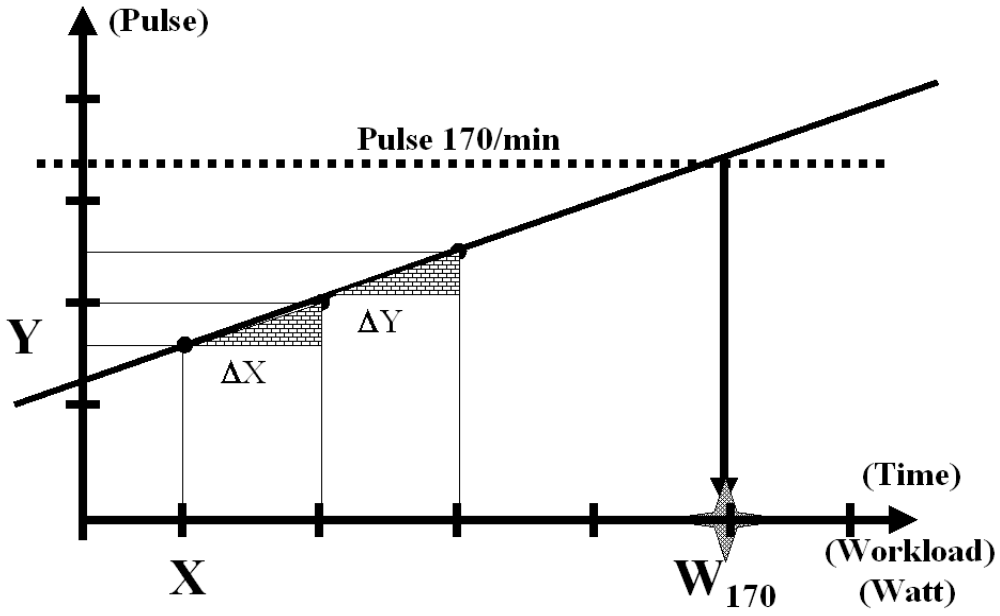
Keywords: Workload, Pulse, Habits, Gender, Fitness, Pulse-Working-Capacity

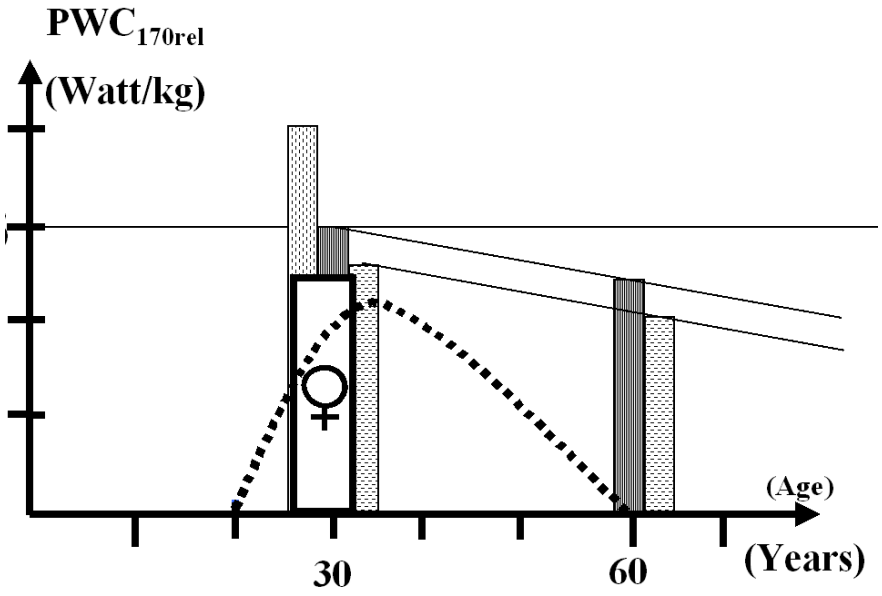
Summary:
The relative pulse-working-capacity170, PWC_{170rel}, is thought to represent the maximum workload which a person kann achieve with constant oxigen-uptake. The general mean of about 3 Watt/kg bodyweight depends on gender and fitness and to a low degree on age. With allowing all kinds of military tasks for women in the german forces it is likely that only women out of the upper regions of the standarddeviation of that special group will be chosen for demanding military tasks.

Under the condition of steady state the highest workload with a constant oxigen-uptake is called „working capacity". It is accompanied by a heart frequency of 155 to 175 beats per minute and this is called Pulse-Working-Capacity, PWC. If you generally refer to 170 beats per minute then the corresponding workload is called PWC170.
The method:

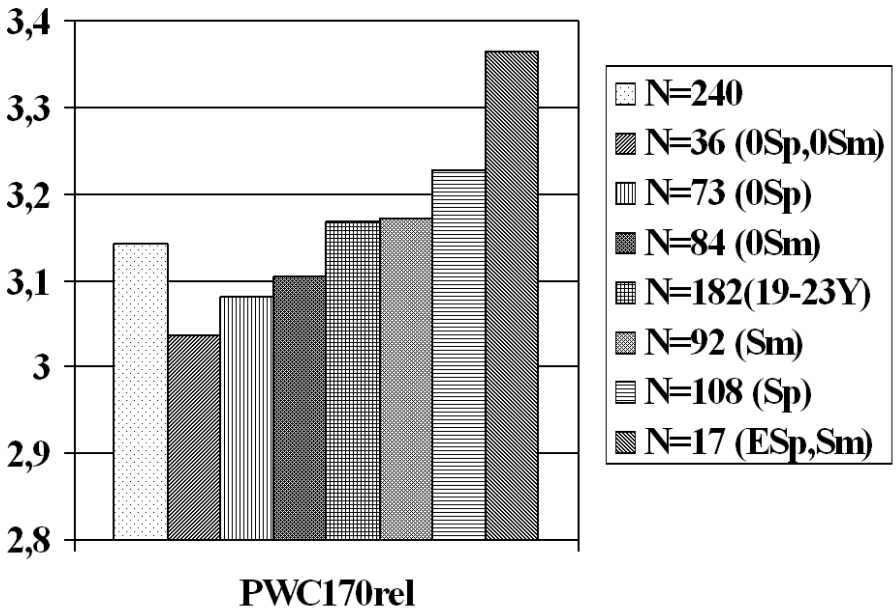


If a person is exposed to a workload of X Watt for a certain period of time on a bicycle then you can register a heartfrequency (Pulse) of Y beats per minute. Raising the workload by a certain amount will lead to a corresponding pulse. In a submaximal range the relation between workload and pulse is linear. The line of pulse-values can be extrapolated to the value of 170 beats per minute.
This is taken as representative for the working capacity and leads to a corresponding theoretical workload (W170). Dividing this W170 by the bodyweight in kilogramm (kg) leads to the relative pulse-working-capacity, PWC_{170rel} and this is the subject I am speaking about.
For the young male person a mean-value of 3 Watt/kg with a standarddeviation of 0,4Watt/kg has been found. The principle of this method has been published as early as 1949 by Wahlund.
But the relative pulse working capacity 170 as a means to determine the muscular effectiveness of an individual, that is it´s fitness, has been gradually added to our diagnostic tools in the early seventies.
The method is widespread since then but nevertheless it is not generally accepted and partly there have grown religious wars out of it.

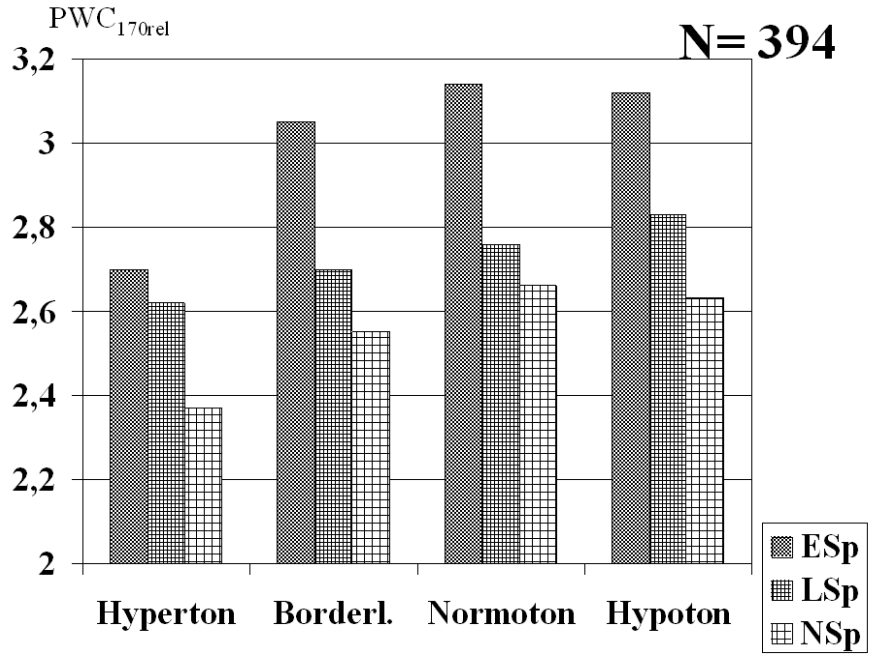
Paper presented at the RTO HFM Symposium on "Operational Medical Issues in Hypo- and Hyperbaric Conditions", held in Toronto, Canada, 16-19 October 2000, and published in RTO MP-062.



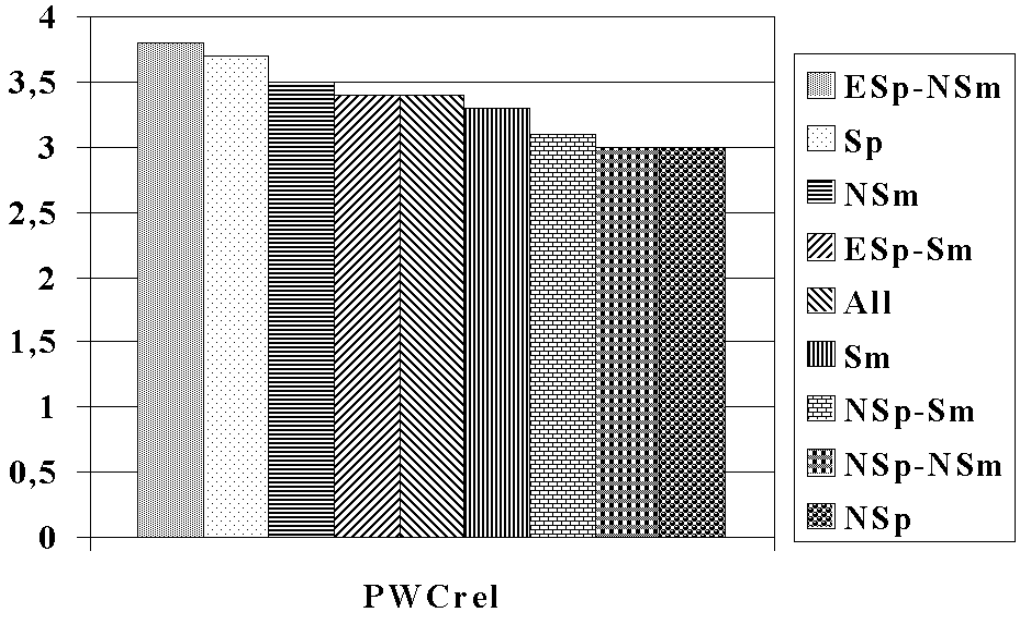
The duration of diving of a professional military diver lies between his 20th and his 60th year of life with more intensity in the earlier years. The scientific efforts to determine normal values lead to a relative pulse working capacity 170 of 3 Watt/kg for the young human being of about 30 years of age. Soon it became clear that the young females presented a value of 2,5 Watt/kg. (Our own female pressure chamber assistants showed a PWC_{170rel} of 2,3 Watt/kg) Well trained allround sportsmen presented a relative pulse working capacity 170 of 4 Watt/kg.
With growing age the relative pulse working capacity 170 becomes smaller, it is 0,2 Watt/kg per decade they say and publish. So it seems to be a generally accepted opinion that the young male person at the climax of his effectiveness has a relative pulse working capacity 170 of 3,0 Watt/kg and the female of 2,5 Watt/kg. Since then all is growing worse. So say the sportsreporters when they speak of the grand old ladies meaning those having just passed their twenties.



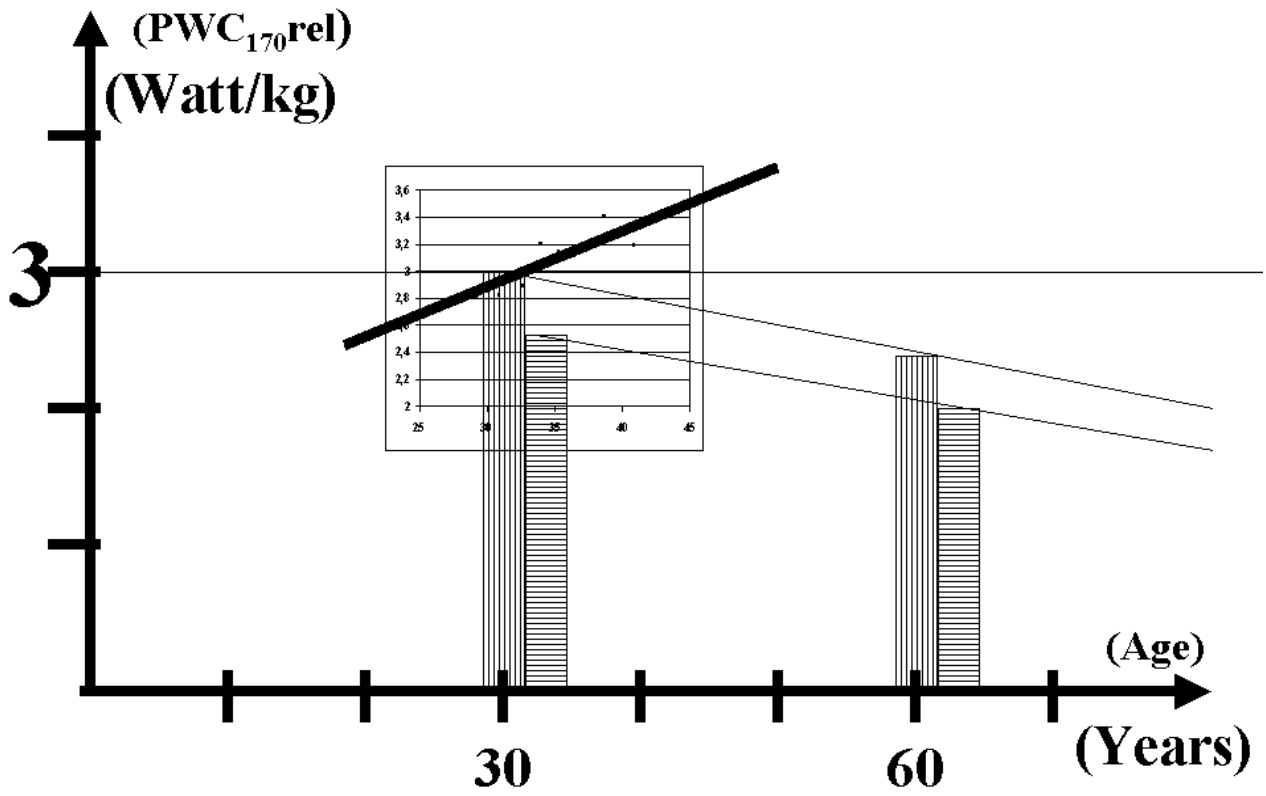
240 soldiers who have been considered fit for duty showed up in a forces hospital for different reasons. Some came because they did not really feel fit, some came to prolong their time in the forces others came for preventive reasons. These 240 soldiers where exposed to the determination of their relative pulse working capacity 170. This crowd could be subdivided according to the smoking habits and the sporting activity and the results where somehow surprising for me. The relative pulse working capacity 170 of all subcrowds was greater than 3,0 Watt/kg, that was considered to be rather good. The no-sport-group presented the lowest value as I suspected. The smoking sport-group presented the highest values which surprised me.



Out of 1200 ergometric examinations of a different forces hospital 394 where taken. This group was divided into the subgroups of hypertonic, borderlinehypertonic, normotonic and hypotonic patients who could either do endurancesport or little sport or no sport. Each subgroup had a relative pulse working capacity 170 smaller than 3,0 Watt/kg. Within the subgroups all endurancesportsmen had greater relative pulse working capacity 170 values than those with little or no activity in sports. The relative pulse working capacity 170 of the subgroup of hypertonic patients doing endurancesport was nearly as low as that of hypotonic patients doing no sport at all.



In the year of 1989 I tried to estimate the mean efficiency of dive-beginners before starting their training. They all were volunteers and I took only those who had a completely normal lungfunction and who ranged close around the mean of all examined divers with respect to length, weight and age. Out of 1200 divers I got 72, who fitted well to the above mentioned criteria. This whole group showed a relative pulse working capacity 170 of 3,4 Watt/kg. Smoking seemed to have no severe negative effect but it is rather satisfactory for physicians to see that not smoking sportsmen presented the highest relative pulse working capacity 170 .



The published opinon that growing age has negativ influence on relative pulse working capacity 170 cannot be confirmed by intraindividual longterm followup registrations. The analysis of those rather few soldiers who have been repeatedly controlled over up to more than twenty years partly till the age of 55 years shows that the relative pulse working capacity 170 -value is growing to an individual climax between the 30th and 60th year of age. Values of 2,6 Watt/kg at the beginning of registration do not prevent the individuals to reach values of more than 3 Watt/kg.
An age of more than 40 years does not prevent values of up to 4 Watt/kg and the latter are values typically found with trained allround sportsmen. Nevertheless these findings are not very surprising because the soldier whose longterm profession is diving gets additional money as long as he is employed as a diver. Standard of living and family situation depend on the money earned. Therefor he is eager to stay fit and the result of this eagerness seems to be a high or growing relative pulse working capacity 170.

To summarize:
the healthy young man has a mean-relative pulse working capacity 170 of 3,0 Watt/kg, the young woman has a mean-value of 2,5 Watt/kg, those are the published nomal values.
State of training or efficiency seem to be linked to relative pulse working capacity 170 -values in the way that high PWC-values allow to suppose good trainingstatus and/or good efficiency.
In the military everyday task the minimum reqirements for personal efficiency do not depend on that what a soldier is able to achieve but on that what the task demands. If in this respect the minimum reqirement for male efficiency is a relative pulse working capacity 170 of more than 2,2 Watt/kg then the same value must be demanded from women.
As a consequence out of their group only those will be chosen who do not show values less than one single standarddeviation below the mean of the female group.
As since the end of this year the forces regulations will allow women to join every task in the forces they are fit for some of them likely will try to become mineclearance divers or attackswimmers.
For them a minimum relative pulse working capacity 170 -value of more than 2,6 Watt/kg will be mandatory as for their male competitors.
This value is higher than the mean for healthy women in general.

Abbreviations:	0Sp; NSp= no sports,	Esp= endurancesports,	LSp= little sports
	0Sm; NSm= no smoker	Sm= smoker	Y= years

Application of Hypo and Hyperbaric Chamber in Czech Air Force

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Summary: The paper provides an overview about using of hypo and hyperbaric chambers at IAM Prague and about hyperbaric oxygen therapy (HBO) indications. Otoscopy and impedance tympanometry are pursued routinely on the instant before all expositions. The pilot's status is monitored by method of pulse oxymetry during all hypoxic tests and demonstrations. The $\%SpO_2$ monitoring provides the most valid longitudinal information about clinical status of examined pilots during hypoxia load. The therapy benefit during HBO is evaluated using transcutaneous oxymetry ($\%PtcO_2$) in the case of peripheral defects of tissue. It is necessary to achieve $\%PtcO_2$ values about 350 – 400 mmHg for successful therapy of tissue defects of the lower extremities.

The complex of three hypobaric and one hyperbaric chambers was installed at the Institute of Aviation Medicine in Prague in 1965. All chambers are routinely utilised for medical examinations, training and other needs of civilian or military pilots and other crew members. All hypo and hyperbaric chambers were rebuilt and redeveloped last year. Modification of our training system to standard STANAG 3114 and increasing of safety of operation were main reasons of that.

Medical status evaluation of each pilot precedes the hypobaric and hyperbaric expositions. Examined persons are fit for exposition providing that the conclusions of all clinic examinations (internal, ENT, ophthalmology, neurology, surgery, basic laboratory etc.) are normal.

We pursue routinely otoscopy and impedance tympanometry on the instant before all expositions. It is necessary to disqualify all events of Eustachian tube block. Otoscopic finding of eardrum's retraction or shift of the top of the tympanometric curve within zero zone (the pressure before and behind of the eardrum are not equal) means unfit for exposition. We use the Hand Tymp 3000 Danplex. It is portable battery operated tympanometer designed for quick and precise screening and diagnosing of the basic functions of the middle ear. Very important is quantification of compliance peak of the tympanic membrane. Compliance peak below -30daPa and peak more than +30 daPa presents most frequently low pressure or overpressure in the middle ear as a consequence of poor Eustachian function. Tympanometric curve without compliance peak presents reduced mobility of the tympanic membrane (perforation), wax lump, otosclerosis, otitis media etc. Examination makes possible to select pilots with probable troubles during exposition. In our opinion it is necessary to do this examination before each hypo and hyperbaric exposition especially if the gradient of the pressure change is high. We observe the dysbarisms in 10% of patients. The most frequent symptoms are pain of eardrums, pain of frontal and paranasal sinuses, nosebleed and pain of abdomen.

HYPOBARIC CHAMBERS

Single, three and thirteen seated hypobaric chambers are located at the IAM. Technical facilities of all hypobaric chambers enable to climb up to 127 000 feet using variable defined velocity of ascent and following descent. The chambers are used for following tasks:

I. selection of pilot's applicants,
II. initial and periodic aeromedical training of the Czech Air Force pilots and cadets,
III. evaluation of pilot's flight ability during his/her professional career,
IV. special exposures (high parachute jumping etc.),
V. expertise aims (oxygen devices and systems qualification etc.).

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I. Selection of pilot's applicants

The clinical examination complex is the base of pilot applicant's selection at the IAM. We do the hypoxia tolerance examination if the applicant's general efficiency is not quite convincing. The applicant is then exposed to hypobaric chamber test at the level 16 400 feet. Duration of the test is 20 minutes. Velocity of ascent and descent is 55 feet.s^{-1}.

II. Initial and periodic aeromedical training of Czech Air Force cadets and pilots

A. Cadets:

1. First year of the academy

Each cadet has to undergo an exposure to reduced pressure in hypobaric chamber to a simulated altitude of 16 400 ft. Duration of a hypoxic exposure is 20 minutes. Velocity of ascent and descent is 55 feet.s^{-1}. Evaluation of visual potency in defined hypoxic conditions is the aim of that examination. Cadets perform simple ophthalmological tests during hypoxic part of examination - contrast vision, colour vision, stereoscopic vision etc.

2. Third year of the academy

a) Each cadet has to exposed to hypoxia demonstration at 25 000 feet level. Velocity of ascent and descent is 160 feet.s^{-1}. The profile of exposition is similar to Type 37 Chamber flight USAF but it is integrated with a higher velocity of decompression (980 feet.s^{-1}) from 8 000 feet to 25 000 feet. Duration of a hypoxic exposure is 5 minutes maximally. The change of colour vision is demonstrated at the level of 18000 feet subsequently.

b) The test of tolerance to the pressure changes precedes Rapid Decompression Exposition. Parameters of that test are following: decompression from 8000 feet to 25 000 feet, ascent velocity is 1400 feet.s^{-1}.

c) The Czech Air Force Rapid decompression is similar to Rapid decompression test in RAF or USAF including the ear and sinus check. Mentioned above exposition is characterised by rapid drop of atmospheric pressure from the level 8000 feet to 25 000 feet. Ascent velocity is 1400 feet.s^{-1}. Denitrogenation (30 minutes) precedes all mentioned expositions.

B. Pilots

a) Flight personnel have to attend a continual training every fifth year. Pilots are exposed to the hypoxia tolerance test and rapid decompression. Parameters of tests are equal to mentioned above cadet's tests.

b) PPB (positive pressure breathing) training (41 000 feet). Pilots of combat aircraft train positive pressure breathing when finishing their basic flying training. The first part is accomplished in the simulator on the ground. The level of the oxygen positive pressure is 30 mmHg. The second part is accomplished in the hypobaric chamber. The pilot "climbs" to altitude 41 000 feet (positive pressure 30 mmHg intrapulmonary). Duration of the load is 2 minutes. Velocity of the climb is about 1 604 feet.s^{-1}. Velocity of descent is as possible as maximal. Former method of PPB training involved climbs up to the level 52 500 and 82 000 feet in hypobaric chamber.

III. Evaluation of pilot's flight ability during his/her professional career

Pilot's flight ability is usually evaluated after treatment of various serious sickness or more frequently during convalescence period. The degree of the load depends on the clinic status. We use generally hypoxia examination at the level 16 400 feet or 25 000 feet. These methods were described in previous paragraphs. Pilot's flight ability after ENT illness is evaluated using test of tolerance to pressure changes. It means a climb to the altitude 13 000 feet. Gradient of ascent is 98 feet.s^{-1} and descent 50 feet.s^{-1}. We can do the tympanometric examination in the case of necessity during the load and we do it routinely after finishing of that test.

IV. Special exposures

Special exposures up to 37 700 feet without PPB and above that level with PPB. Ascent and descent velocity depends on circumstances or requirements. These expositions are doing for example by reason of

evaluation of mountain-climber's hypoxia tolerance, test work of a new oxygen equipment, high altitude parachute jumping training etc.

We monitor the pilot's status by method of pulse oxymetry during all hypoxic tests and demonstrations. We use hand held pulse oxymeter Nonin 8500 M. That device makes possible to monitor the level of oxygen saturation of capillary haemoglobin continuously, to storage of measured data and to print it as a table or diagram.

The relationship between haemoglobin oxygen saturation and psychophysiological ability is evaluated. We count $\%SpO_2$ decreasing below 60 critical and in this case we supply the oxygen for the pilot immediately.

Our actual experience shows that it is possible to select pilots with a low hypoxia tolerance during the third minute at the level 25 000 feet (Figure 1). The statistical significant difference of $\%SpO_2$ is 68 % opposite 62 % in the group of volunteers with insufficient tolerance. The difference of these values increases progressive and a lot of volunteers with low tolerance have to finish before the 5^{th} minute of the test. The $\%SpO_2$ recovery of all pilots after oxygen breathing initiation is very prompt (up to 1 minutes to the value 98% at all pilots) and without significant difference (Figure 2). The critical value 60% of $\%SpO_2$ is correct and signalises a drop of psychical efficiency very well. We suppose that the monitoring of $\%SpO_2$ provides the most valid longitudinal information about clinical status of examined pilots during hypoxia load.

HYPERBARIC CHAMBER

Five seated hyperbaric chamber is located at the IAM. Dimensions of the cylindrical chamber are: length - 4 m, diameter - 2 m. Technical facilities of chamber enable to increase the pressure up to 1 MPa using variable defined velocity of descent and following ascent. The chamber is used for following tasks:

I. Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBO) exposition is defined by air pressure 0,3 MPa in the chamber. Patients breathe oxygen from oxygen masks during 120 minutes. Duration of the compression is 15 minutes in average. That time depends on patients' ability to tolerate the pressure change. Oxygen breathing is interrupted for 5 minutes after 1 hour of exposition as a oxygen toxicity prevention. The decompression phase is interrupted twice at 6 and 3 meters for 5 and 10 minutes. HBO method is usually used at the IAM Prague in following indications:

a) Absolute indications:
- anaerobic clostridial infection,
- decompression sickness,
- air emboli,
- CO and CN^- poisoning .

b) Relative indications:
- peripheral circulatory insufficiency,
- diabetic microangiopathy,
- gangrene,
- refractory cutaneous defects,
- trombagitis obliterans and other vasculitis,
- crural ulcer,
- chronic bone infection,
- acute hypacusia, acutrauma, Menier disease, tinnitus, vestibular dysfunction etc.

Over 120 patients are treated by oxygen in hyperbaric conditions in our pressure chamber every year. The spectrum of patients is in fact more wide than I mentioned. Nevertheless, ischaemic status of a limb or an inner ear is the most frequent indication of HBO application. This involves about 80% of our outpatients. The number of HBO expositions depends on diagnosis, patient's clinical status, therapeutic response etc. and it fluctuates from 5 to 50 expositions.

We evaluate the therapy benefit using transcutaneous oxymetry ($\%PtcO_2$) in the case of peripheral defects of tissue. This method is also used for selection of candidates for HBO therapy by identifying the

presence of tissue hypoxia. We use the Kolormon MC 7250-700 unit (fy. Kontron Instruments). An electrode is usually located on a tarsus or on a crus. The $\%PtcO_2$ values are monitored continuously during all expositions.

We concentrated on comparison of %PtcO2 values between normal and ischaemic tissues of the lower extremities last year. We demonstrated the significant difference of %PtcO2 between the healthy and ischaemic tissues during HBO. The $\%PtcO_2$ values rise during HBO eight to ten times in the case of normal tissues opposite five to six times increasing at patients with insufficient blood circulation. The $\%PtcO_2$ absolute values enhance from 65 to 650 mmHg at healthy tissues opposite 60 to 360 mmHg at ischaemic tissues. The course of $\%PtcO_2$ changes during HBO are presented in Figure 3. Both curves of $\%PtcO_2$ changes also manifest the significant increase of oxygen supply of peripheral tissues during HBO.

Our experiences show that it is necessary to achieve $\%PtcO_2$ values about 350 – 400 mmHg for successful therapy of tissue defects of the lower extremities. If the $\%PtcO_2$ value is less than 200 mmHg the therapy will be probably unsuccessful.

II. Test of tolerance to the oxygen

This test represents a basic evaluation of risk of oxygen toxicity. Divers are exposed to the pressure 0,3 MPa and they have to breathe oxygen for 15 minutes without any troubles.

III. Test of tolerance to the pressure changes

Divers are exposed to the defined level of pressure (up to 1 MPa).The scheme of decompression depends on the level of pressure and duration of exposure and corresponds to a decompression table.

Figure 1

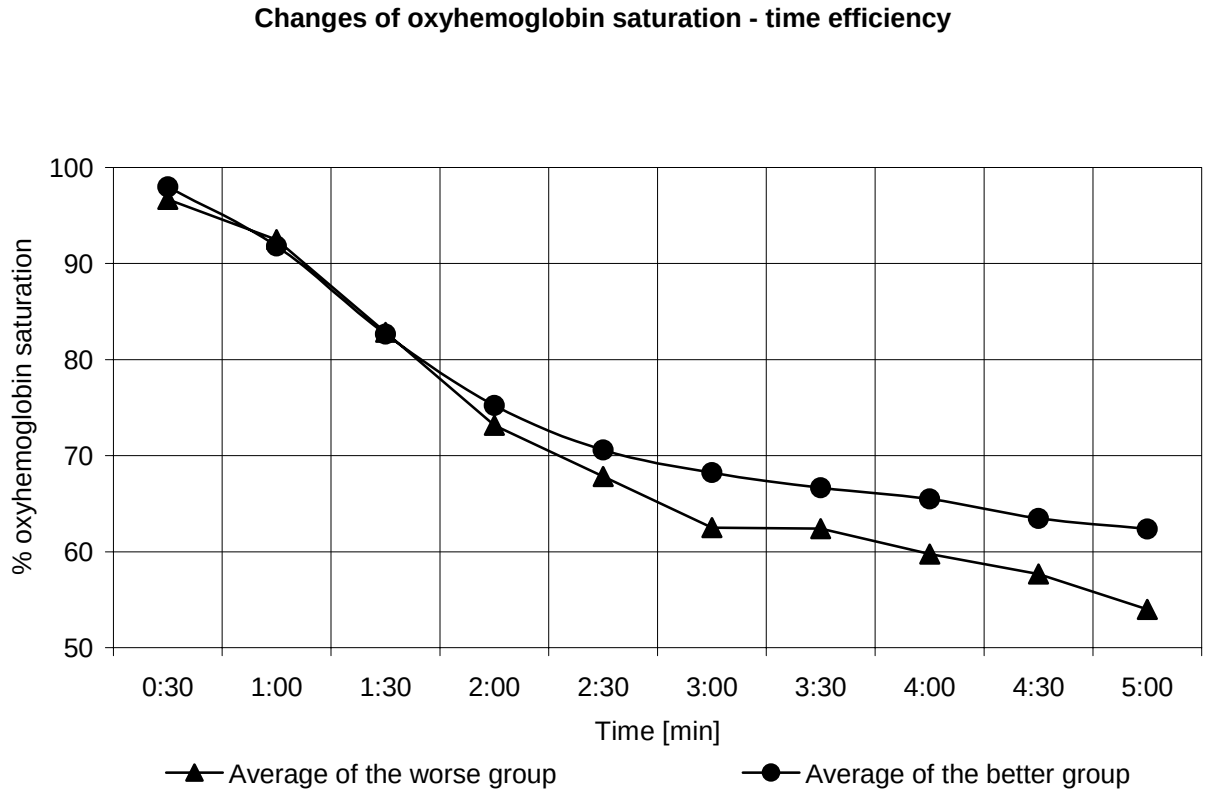


Figure 2

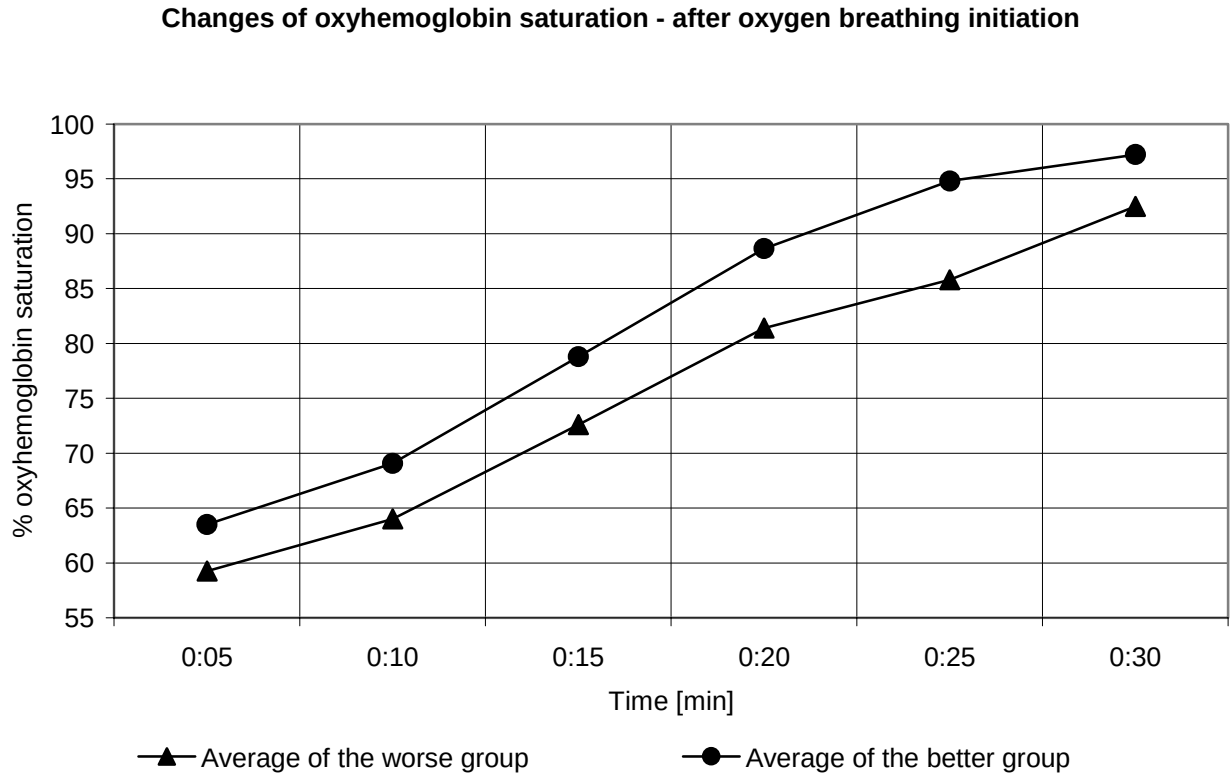
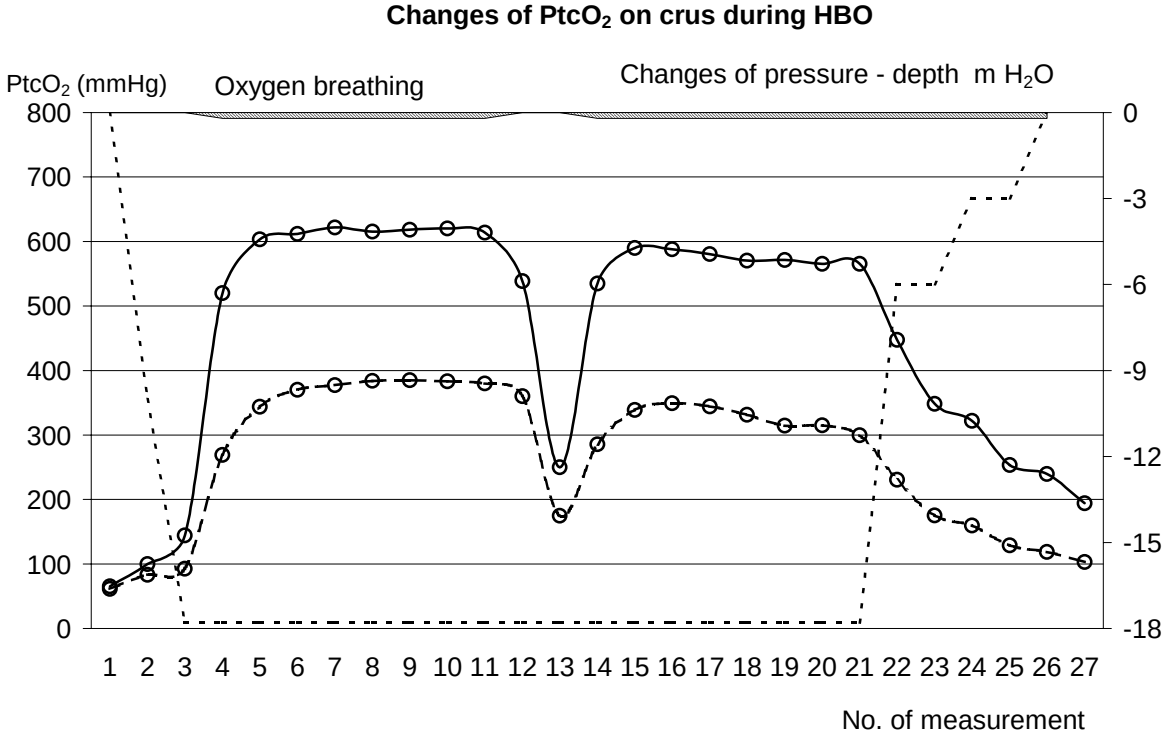


Figure 3



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The Effects of Normobaric Hypoxia in P_{300} Performance and in the Performance of Working Memory Tasks (CPT, N-back) in Pilot Cadets with Normal and Slow Waves Screening EEGs

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Summary: Electroencephalograms (EEGs) are currently used in many countries to screen Air Force pilots candidates. The usefulness of EEG to predict the likelihood of abnormal activity during the training of cadets remains controversial. We investigated whether effects of normobaric hypoxia on P_{300} ERP and memory scanning performance are related to the existence of slow waves in the EEG records of cadet pilots. If so, the EEG could serve as a tool for cognitive assessment in candidate pilot screening. Some 30 screening EEG records were re-evaluated for the presence of slow wave activity. Cadets with positive records (N=15) and a control group (N=15) performed first, at sea level and then at a normobaric hypoxia, a) cognitive performance tasks, which were, i) Active memory (N-back) and ii) Focal attention (CPT) and b) the auditory "OddBall" behavioral task for eliciting the P_{300} evoked response. The salient finding of this study was that the focal or bilateral brief periods of slow activity in the EEG records of Hellenic air Force cadets combined with conditions of hypoxia did not affect their performance of the memory scanning tasks or their ERPs measured from the auditory “OddBall’ task

Electroencephalograms (EEGs) are currently used in many countries to screen Air Force pilot candidates for epileptiform activity (spikes or spike-waves)(10). These EEG records are used as a baseline for the evaluation of brain function in the event of brain injury (10). The usefulness of EEG epileptiform activity to predict the likelihood of seizure development remains controversial (2,6,9,12). Another issue of controversy is the significance of the presence of brief periods of bilateral or focal slow activity in the form of theta (4-7.9 Hz) or delta (0-3.9 Hz) waves in these EEG records. Picard et al. showed (15) that 36% of a population of aircrew applicants had brief periods of bilateral theta

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activity in their EEG and 7% had bilateral delta activity. LeTournau and Meren (9) categorized focal or generalized slowing as abnormal while King and Liske (6) commented that these EEG findings are not necessarily abnormal and must be considered on an individual basis. In the EEG literature, brief periods of slowing are considered to be in a gray area between normal variant and abnormal EEG (13,14,16). Slow wave activity with posterior predominance is considered normal in adolescents whereas in young adults is not. However the age categories are ill defined (13). The appearance of bilateral delta and theta activity is considered abnormal in the EEG of the awake adult, although the distinction is based on the total amount of slow activity in the record and is again ill defined (14). The appearance of focal slowing of the EEG is considered to be abnormal but it does not always correlate with underlying brain pathology (16).

In a recent research we investigated whether the existence of slow waves in the EEG records of cadet pilots was related to differences in their cognitive performance, as this was assessed with memory scanning task and auditory "OddBall" task. The finding of this study was that brief periods of slow activity in the EEG records did not affect the results of the performed tasks (17)

It is well known that hypoxia affects cognitive performance (5,8) and P_{300} task (1).

In this study we investigated whether effects of normobaric hypoxia on P_{300} ERP and memory scanning performance are related to the existence of slow waves in the EEG records of cadet pilots. If so, the EEG could serve as a tool for cognitive assessment in candidate pilot screening

There are studies that have shown the appearance of EEG slow wave activity when specific cognitive tasks are performed. Mizuki et al. (11) using a paired association-learning task, found that the appearance of frontal midline theta activity was correlated with the memorization and retention processes. Gundel and Wilson (4) using topographical EEG analysis showed that during the performance of memory scanning tasks there was a reduction of alpha rhythm in parietal and occipital areas and an increase in theta activity in the left frontal area. Moreover it is believed that the appearance of focal EEG slowing may be correlated to a specific functional brain impairment that cannot be detected using brain-imaging techniques (i.e. CT scan, MRI) (16). This functional brain impairment might be reflected in subtle differences of cognitive performance. A relationship between spontaneous EEG slowing in some individuals and subtle differences in the performance of cognitive tasks could exist. A simple screening EEG could provide useful information about cognitive function and could serve as a starting point for further cognitive evaluation of these individuals.

MATERIALS-METHODS

The EEG records of 29 Hellenic Air Force Academy cadets were retrieved from the archives of the Neurology Department of the Hellenic Air Force Center of Aviation Medicine. The EEG records were obtained using an 18-channel electroencephalograph (Nihon Kohden Model EEG 4317F). The 10-20 system was used for electrode placement on the skull. Recording time was approximately 20 min and the procedure included 3 min of hyperventilation and 4-5 brief periods of photostimulation. All subjects had received food 1-2 h before the examination. The EEGs were performed approximately 18mo before our testing when the cadets were medically examined after admission to the Academy. The cadets' age range at the time the EEG was obtained was 17-20 yr with a mean of 18,43 yr (standard deviation [SD] ± 0,84). All cadets were male.

The EEG records were retrospectively evaluated by three experienced neurologists and categorized as: a) normal (normal with no slow wave activity); b) Bilateral slow (bilateral brief periods of focal slow activity during rest EEG); c) Right Slow (brief periods of focal slow with right dominance); d) Left Slow (brief periods of focal slow activity with left dominance and e) undecided (the cases for which the evaluators disagreed in classification) (**Table 1**).

Normobaric Hypoxia:

Each subject was exposed acutely to normobaric hypoxia breathing through a mask a given mixture of O_2 and N_2. Percentage arterial oxyhemoglobin saturation (SaO_2) was continuously measuring at the finger tip with an infrared device, so as, through adjustments of the percentage of the mixture, the level of SaO_2=90% could always be maintained.

Groups	EEG record
Normal	15
Bilateral slow	8
Right slow	4
Left slow	2
Total	29

Table 1: Classification of the EEG records

Memory Scanning Task:

Cadets with positive records (N=14) and a control group (N=15) performed first at sea level and then at normobaric hypoxia:

1) Cognitive performance tasks that were:

a. Active memory (N-back). During this task the cadet should keep in his memory either letters or the position of a symbol in space and respond in a few seconds. The rule is that the subject has to compare every symbol he sees with the pre-previous symbol (2-back). (**Fig.1**). We used a PC computer and a two-key Microsoft™ mouse for the performance of the visual memory-scanning task. The subject sat comfort-ably at his preferred distance in front of a color computer monitor. The subject was instructed to place two fingers of the dominant hand on the two mouse keys. The left key was designated as a "Yes" response and the right key as a "No" response for all subjects. Subjects were instructed to make as few errors as possible and to respond as soon as possible. The time from probe presentation to response (in ms) was the subject's response time for the particular trial. The temporal sensitivity of the mouse keys was 1 ms. We allowed a maximum response time of 3 s after which the trial was classified as a "Delay error". If the subject pressed the wrong key the trial was classified as a " Wrong Response Error". Response times, errors and other trial information were saved in ASCII files for the statistical analysis.

b. Focal attention (CPT). During this task the subject should compare a 4-digit number with the previous number and respond if are the same. We also used a PC computer and a two-key Microsoft™ mouse for the performance of this task. The subject sat comfort-ably at his preferred distance in front of a color computer monitor. The subject was instructed to place one fingers of the dominant hand on the left key of the mouse. Subjects were instructed to keep continuously the key down until the shown 4-digit number was the same with the previous. Then they had to leave instantly the key and keep it down again as soon as possible

2) Auditory "OddBall" Task

We used the Nicolet Spirit™ Evoked Potential System for stimulation and recording the ERP study. In particular we used the Nicolet P300 Cognitive Response software package. The task used was the auditory version of the "OddBall" paradigm. A series of auditory stimuli (tones, 80 dB, 20 cycles, ramp at 5 cycles, Blackman Envelope) was delivered to the subject's left ear through headphones. The rare stimulus (2000 Hz) was presented at random among the frequent stimuli (500 Hz). The frequency of occurrence for the rare stimulus was 20%. The subject was instructed to count the rare stimuli silently and report their number at the end of the examination. We repeated the testing if the subject was not at least 95% accurate in his count.

We used a 2-channel recording set up. The first channel recorded the potential between an electrode at vertex (Cz) and an electrode at the left earlobe. The second recorded the potential between an electrode at the parietal midline (Pz) and an electrode at the right earlobe. The reference electrode was at the frontal polar midline (Fpz). The signals were filtered (Bessel 2^{nd} order digital low-pass filter, SNR -13.6 dB) with a low frequency cut off at 0.1 Hz and a high frequency cut off at 30 Hz. The sensitivity of the amplifiers was set at +/- 100uV. Artifacts were rejected on line by exclusion of all trials where the waveform exceeded +/- 90 uV in amplitude. Each record was 1 s ling with 200 ms of pre-stimulus baseline recording, stimulus presentation and 800 ms of response recording. The inter-stimulus interval was 1.1 s.

The waveforms for 220-375 frequent stimuli and 45-75 rare stimuli were averaged on line for each one lf the two recording channels producing four averaged waveforms for each subject. These waveforms were stored on the controlling computer's hard disk and off line latency and amplitude measurements were obtained using cursor markers. The latency of the beginning of N1 (in ms) was the time from stimulus onset to the beginning of the first post-stimulus negative wave. The latency of N1 was the time from stimulus onset to the occurrence of the peak of the first negative wave. The amplitude of N1 was the potential difference (in uV) between the peak of the first negative wave and the baseline pre-stimulus activity. The latency of P2 was the time from stimulus onset to the occurrence of the peak of the positive was following N1. The amplitude of P2 was the potential difference between the peak of N1 and the peak of P2. The latency of the beginning of P300 was the time from stimulus onset to the beginning of the positive wave after P2. The latency of P300 was the time from stimulus onset to the occurrence of the peak of the positive wave after P2 and the amplitude of P300 was the potential difference between the peak of this positive wave and the baseline pre-stimulus activity. A P300 ERP is elicited only when the rare stimuli are presented. At least two P300 components have been identified: P3a has a more frontal distribution and is elicited when the subject is not specifically attending to the rare stimuli (automatic detection); and P3b has a parietal distribution and is related to attended rare stimuli.

The amplitude of the P300 wave increases with the decrease in the probability of occurrence of the rare stimuli and is related to task difficulty and motivation. The latency of P300 is related to the perceptual evaluation of the stimulus and is not affected by the processes of response selection and execution. The prior administration of scopolamine reduces the amplitude of P300 wave and increases its latency, thus suggesting a relationship between P300 and CNS cholinergic pathways. Suggested brain generators of the P300 ERP include the hippocampus, amygdala, and the inferior parietal lobe. It has been proposed that the P300 ERP reflects the information processing to update the context of working memory. This hypothesis has been questioned. Alternative hypotheses postulate that the P300 reflects the

closing of a behavioral epoch or that it is an after-effect of earlier negativities that reflect stimulus evaluation. Although the origin of P300 ERP and the exact mechanism of its elicitation have not been conclusively defined, this ERP has been intensively used as a tool to study human cognitive processing. Auditory stimuli in the “OddBall” behavioral task elicit the N1-P2 wave complex. This wave complex occurring prior to P300 has been correlated with physical parameters of the stimuli (e.g. intensity). Three components have been identified in the N1 latency that are related to cognitive operations (endogenous components). The most interesting for our purposes is the mismatch negativity (MMN) that is elicited when a novel stimulus is compared to a previous one. The MMN has been correlated with the short-term memorization and recall of the stimuli for the comparison process.

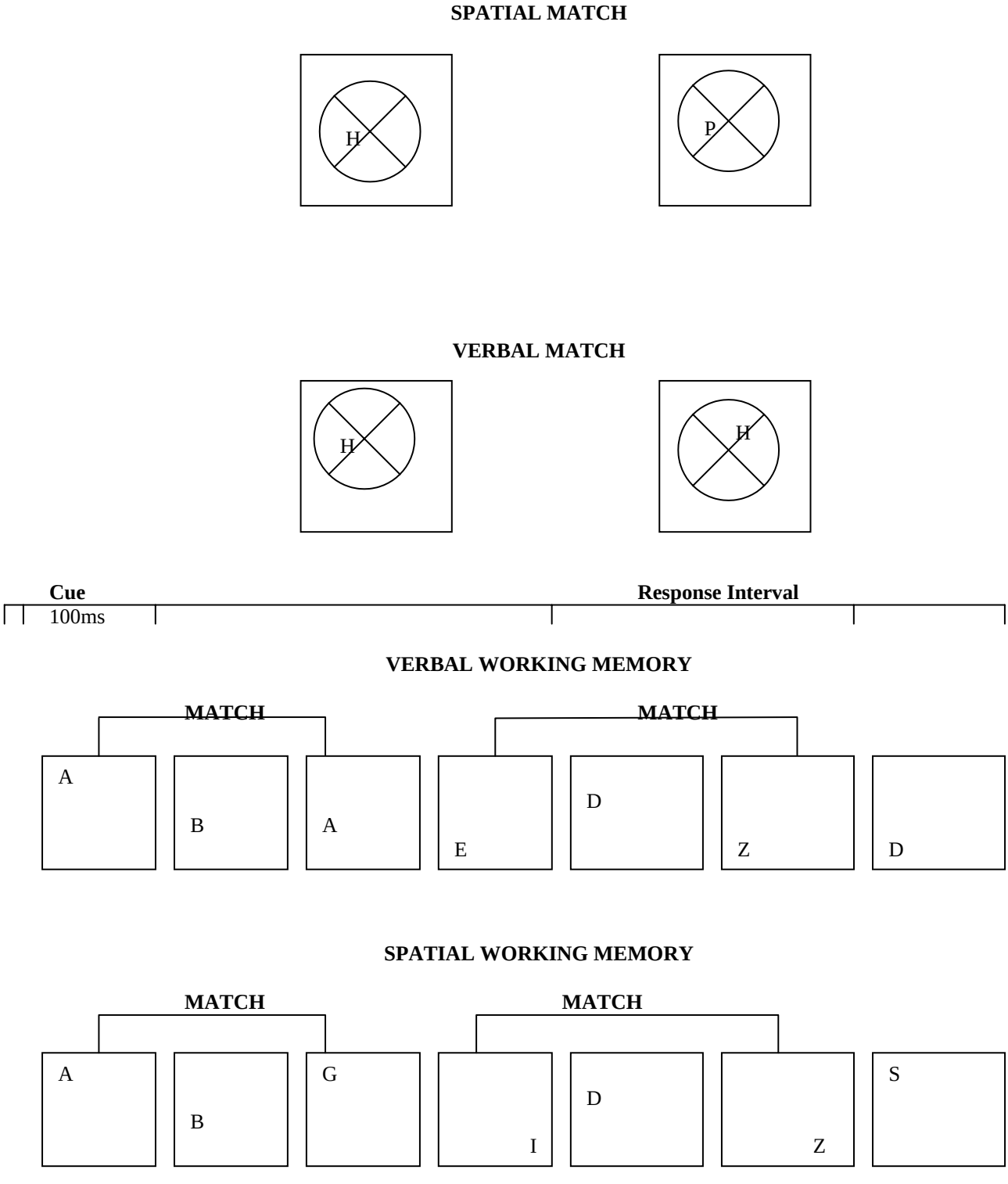


Fig.1 Schematic diagram of the course of events during the N-back task (3)

The statistical analysis of the behavioral and neurophysiological data was performed using univariate analysis of variance of SPSS 8.0 statistical package

RESULTS

1) Cognition tasks

We didn't find any statistically significant effect of the interaction of hypoxia and non-specific EEG abnormality (**Table 2**).

Factor Studied	Non-specific EEG abnormality (F stat.)	Hypoxia Effect (F stat.)	Interaction (F stat.)
Verbal N-back d'-prime	4.53*	0.29	0.55
Verbal N-back False alarms	4.355*	0.549	0.753
Verbal N-back Log Beta	0.38	4.27*	0.06
Spatial N-back d'-prime	6.7*	0.18	0.02
Spatial N-back Hits	5.968*	0.071	0.547
Spatial N-back Misses	5.658*	0.003	0.766
Spatial N-back Log Beta	0.000	0.003	0.4
CPT d'-prime	0.04	0.16	2.9
CPT Log Beta	2.56	0.86	0.02
P300 Latency	0.28	1.13	0.43

*= $p<0.05$

Table 2

A statistical significant association was found between Verbal N-back d'-prime and non-specific EEG abnormality (**Table 2** and **Fig. 2**). The subjects with normal EEGs made better scores presenting statistically significant less false alarms (**Table 2** and **Fig. 3**).

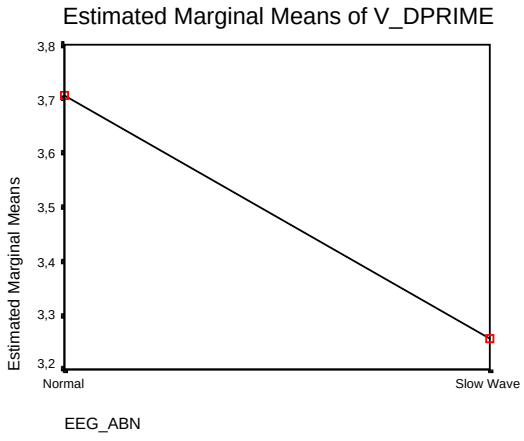


Fig. 2

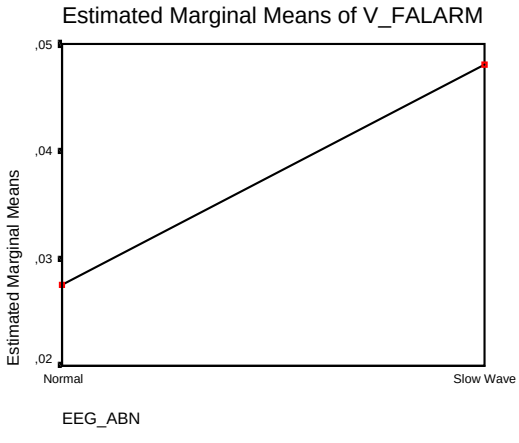


Fig. 3

A statistical significant association was found between Spatial N-back d'-prime and non-specific EEG abnormality, but in the opposite way. The subjects with "abnormal" EEGs made better scores (**Table 2** and **Fig. 4**), presenting statistically significant statistically more hits (**Table 2** and **Fig. 5**) and less misses (**Table 2** and **Fig. 6**)

The statistically significant effect of hypoxia was concerning the Verbal N-back Log Beta scores (**Table 2** and **Fig. 7)**, which presents the level of taken risk. This result is in order with the early symptoms of hypoxia concerning euphoria and increased self-confidence

Fig. 4

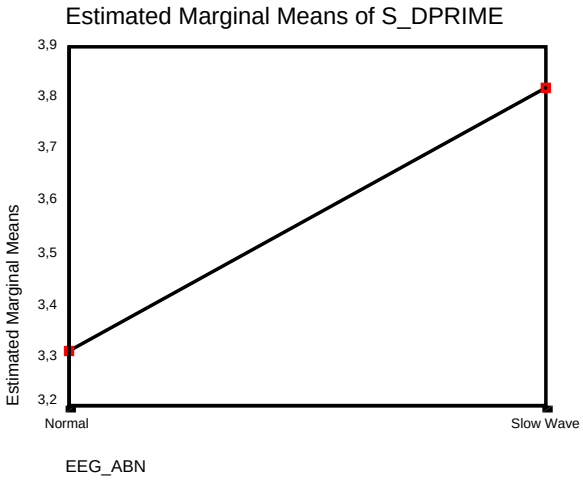


Fig. 5

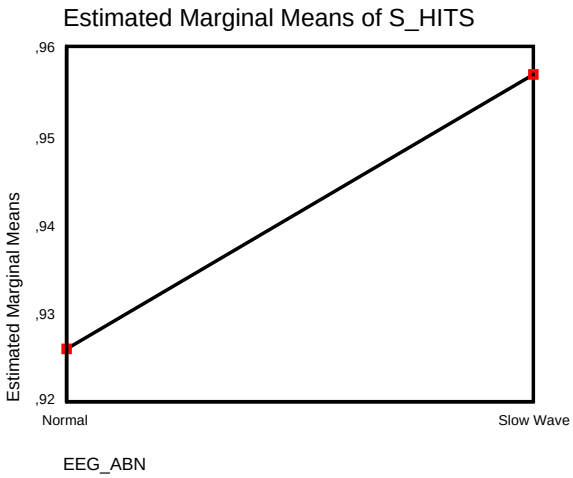


Fig. 6

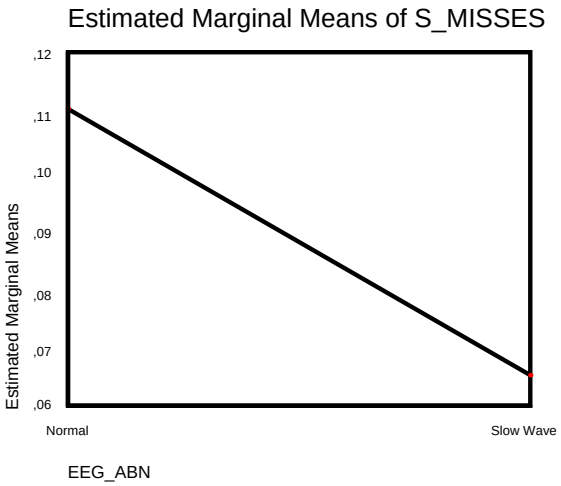
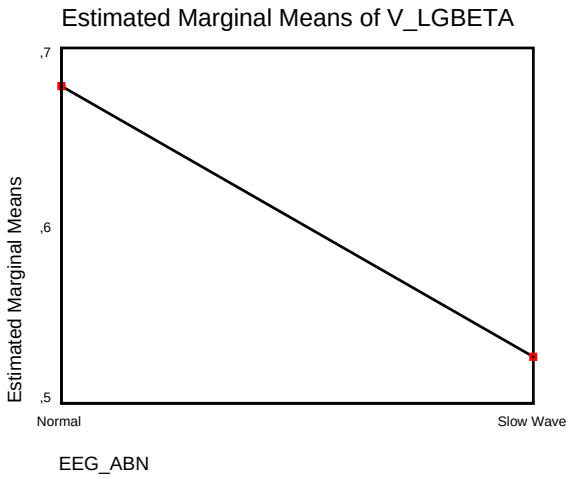


Fig.7



2) Auditory "OddBall" Task

We didn't find any significant effect of either hypoxia or presence of non- specific EEG abnormalities, or even of the interaction of these two factors (**Table 2**)

DISCUSSION

The salient finding of this study was that the focal or bilateral brief periods of slow activity in the EEG records of Hellenic air Force cadets combined with conditions of hypoxia did not affect their performance of the memory scanning tasks or their ERPs measured from the auditory "OddBall' task

The controversial results concerning the effect of EEG abnormality on the cognition tasks support the theory that the EEG slow activity is not predictive of a difference in cognitive function of Air Force cadets (17).

Cognitive function is an important component in the evaluation of pilot candidates. Our study will be fulfilled in about 2 years, when there will be a complete investigation whether there is an association between the scores of the aviation training and the scores of the cognitive tasks of the subjects who participated in this study.

ACKNOWLEDGMENTS

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Severe Decompression Illness Following Simulated Rescue from a Pressurised Distressed Submarine

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Summary
If adequate transfer under pressure or recompression assets were not available after rescue from a pressurised Disabled Submarine, the rescuees may suffer from severe or fatal decompression illness (fDCI). Effective methods of reducing the risk of fDCI require characterisation. This study uses a large animal model (goat) to estimate the dose (pressure) response (fDCI) relationship. It also addresses the putative intervention measures of breathing oxygen after surfacing or slowing the rate of decompression, as much as the operational cycle time of the rescue vehicle will allow.

The efficacy of interventions was determined by exposing a group of twelve animals to the LD_{75} pressure. After surfacing at the standard rate, oxygen was delivered by oro-nasal mask for one hour. Alternatively, animals were decompressed through a slow, stepped decompression profile, designed to prevent any microbubble formation on ascent to the surface. Animals were observed for signs of decompression illness (DCI) for up to 10 hours post decompression. They were then humanely killed for necropsy. Animals showing continuously declining vital signs were considered to be dying and were humanely killed.

It was shown that respiratory DCI is the most likely cause of death after rapid decompression from deep air saturation. Interventions, such as slowing the rate of decompression, which reduce the bubble load on the lungs on surfacing are likely to be the most effective. Non-recompression therapies, which target improving gas exchange in the lungs, should also improve the outcome.

Introduction
The submarine's primary role is to deliver its payload to the selected target. This requires it to be covert, fast and manoeuvrable. Constraints are present which prevent the designer from building a totally reliable boat and despite the emphasis on design for high reliability, equipment failures can and do happen. The Russian submarine KURSK highlights the most recent example of such an incident. The covert nature of the submarine's role also makes it vulnerable to collision when at or near the surface, e.g. the Peruvian boat PACOCHA (Harvey, 1989). In both of the cases cited above, further complications occurred when flooding raised the ambient pressure within the boat, increasing the likelihood of rescuees developing serious decompression illness (DCI) on reaching the surface.

If the pressure is greater than about 1.7 bar for more than 24 hours, the survivors will require a controlled decompression to avoid DCI (Bell *et al*, 1986; Eckenhoff *et al*, 1986). Logistical constraints to operators of submarines with large crews (>~80), may mean that rescue vehicles arrive at the scene prior to the arrival of the transfer under pressure facility. If the conditions in the submarine are deteriorating, then the on-scene commander will have to consider commencing the rescue operation without the means to control the decompression or to treat the survivors for DCI.

Limb pain only decompression illness has frequently been shown to respond to delayed therapy (Bennett and Elliott, 1993), with little risk of long term adverse health effects. Experience of diving accidents has shown that severe 'missed' decompression can cause permanent neurological damage or even be fatal. The rescue teams require advice to allow the best decisions to be made under such adverse circumstances.

Obviously these "bad outcomes" need to be avoided if at all possible. There is a lack of information upon the relationship between pressure exposure and risk of a bad outcome, which needs to be elucidated. Additionally, any non-hyperbaric methods of reducing the risk of a bad outcome (i.e. prophylactic measures) for a given pressure exposure would be of great advantage and also warrants thorough investigation. Obvious ethical considerations prevent the execution of this study with human volunteers. Therefore, the US Navy has sponsored a three Centre study using large animal models to provide the best data on which to base the advice to be given to on-scene commanders.

Methods
The goat has been used in our laboratory for many years, having been shown to be a good model for human decompression illness (Boycott *et al*, 1906; Seddon, 1997). The species has been found to be slightly more resistant than man to DCI arising from long near saturation exposure. Previous work has demonstrated that for practical purposes 24 hours exposure to raised pressure is sufficient to achieve saturation (Seddon, 1997). The protocols used here were approved by our local animal use review board.

Paper presented at the RTO HFM Symposium on "Operational Medical Issues in Hypo- and Hyperbaric Conditions", held in Toronto, Canada, 16-19 October 2000, and published in RTO MP-062.

Dose Response Curve

To determine the dose response curve, 48 adult female and male castrated goats were exposed in groups of three to an ambient pressure in the range of 55-85 fsw for 24 hours. Mean body mass was 48 kg, with a range 36 - 62 kg. No animal was exposed to pressure in the preceding 4 weeks to avoid risk of acclimation hyperbaric exposure. If an animal had experienced DCI in a previous study it must have been shown to have fully recovered, following a single hyperbaric treatment on USN Table 5 (RN Table 61), before entering the present study. The animals were exposed to 2.67 – 3.58 bar (55 - 85 fsw) for 24 hours, with compression on air at 1.0 bar/min, inside a $14m^3$ chamber. Environmental gases were such that CO_2 <0.2 kPa, O_2 = 20.9+/- 0.2% (v/v) and CH_4< 0.1 kPa throughout the exposure. The ambient temperature remained at 15 - 22^oC, except during pressure moves upon initial compression and decompression to the surface. Food and water were given to the animals *ad libitum* up to 8 h prior to decompression, then food alone was withheld. Decompression following the 24 h exposure occurred at 1.0 bar/min (except in 9 animals at 3.46 bar (82 fsw) where decompression occurred over 15 min; there was no difference in outcome in these cases).

Although goats are hardy, feral animals, they do express discomfort strongly, either through vocalisation or altered body language. A protocol for managing pain was developed in the early stages of the experiment. Intra-venous (IV) Torbugesic was administered within 5 min of surfacing. Subsequently Benzodiazepam was given by slow IV injection to sedate the animals if required. The animals were observed for up to four hours after surfacing. If at 4 hours the animals were showed no signs of terminal cardiorespiratory or CNS damage, it was assumed that they would survive. The following clinical signs were recorded:

- Presence of limb pain
- Motor control
- Respiratory rate, pattern and end tidal gases
- Heart rate
- Arterial oxygen saturation by pulse oximetry
- Cyanosis
- Blood gases (CO_2, O_2 and pH)

The Kisman – Masurel (KM) method was used to detect intra-vascular gas bubbles.
Trans-thoracic 2-D imaging was also conducted on an opportunity basis. The carotid artery and jugular veins were also observed for the presence of bubbles.

Animals were considered to be “bad outcomes” if their vital signs were poor (respiratory rate > 50 and heart rate > 180) and continuing to decline over a 20 min period. Such signs were occasionally accompanied by strong visceral pain, which could not be relieved. It was assumed that these animals too would be bad outcomes, and were killed humanely. Clear indications of cerebral damage were also assumed to be fatal and the animals were killed humanely. Examples included convulsions or nystagmus.

These observations were made at 15, 30, 60 minutes after surfacing and at 30minute intervals thereafter up to four hours. The time of any significant changes was also recorded. A gross post mortem was conducted at about 5.5 hours after reaching the surface in this component of the study.

Intervention methods

Two possible prophylactic DCI interventions were tested; post exposure O_2 breathing and a four hour decompression. The estimated lethal dose 75% (ED_{75}) point of 3.35 bar (see Figure 2 for dose response curve) was taken as the standard saturation depth. The animals were compressed in the same way as in the dose response study, and the environmental parameters were also maintained as previously. These animals were either decompressed to the surface at 1 bar/min followed by 1 h O_2 breathing or a staged decompression taking 4 h.

Twelve animals were exposed to this pressure exposure in each test and if the incidence of DCI fell to 33% the intervention would be accepted as effective.

Post exposure oxygen breathing

The effect of oxygen breathing at the surface was tested. 100% oxygen was administered by oro-nasal mask for one hour after surfacing. A limit of one hour on oxygen post surfacing was set, as the provision of unlimited oxygen to 100 plus rescuees by open circuit requires vast quantities of bottled oxygen, and is unlikely to be practicable. Also, the gradient of the dose response curve predicts that only a small reduction of gas load is required to produce significant benefits.

In this set of studies, observations continued on the subjects for up to 10 hours (rather than 4 h) depending on the condition of the goat. Animals were sent for post-mortem the following day.

Four hour decompression
A four hour decompression profile was also tested following the 24 h saturation period at 3.35 bar. The objective of the decompression profile was to prevent the formation of gas bubbles that would slow further gas washout. To be sure that bubbles had not formed, the first stop had to be at least two hours duration, which would allow KM Doppler scores to be observed. The aim was for a supersaturation ratio (PN_2tissue/Pambient) as close as possible to 1, though stop times and depths were refined by common sense to avoid confusing decompression rates. A single tissue compartment model (based on previously obtained saturation data) with a half-life of 106 minutes was used to calculate the profile (see Figure 1).

Again, the animals were watched for a period of up to 10 h post surfacing, then humanely killed and sent for post-mortem the following day.

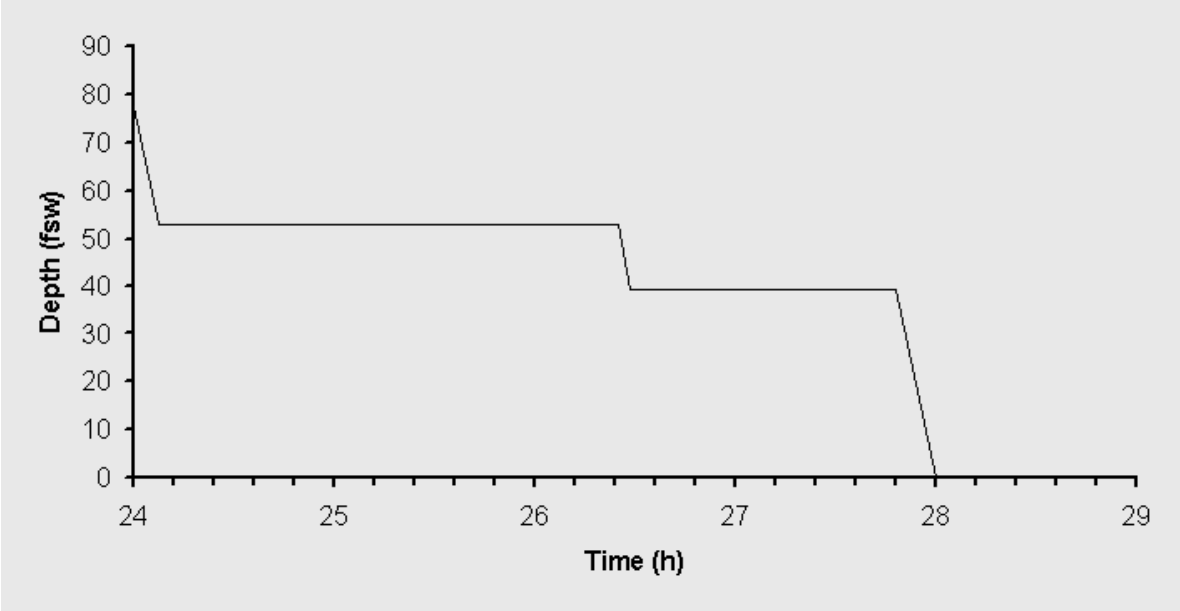

Figure 1 – Slow decompression profile calculated to avoid bubble formation.

Results

Dose response curve
All 48 animals presented with limb pain affecting one or more limbs. All animals also presented with respiratory decompression illness (chokes) to varying degrees. Those least affected had an increased resting respiratory rate, while those most severely affected had severe tachypnea, were hypo-ventilating and were cyanosed. Measurement of venous blood gases showed an elevated PCO_2 and a depressed PO_2. Three animals presented with central nervous system signs and were diagnosed as bad outcomes. Figure 2 shows the spread of bad outcomes related to depth, producing the dose response curve. From this curve it was estimated that ED_{75} saturation depth was 3.35 bar (~75 fsw).

Venous gas emboli were present at Kisman-Masurel score of four at all observations. 2D imaging showed relatively few bubbles in the periphery compared with the pulmonary artery. No bubbles were observed in the left ventricle or the carotid artery.

Common examples of post mortem findings are:
- Pulmonary oedema.
- Foam in bronchi.
- Gas in major vessels.
- Haemorrhage in brain/mid-brain/spinal cord (C1 - T5).
- Excess Cerebrospinal Fluid in C1 - T5 area.
- Pale brain and coning (compression).

There were no obvious post mortem differentiating signs between the bad outcome group and those that survived.

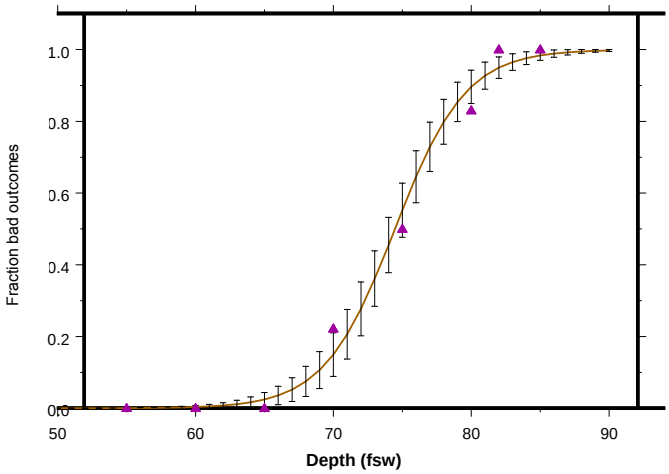

Figure 2 - Showing the derived dose response curve for bad outcomes. The error bars are the predicted 95% confidence intervals on the mean.

Post exposure oxygen breathing
In this case, there were five bad outcomes. This was significant at the P=0.06 level indicating a strong trend to a significant benefit. One animal was completely asymptomatic; the 11 remaining animals all exhibited limb bends, while 5 had chokes (chokes being defined as increased respiratory and heart rates) and were deemed to be bad outcomes. One of the latter also suffered from severe CNS complications. All animals in this part of the study exhibited KM pre-cordial Doppler ultrasound scores of four at the surface.

The general pathology on post mortem was as in the dose response part of the study.

Four hour decompression.
In this trial, the number of bad outcomes dropped to 2 out of 12 (17%, P>0.002 – a significant improvement on the ED_{75}). No bubbles were detected during the decompression, fulfilling the aim of the model, however KM scores at surface were still four. Some of the animals were affected by respiratory compromise, but not as severely as the controls. There was only one case of cerebral involvement. Again, the general pathology was the same as the earlier parts of the study.

Discussion
It would seem that bad outcomes are largely due to respiratory decompression illness, with a few due to cerebral damage. Therefore, to decrease the risk of a bad outcome, the insult to the lungs needs to be reduced. Oxygen administered post decompression showed a beneficial trend. In addition, anecdotal evidence indicates that oxygen post decompression is effective at reducing the incidence of symptoms following diving accidents. Oxygen administered during decompression should be of even greater benefit as is found in diving and acute altitude exposure. However, at the onset of this study none or very few rescue submersibles are equipped with an oxygen delivery system.

It is accepted that slowing the decompression will be effective, but what is practical? Assuming that the commander wished to evacuate the DISSUB quickly, the Deep Submergence Rescue Vehicle operators have advised that up to four hours could be required to recycle the submersible for its next flight. This would make a four hour stepped decompression to avoid DCI an eminently suitable method of treatment.

Fatalities occurred in the goat model at pressures greater than 2.8 bar saturation. The predicted ED_{50} is 3.25 bar with 95% incidence at 3.5 bar. Other work is in progress to establish the likely figures for man. This work has shown that slowing the decompression will reduce the risk; oxygen breathing is showing a trend to reducing the risk and it can be inferred that measures to improve gas exchange could also improve the outcome. As respiratory DCI is complicated by

pulmonary oedema, a diuretic may be beneficial as a prophylactic measure, and this option should also be investigated in a further study. All of these three options address different mechanisms; they accelerate gas washout, decrease bubble formation and reduce pulmonary oedema, and therefore combinations of the above may be more effective than any alone. Future work will address this question.

In summary this study has confirmed that severe missed decompression can be fatal but the risk of fatalities may be reduced without immediate need for recompression facilities. Although acute symptoms of missed decompression may be alleviated by the varying intervention methods discussed, the gross pathology of all groups showed a similar level of decompression insult. This indicates that post intervention, rapid hyperbaric therapy should be carried out as soon as practicable to reduce the likelihood of chronic DCI.

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Decompression Sickness Research: New Directions

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Summary: DECOMPRESSION SICKNESS RISK REDUCTION was sought throughout the twentieth century by adjusting dive duration and depth combinations. These adjustments hypothetically minimized inert gas supersaturation in tissues during decompression. The newest efforts in decompression sickness research by scientists at the U.S. Naval Medical Research Center in Silver Spring, Maryland, are focused on fundamentally different approaches. We are seeking means of reducing decompression sickness risk by actively eliminating a critical portion of the body's inert gas load; by increasing the volume of inert gas held in solution by the blood; or by blocking the body's response to intravascular bubbles.

Biochemical Decompression

The role of nitrogen in diving and decompression sickness is familiar to all. Fewer people are familiar with the potential for using hydrogen in ultradeep diving, and how this gas may affect decompression sickness risk. Biochemical decompression is the name that we have created for our most radical new approach to reducing decompression sickness risk. Hypothetically, biochemical decompression can be performed using either hydrogen or nitrogen as the diluent for oxygen in a hyperbaric breathing mixture. Both hydrogen and nitrogen have the properties of being inert to mammalian metabolism, but substrates for metabolism by numerous microbial species. If divers were provided with the biochemical machinery to metabolize even a small amount of the hydrogen or nitrogen dissolved in their tissues, significant reduction in decompression sickness risk could be achieved.

Again speaking hypothetically, one might imagine that this biochemical machinery could be offered to the diver in a variety of forms, such as a subdermal or peritoneal implant, a dialysis-type device connected to the blood circulation, or a pulmonary spray. However, even a brief consideration of these approaches makes it apparent that most body locations are unsuited for this purpose. Most locations within the body are approachable only by invasive means, and we certainly would not want the biochemical decompression to be a higher risk procedure than the treatment of decompression sickness itself. Furthermore, most body locations would not accept the implantation of microbial material, due to the response of the immune system.

We have nevertheless succeeded in finding a body location and an approach that have been successful for hydrogen biochemical decompression in both a small and a large animal model (Kayar et al., *Am. J. Physiol., 275*:R677-R682, 1998; Kayar et al., unpublished observations). The large intestine is ideal for our purposes. There are numerous species of microbes that metabolize hydrogen and are part of the normal flora of the large intestines of humans and other mammals, thus eliminating the concerns about an immune reaction. There is a rich blood supply to the intestine, assuring the microbes of good access to hydrogen. The microbes can be delivered to the intestine by mouth, and the end products of their metabolism can be readily lost from the intestines along with other waste products.

The microbial species we selected, *Methanobrevibacter smithii*, has been well studied and is known to be non-pathogenic in humans (Miller and Wolin, *Appl. Microbiol. 131*:12-18, 1982). Its metabolic pathway is:

$$4H_2 + CO_2 \rightarrow 2H_20 + CH_4$$

in which four molecules of hydrogen are converted to two molecules of an innocuous, non-gaseous end product (water). The electron acceptor, CO_2, is abundant in tissues. The secondary end product, methane, is already produced in the intestines of most animals, and escapes harmlessly with other intestinal gases.

Our approach was to surgically inject live cultures of *M. smithii* into the proximal end of the large intestines of rats and pigs. The animals were then placed in a dry hyperbaric chamber that was specially designed for compression with mixtures of hydrogen and oxygen. As the animals breathed hydrogen, some of this gas was metabolized by the microbes in the intestines. Chamber gases were monitored by gas chromatography. The rate at which the animals released methane was measured as a simple and non-invasive method of following the rate of hydrogen removal by the microbes (Figure 1). Animals that received these microbial treatments had a significantly lower incidence of decompression sickness compared to untreated animals, and also compared to surgical control animals that received intestinal injections of saline (Figures 2 and 3). For both rats (Figure 2) and pigs (figure 3), decompression sickness incidence was cut approximately in half by the microbial treatments. Mathematical analysis suggests that this decreased risk of decompression sickness was achieved by eliminating only roughly 5% percent of the total body burden of hydrogen in these animals.

Paper presented at the RTO HFM Symposium on "Operational Medical Issues in Hypo- and Hyperbaric Conditions", held in Toronto, Canada, 16-19 October 2000, and published in RTO MP-062.

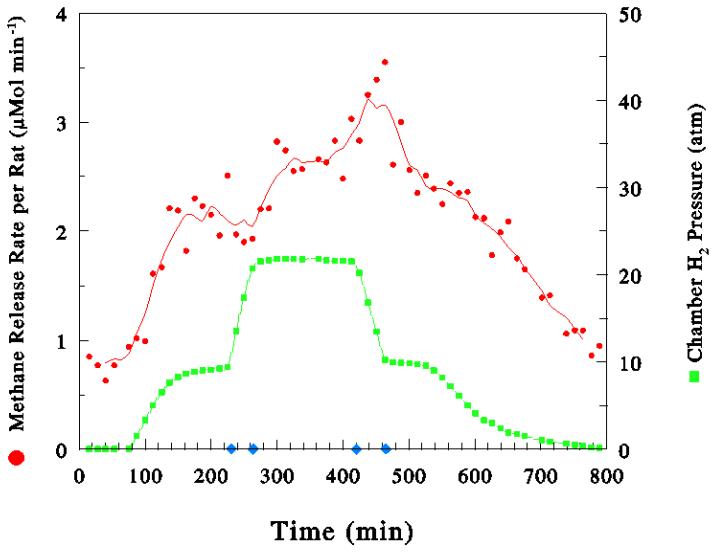

Figure 1. As rats treated with hydrogen-metabolizing microbes breathed hydrogen at increasing pressures, the amount of methane they released increased. As hydrogen was removed from the chamber, methane release rate from the rats increased briefly (probably reflecting supersaturation with hydrogen), and then decreased.

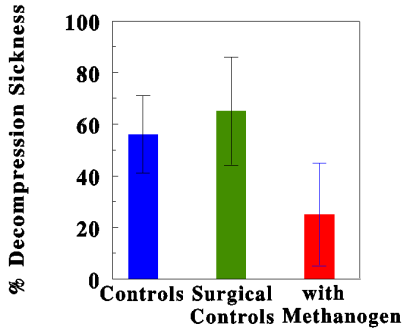

Figure 2. Rats treated with methanogenic microbes in their intestines had a significantly lower incidence of decompression sickness than untreated control animals or surgical control animals, following a chosen compression and decompression sequence in hyperbaric hydrogen. (Error bars are 95% binomial confidence limits.)

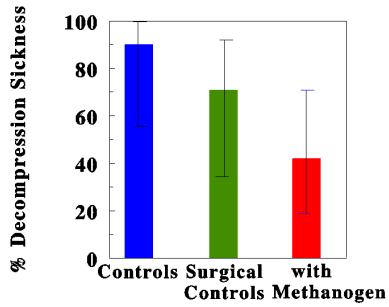

Figure 3. Pigs treated with methanogenic microbes in their intestines had a significantly lower incidence of decompression sickness compared to untreated and surgical control animals, following a chosen compression and decompression sequence in hyperbaric hydrogen. (Error bars are 95% binomial confidence limits.)

Based on these results with animals, the course of action to follow with human divers is clear. The microbes must be prepared for inserting into capsules to be taken by mouth. These capsules must be designed to withstand a 12-hour transit through the stomach and small intestine, since stomach acids and oxygen are fatal to the microbes. Much work remains to determine the optimal dose and timing of the microbial treatments, and of course safety issues must be continually addressed. However, the concept of hydrogen biochemical decompression is assured.

Given the limited application of hydrogen as a diving gas, it is far more intriguing to consider nitrogen biochemical decompression. There are nitrogen-metabolizing bacteria that are native to the intestinal flora of humans. The same general principles of the physiology of gas transport and the benefits of gas scrubbing on decompression sickness risk should apply to nitrogen as well as to hydrogen. However, the rate of nitrogen fixation is one to two orders of magnitude slower than for hydrogen metabolism. It would require a volume of bacteria too large to insert into the intestines of a person to remove a useful volume of nitrogen on a time scale of minutes to a few hours. Genetic engineering of nitrogen-fixing bacteria may some day advance to the stage at which we can actually envision a pill against decompression sickness for air divers.

Perfluorocarbons

We have also been developing at our institution an approach to reducing decompression sickness risk that is much easier to envision having an impact on diving safety very soon. Liquid perfluorocarbons are synthetic oils that can dissolve and transport large quantities of gases. Due to their high solubility for oxygen, perfluorocarbons are currently being tested in other laboratories as blood substitutes, and are also well-known as the substance to be used to fill the lungs in “liquid breathing”. Less-often considered is that perfluorocarbons have high solubilities for nitrogen and helium as well, which makes them potentially useful for treating diving casualties (Spiess et al., *Undersea Biomed. Res. 15*:31-37, 1988). Due to increased solubility of gases, intravenous injections of perfluorocarbons could improve inert gas elimination from tissues and decrease the number of circulating bubbles. These two actions should decrease the incidence or severity of decompression sickness for people at unusually high risk for decompression sickness, such as military divers on combat missions, or submariners in a rescue from a disabled submarine.

Research results so far with pigs are highly encouraging. Animals were exposed in a dry hyperbaric chamber to a compression and decompression sequence in air. Untreated animals had a 90% incidence of decompression sickness, whereas animals treated with perfluorocarbons had only a 53% incidence (Figure 4). This treatment was given to animals within a few minutes after decompressing, with initial symptoms of decompression sickness typically manifesting themselves within 5 to 20 minutes of decompression. The possibility exists that decompression sickness risk could be lowered further with more testing of doses or timing of perfluorocarbon delivery.

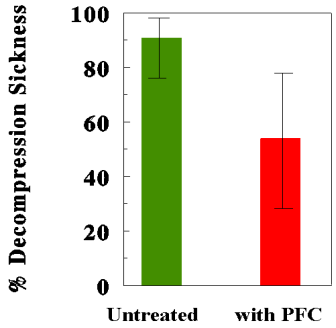

Figure 4. Pigs treated with intravascular injections of perfluorocarbons have a significantly lower incidence of decompression sickness than untreated pigs, following a chosen compression and decompression sequence in air. (Error bars are 95% binomial confidence limits.)

Immune System Interactions

Research from our laboratory and that of a number of others in recent years has indicated that much of what we associate with symptoms of decompression sickness may be an inflammatory response to bubbles or to tissue damage, rather than a direct embolizing effect of the bubbles themselves (Ward et al., *Undersea Biomed. Res. 17*:51-66, 1990). If the immune system plays a significant role in the manifestations of decompression sickness, then it may be possible to prevent or treat decompression sickness through manipulation of the immune system. Researchers at our institution are analyzing the plasma of animals with decompression sickness for such inflammatory marker molecules as interleukins, tumor necrosis factor, complement, and intercellular adhesion molecules. Results of these experiments are not yet available. However, this direction may well prove to be the most fruitful of all in identifying a safe and effective means of decreasing decompression sickness risk for all divers.

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Using "Technical Diving" Techniques for Short Dives in the 80-100 MSW Range

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Abstract

Introduction: Advanced recreational divers over the last 10 years have developed new techniques for open circuit scuba diving in the range to about 100 metres of sea water (msw). These techniques have potential application in military diving. This report describes the new practices, the equipment, procedures, and training required, and some results of several significant operations.

Methods: The techniques known popularly as "technical diving" involve the use of special breathing mixes, means of carrying the mixes, custom-designed decompression tables which include oxygen exposure management, means of performing proper decompression, adequate thermal protection, and appropriate redundancy. A typical dive to 80 msw for 20 min could use for the bottom mix a "trimix" of about 17% oxygen, 50% helium, and the balance nitrogen. This is carried in twin back-mounted tanks each of perhaps 3000 liter capacity, with two side tanks containing an oxygen-enriched air decompression gas and oxygen or a high-oxygen mix. The diver does a stage decompression, switching to the intermediate mixture at a depth appropriate for its oxygen content, say 33 or 30 msw for an enriched air mix of 36% oxygen, and then breathing oxygen at the stops at 6 and 3 msw. Decompression may be carried out in open water with the diver hanging on the vessel's anchor line or some other attachment, or the diver may get partially out of the water inside or some sort of air-filled decompression station. Because high oxygen partial pressures are used to optimize decompression, it is necessary to plan and monitor the oxygen exposure as a component of the dive. Although operating standards have yet to be put in place, technical diving practice has become fairly uniform worldwide, and training can be obtained from a number of organizations.

Results: Divers in pairs or small groups routinely dive on sunken vessels such as the *Andrea Doria*, but there have also been a number of well organized team efforts, including dives in the 80 to 100 msw range to wrecks such as the *Lusitania*, *Brittanic*, and *U.S.S. Monitor*. A number of significant dives have been done in water-filled caves in the same depth range. Considering the extent of the exposures decompression sickness is relatively rare, but there have been a number of accidents of an operational nature, due to such things as breathing the wrong gas mixture. In any case technical diving techniques using "trimix" are regarded as being considerably safer than making equivalent dives with air as the breathing gas, because this avoids the narcosis in the air dives.

Conclusions: Some U.S. Government agencies are showing serious interest in technical diving. NOAA is conducting technical diving operations on the U.S.S. Monitor, and the U.S. Navy has plans to provide technical diving training for some Navy divers. For diving organizations with the commitment to be able to operate in this depth range, technical diving methods are worth considering.

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Technical diving

A new category of self-contained diving that greatly extended the range of recreational scuba diving began to be practiced in the late 1980s. At one time recreational diving was limited to air, but some advanced sport divers began to use special breathing gas mixes that permitted them to extend this range, at first to about 75 msw, and later even to 100 msw on a routine basis. The method they developed consisted of adding enough helium to air to relieve the narcosis, resulting in a "trimix" of oxygen, helium, and nitrogen The reason such mixes had not been used before was that there had been no available decompression tables for these kinds of mixtures. Other considerations were the management of oxygen toxicity, the ability to carry enough gas, and other exposure-related factors having to do with long decompression times

The development of technical diving was done primarily in the recreational and scientific communities, far removed from military diving, but the capabilities of the techniques could be of great relevance to some military operations. Making this point is the main objective of this paper.

The term "technical diving" has developed as a description of this category of special-mix diving. Strictly speaking as it has been developed this is still "recreational" diving—it is recreational in the sense that most practitioners do it for fun rather than employment, but is still a highly disciplined and professional undertaking that does not belong with traditional recreational diving. This is a method of self-contained or untethered diving (that is, no gas hose to the surface) that extends well beyond the traditional envelope of "recreational" diving; it relates to that as technical mountain climbing does to hiking.

Figure 1. Technical trimix diver. Diver has manifolded "back" tanks and one sidemount of oxygen-enriched air, with regulators, a light and a dive computer. Photo by Joel Silverstein.

Technical divers use special breathing mixtures and custom decompression tables, but they do other things involving technology (Figure 1). They use special tactics to carry the amount of gas needed, either by means of larger tanks or by using higher pressures or both. Special attention is given to buoyancy control. Divers working in a current or exploring a cave often use battery-powered diver propulsion vehicles or "scooters" to increase mobility. Various techniques are used to protect divers during long decompressions. Because exposures may be long, special thermal protection is required.

To view technical diving from the proper perspective, keep in mind that it was developed to avoid having to use air for deep dives.

Deep recreational dives

By way of background, recreational diving is well recognized as having strict limits, with depth generally limited to the range to 40 msw, and it is further limited to dives with air as the breathing gas and not involving decompression stops. Realistically, these are not the limits within which all recreational divers operate, but they are the limits to which divers are trained by the

Figure 2. Technical trimix diver. Diver has manifolded "back" tanks and sidemount of oxygen-enriched air, with regulators, a light, and a dive computer. Photo by Joel Silverstein.

recreational diving training agencies, particularly in the U.S.A. “Deep” is a relative term which involves the diver's own skill and preparedness as much it does the water depth. Even within these limits special “deep” training is needed to go even as deep as 130 fsw.
For some years now some scuba divers have exceeded the 40 msw (130 fsw) limit, using decompression stops when necessary, and under some conditions have even used oxygen for decompression. This tactic can make the otherwise unreliable USN Exceptional Exposure air decompression tables work quite well. These divers to go well beyond the depth at which nitrogen narcosis can become seriously debilitating. As depth increases much beyond 60 msw (200 fsw) the PO_2 in air also becomes a risk factor due to CNS toxicity.

As mentioned above, because of the narcotic risk, in the late 1980s deep cave divers began to add some helium to their bottom mixtures. This worked well for some depth ranges, and the practice soon expanded to the use of trimixes with all three components controlled. This also allowed the oxygen fraction to be reduced, allowing lower PO_2s at bottom depth and making longer bottom times feasible from an oxygen toxicity viewpoint. Another factor in selecting the exact composition of the breathing mix was ease of mixing, using air as the major component. For a certain depth range a mix can be made by adding helium to air. The use of special mixtures made special decompression tables necessary, and these were developed. This technology quickly spread to deep wreck divers, who learned to do this same pattern with diver-carried gas.

Because these divers were “recreational,” they were not limited by having to comply with occupational safety codes. Their main motivation was to do extended range diving safely, and they were able to be quite creative in the process.

Oxygen-enriched air or “nitrox”

It is pertinent to mention another related development in scientific diving, and later recreational diving, starting a few years before technical diving. This is diving with oxygen-nitrogen breathing mixtures with more oxygen than air, referred to as oxygen-enriched air or “nitrox” or by compromise, “enriched air nitrox” (Hamilton , 1989; NOAA, 1991). The term “nitrox” paradoxically seems to focus on the nitrogen component of the mix, but the term refers to an oxygen-rich mixture. Diving with oxygen-enriched air provides advantages in decompression, either as longer time without the need for decompression stops, or faster decompression where stops are used. Although it is different from normal scientific and recreational diving practice, it does not in any way allow access to deeper depths, which is the focus of this paper, so is not discussed further here. Diving with “nitrox” or oxygen-enriched air as the only mix on a dive is not properly regarded as technical diving.

Comments on the terminology

Since there is possible confusion over the term “technical diving,” it is pertinent to define it. By one definition the minimal requirement of a technical dive, the characteristic that sets it off from other kinds of scuba-based diving, is that on a technical dive the diver uses more than one breathing mixture. Just diving beyond the limits defined for recreational diving is not enough to qualify as technical diving, especially if air is the only breathing gas. However, deep air diving using other gas mixtures and oxygen for decompression, for example, would be regarded as technical diving. Also, a dive with rebreather apparatus might be regarded as a technical dive.

In fact, British terminology, especially with respect to military diving, has regarded diving with rebreathers as “technical diving” for over half a century.

This paper focuses on diving in the 80 to 100 msw range. For this there is a reasonably uniform practice, and this requires using the appropriate breathing gas mixtures. Bottom mix is usually a “trimix” of oxygen, helium, and nitrogen, and intermediate mixes are usually oxygen-enriched air. Oxygen level is controlled to

maintain efficient decompression yet avoid toxicity. Thus a “technical” dive as we are using the term is essentially a “technical trimix dive.”

The term “trimix” is also used elsewhere in another sense. It may refer to the addition of a small amount of nitrogen to the breathing mixture to reduce the effect of the High Pressure Nervous Syndrome in a very deep saturation dive.

Previous technical trimix diving operations

In the 1970s Italian coral gatherers with the help of diving physiologists began performing dives remarkable similar to the technical diving practice described here (Zannini and Magno, 1987). Their practice included routine dives in the 70 to 100 msw range. Their breathing mix was 10% oxygen, 40% helium, and 50% nitrogen. Decompression procedures were based on a Haldane-Workman-Schreiner algorithm very similar to the one used for the procedures covered below, and the dive profiles appear to be similar in shape and duration, except that coral gatherers performed surface decompression in a deck chamber. Decompression from a 30 min dive to 80 msw required 140 min of decompression time, and about half that was on oxygen. In a series of 860 trimix dives no decompression sickness was reported.

The British Navy began a trimix program in the late 1970s, using a mix of 20% oxygen, 40% helium, and 40% nitrogen with a target depth of 15 min at 75 msw (Shields et al, 1978). Laboratory trials were used to develop parameters for a computational model (Shields et al, 1978), and trials at sea were conducted later (Shields et al, 1982). Efforts to work out a satisfactory decompression plan were essentially stymied because of excess oxygen toxicity, and the project was eventually discontinued.

Decompression from trimix dives

As mentioned, the key to implementing technical trimix diving was the ability to perform an efficient and reliable decompression that did not pose a substantial risk of oxygen toxicity. This was worked out with field trials (Hamilton and Turner, 1988) based on an algorithm that had been empirically developed and laboratory validated for extreme exposure air dives (Hamilton et al, 1988). Since that time the computational methods have been refined, and methods for handling oxygen exposure have been worked out.

Selection of the optimal breathing mixtures is a key part of planning a trimix decompression. For the bottom mix one wants enough helium to eliminate significant narcosis. However, the more helium in a trimix the longer the decompression; while this effect is moderate, it is felt to be important. Also, the divers who worked out these techniques regarded the cost of helium as significant, so they normally used only enough to get what they regarded as an adequate reduction in narcosis. There is some uncertainty involved in calculating the “equivalent narcotic depth” of a trimix. There is a common belief that the oxygen can be ignored as it is in making some decompression calculations, but the properties of oxygen say it should be even more narcotic than nitrogen. Unfortunately there is no way to know exactly how much oxygen is present in the cells of the nervous system that regulate narcosis. This topic is in need of further study. Limited data suggest that with regard to narcosis the oxygen should not be ignored (Bennett, 1970; Linnarsson et al, 1990).

A technical dive normally includes descent, time on the bottom, and ascent to the first decompression stop breathing a bottom mix with helium to avoid or reduce narcosis, and having the appropriate oxygen level. The ascent or decompression calls for one or more intermediate breathing mixtures, and usually ends with oxygen breathing at the shallow stops. The intermediate mixes are generally oxygen-enriched air (“nitrox”). This does two things. It allows a higher oxygen to be used, and it reduces the helium component. The diver after a bottom time on trimix will usually have a significant load of helium.

After the intermediate or “deco” mix the diver usually switches to 100% oxygen for the last two stops, normally at 6 and 3 msw. As long as the diver is breathing oxygen the last stop can be taken at the depth of the next deeper stop. That is, the 3 msw stop can be taken at 6 msw. This is often helpful if the sea is rough. This has been found to make no difference as far as the decompression is concerned, but taking the stop at the deeper depth does increase the oxygen exposure, and this has to be taken into account.

Decompression tables

As mentioned above, a key factor in making trimix diving accessible to a variety of recreational and scientific divers was the development of methods of decompressing. These began with custom tables calculated specifically for the dives to be done, including such details as following the profile of a cave, and adjusting the gases to those that would be optimal for the profile to be followed or that would be relatively easy to get. Other approaches have been developed including dive computers designed for trimix diving, and computer programs that allow divers or diving engineers or operations managers to generate their own custom tables. As sample of one of the early tables, from a set that is still in wide use, is shown in Figure 2. Because of the importance of oxygen exposure and the fact that mixtures are not always precisely mixed, this table calculates the oxygen as a range, with the decompression figured on the lower end, and the toxicity on the higher end of the oxygen range.

```
SAMPLE TRIMIX DIVE                                  DEPTH          75 MSW
RWH/DJK              91Aug07                        BOTTOM TIME    30 MIN
DA59T0.H00           MM11F6.DCP                     BOTTOM MIX     17TX50
                                                    BOTTOM PO2   1.45 BAR
DEPTH STOP DECOM        PO2.RANGE                   Times are in minutes
 MSW  TIME TIME MIXTURE BAR   BAR COMMENTS
_____________________________________________________________________________
  00    00   00 AIR     0.21_0.21 DESCEND AT A COMFORTABLE RATE
        00   00 17TX50  0.16_0.17 BREATHE 17TX50   FROM SURFACE
  75    30   00 17TX50  1.36_1.45 ASCEND TO FIRST STOP AT _20 MSW/MIN
  36    02   04 17TX50  0.74_0.78 FIRST STOP: ASCENT RATE NOW _10 MSW/MIN
  33    02   06 36EANX  1.51_1.55 SWITCH TO EANx INTERMEDIATE MIX 36EANX
  30    01   08 36EANX  1.40_1.44
  27    01   09 36EANX  1.30_1.33
  24    03   12 36EANX  1.19_1.22
  21    04   16 36EANX  1.09_1.12
  18    05   22 36EANX  0.98_1.01
  15    07   29 36EANX  0.88_0.90
  12    16   45 36EANX  0.77_0.79
  09    10   56 OXYGEN  1.71_1.90 BREATHE O2, 9 MSW TO SURFACE, RESTING.
                                  O2 CYCLES: 20 MIN ON, 5 MIN OFF
  06    20   76 OXYGEN  1.44_1.60
  03    31  107 OXYGEN  1.17_1.30
  00    00  108 AIR     0.21_0.21 REACH SURFACE
                                  TOTAL TIME = 02:18 HR:MN
                                  DECOM TIME = 01:48 HR:MN

                                         OTU =  188 VC DROP =_1.1%
```

Figure 2. Sample trimix table. This format shows the stop depths and times, with the mix names and the range of oxygen used, plus operational comments on how to run the dive. This table uses oxygen at 9 msw, breathed in cycles; this is considered too deep for oxygen under most circumstances.

Oxygen in decompression

It has been know for some time now that oxygen is beneficial to decompression (Behnke, 1942; 1955; 1967; Lambertsen, 1967). One of the characteristics of technical diving is that it takes full advantage of oxygen. This requires that oxygen be used in the decompression calculations, and further that methods for tolerating these oxygen levels be an integral part of every operation. The latter point can be stated another way, that procedures for avoiding oxygen toxicity always be used.

The use of oxygen is integral to the basic technical trimix dive pattern; it is implemented by adjusting the level of oxygen in the breathing mixes at the various stages throughout the dive. Oxygen in the bottom gas is kept at as high a level as it can be, consistent with its toxicity. Wise technical divers do not push the oxygen limits in the bottom mix because the diver is usually exercising (see next section), and during that part of the dive is necessarily at the farthest distance from the surface. After the diver leaves the bottom and ascends through the first few short stops the mix is usually switched to an intermediate or “deco” mix. This mixture is selected to be at nearly the highest tolerable level during the first stop it is breathed, but its oxygen partial pressure is reduced at subsequent stops. Sometimes if the dive is deep and/or long a second intermediate mix

is used so that the oxygen can once again be increased to the optimum level. As mentioned, the final stops near the surface are taken on pure or almost pure oxygen.

These changes of breathing mix are needed for the open-circuit scuba mode of diving, but with a fully-closed, oxygen-controlled rebreather the oxygen level—the partial pressure—can be set at an optimal but tolerable level such as about 1.4 atm and kept there throughout the dive. This is more efficient than switching mixes.

Another less important benefit of switching gases during decompression is to change the inert gas. Most computational models for computing decompression tables show an increased elimination of one inert gas from the body when the diver is breathing a mix which is rich in a different inert gas. Thus an oxygen-nitrogen intermediate mix is favorable when the diver's body is loaded with helium.

Oxygen tolerance

Since optimizing decompression procedures is very much a matter of optimal use of oxygen, dives are usually planned so that the diver uses the maximum level of oxygen consistent with avoiding toxicity. By way of review, two specific forms of oxygen toxicity are of concern to divers. The most important of these is toxicity to the central nervous system that can result in an epileptic-like convulsion. CNS toxicity can follow short exposures, minutes, to a relatively high oxygen level. A slower moving toxicity affects many other parts of the body, including peripheral nerves, but is manifest primarily in the lungs. This has been called "pulmonary" toxicity because the development of toxicity effects can be monitored by measurements on the lungs, changes in vital capacity. A more general term is "whole body" toxicity, to recognize the general effects as well. This toxicity results from longer exposures, many hours or days, to levels of oxygen above normal but less than those required to cause CNS effects.

Avoiding CNS toxicity

The main tactic to avoid CNS toxicity is by means of **limits**. The traditional way this is implemented is to limit exposure to a dose believed to be tolerable and without problems. A "dose" is an exposure level for a given time. This is usually implemented as a limit on exposure duration at a given oxygen partial pressure. Tolerance limits are usually determined empirically, either by means of explicit experiments (e.g., Butler and Thalmann, 1984, 1986; Butler, 1985, 1986) or by an accumulation of experience.

The dive operation has to consider factors that affect oxygen tolerance as well as the exposure doses. For example, exercise and breathing a dense gas tend to make a diver more susceptible to CNS toxicity. Extremes of temperature also reduce tolerance, as does immersion. There are significant individual factors, both between different individuals and in the same individual at different times.

For some years the limits used by the U.S. Navy were the only ones available. These served a purpose and defined the concept, but they were not physiologically realistic in terms of present day understanding. A set of limits drawing on more recent data has been prepared by NOAA, the National Oceanic and Atmospheric Administration of the U.S. Department of Commerce. These widely used procedures are published in the 1991 edition of the NOAA Diving Manual and are essentially unchanged in the 2000 edition.

Whole body or pulmonary toxicity

Another classical symptom of oxygen poisoning in addition to those of the CNS is "pulmonary," the result of oxygen's effect on the lung. This takes hours or longer to develop from exposure levels that are usually be lower than those that cause CNS symptoms; it is seen as chest pain or discomfort, coughing, and a decrease in vital capacity. Because this can be measured with careful technique, this tends to focus this form of oxygen toxicity on the lung, but there are a collection of symptoms in addition to the lung problems that

include paresthesia, headache, dizziness, nausea, effects on the eyes, and a dramatic reduction of aerobic capacity. These symptoms have been found to be, in time, fully reversible. The type of long, low-level exposure used in technical trimix diving is not likely to result in these symptoms unless the diver has to be treated for decompression sickness.

Equipment for technical diving

As suggested by its name, technical diving involves some "high tech" equipment, but much of the equipment involved in technical diving is the same as for ordinary diving, but perhaps of higher quality (regulators, thermal protection) or greater range (depth gauges, tanks, etc.), etc. Some equipment items are specialized for the specific mission and are not specific to technical diving, such as survey equipment or lights for cave diving, or a diver propulsion vehicle ("scooter") where long swims are to be done. Technical divers do not have the option that is more or less available to sport scuba divers to ascend to the surface when in trouble, so most technical divers have some degree of redundancy for each item or function.

In the early days of technical diving in order to carry enough gas for long dives divers often overpressurized their tanks. Now larger tanks that take higher pressures are readily available. The manifolds and valves to connect such tanks need not be fabricated by the user, but can now be purchased ready made. They are configured to conserve the remaining gas if a single regulator or valve fails. High quality regulators are attached to each tank. For the deeper dives there may be a problem with the depth range in which a mix can be used, such that the intermediate "deco" mix has too much oxygen to be used at bottom depth for more than a short time, and perhaps the bottom mix has too low an oxygen level to be used at the surface; provisions have to be made to ensure that the gases are breathed in the right sequence. In fact, proper identification of all mixes can be as important as having the right mix, because breathing a mix at the wrong depth can easily be a fatal mistake. One diving group puts the maximum operating depth, "MOD," on each tank in big letters. Various safeguards prevent the wrong regulator from being used. A small "pony bottle" of extra gas suitable for the deeper part of a dive provides a means of escape to a safe area. Gas analysis equipment for checking mixes is essential for field operations.

Both conventional wet suits or dry suits are used, with the choice influenced by the conditions of the dive. Dry suits are made even more efficient by filling them with argon, which has a lower thermal conductivity than air and especially lower than helium.

Buoyancy control is especially important in technical diving, because unintended ascent can be dangerous, and because the gear may be quite heavy. A dual-bladder buoyancy compensator would be used with a wet suit, but a dry suit may act as additional buoyancy. It is felt that dehydration makes a diver more susceptible to decompression sickness, so divers are advised to stay well hydrated; because of this for very long dives some method of handling urine is needed. The long stops of long decompressions are often carried out in underwater decompression stations that may be made of an inverted tank or well-anchored air-filled lift bags. Divers with a high oxygen exposure sometimes use full-face masks instead of mouthpieces to improve chances of survival in the event of a convulsion.

Another aspect of buoyancy control has to do with decompression. Divers in the open sea carry an inflatable float or lift bag with the necessary lines to manage their own decompression. Where there is a current the divers may decompress while hanging from a float, and the boat follows the floats to pick up the divers when they surface. An essential part of the rig of open sea technical divers is rescue and location equipment, to help the dive boat find a diver and in the event that that does not happen, to help rescuers locate a lost diver.

Training and organization

As one might expect from the description, technical diving demands intense dedication and discipline, and special training (Irvine, 1995). Although training is available, one thing lacking in the technical community is a set of peer-developed operating standards. Diving with this degree of commitment and risk requires teamwork, and those organizations or groups that have developed their own standards have been effective and safe, whereas there have been accidents among the independent and unsupported diving teams or individuals.

Some operations conducted with technical diving

To further emphasize that technical diving belongs in the real world of diving we her e review some operations that have been conducted with open-circuit scuba technical diving techniques. We are not necessarily endorsing these operations, but rather are just describing them to provide an idea of what has been done.

The first operation in this mode of diving was a series of dives conducted in the aquifers on north Florida, an early operation by the Woodville Karst Plain Project. These divers conducted 27 man-dives at 60 to 75 msw for times up to 90 min (Hamilton and Turner, 1988). Later operations by the same project in Wakulla Springs involved swims of up to 90 min at a depth of 87 msw (Irvine and Hamilton, 1995).

Shortly after these techniques became available divers began more actively to dive the wreck of the *Andrea Doria*, which lies on her side at about 70 msw depth 160 km off Nantucket in the north Atlantic. Most dives by recreational divers on the *Andrea Doria* as they are normally conducted are not really "operations," in the sense that they are not organized with a leader and an operational plan, but rather are individual divers or pairs of divers who dive from charter boats whose purpose is to deliver the divers to the site but not to supervise or manage them. Despite the lack of operational control, hundreds of successful dives are done each season to the *Doria*. There have been a number of fatalities among trimix divers; most of these have been "operational" accidents that would not be likely to happen on a closely supervised team operation, but many of them are not explained. It is not uncommon for as many as 100 repetitive trimix dives to be done on this wreck over a 3 day period, with little or no decompression incidents occurring. A typical "season" can see as many as 750 dives on the *Doria*.

During the summer of 1994 some 120 technical trimix dives were made on the wreck of the *Lusitania*, which is located at about 100 msw just off the west coast of Ireland. Significant about this well-organized operation—*Starfish Enterprise*— was that from a team of 12 divers there were always two who were not diving but were serving as standby diver or topside supervisor. The team had a pentagon-shaped rig to hang on during decompression, and the divers were monitored; detailed records were kept on both divers and equipment (Gentile, 1995). The operation was continued in 1995. This time the organization paid off in the successful rescue of a diver who had an oxygen convulsion while decompressing at 6 msw; no special circumstances were found that might explain the convulsion.

Two expeditions have been conducted on the *Brittanic*, sister ship to the *Lusitania*. She lies at 120 msw in the Mediterranean offshore Greece. Because the vessel is covered by the rules for antiquities, no salvage was done, only photography.

Several of the more high-profile technical diving operations have been on the *USS Monitor*, a historically important Civil War vessel at about 60 msw off Cape Hatteras, NC, by NOAA, the National Oceanic and Atmospheric Administration of the U.S. Department of Commerce. Certain things about these operations made them significant. First, they were done by NOAA and contract divers using decompression tables prepared especially for NOAA, and they represent official government recognition of technical diving

practice. Some dives were conducted off a U.S. Navy vessel, another “first” in the development and growth of technical diving.

Most of the early dives on the USS Monitor were conducted by civilian volunteers who employed the use of technical diving to accomplish specific goals. These dives were conducted with a NOAA archeological manager on board, but with the team managing their own diving operations. One specific operation in 1997 utilized only 8 persons, yet they were able to conduct 12 hours of on-the-bottom time achieving over 600 measurements, 6 hours of digital imagery, and over 900 frames of still images, which could not have been done nearly as well or possibly at all by divers breathing air.

Application to military operations

Technical diving techniques make the depth range to 100 msw readily available to properly trained and equipped divers using open circuit scuba equipment, for bottom times of up to 30 min and with inwater decompression times of 1 to 3 hr. Greater depths and times are possible, but will of course cost extra decompression time and require sufficient gas. Advanced military development might include a variety of gas staging techniques, gear configurations, propulsion and communication hardware, computers, and mission-related equipment. There is room for improvement in decompression and gas manipulation techniques.

It makes good sense for military operations using divers to include technical diving capability.

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Into the Theater of Operations: Hyperbaric Oxygen on the Move

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Abstract

Introduction/rationale: Hyperbaric support for mass casualty injuries resulting from military operations or catastrophic events (i.e., earthquakes, tornadoes, etc.) presently relies upon host country, or at best, local hospital facilities for administration of this therapeutic modality. To get HBO as close to the point of wounding as tactically possible, thus advancing our wartime readiness mission, and addressing the Joint Health Service Support Plan: Vision 2010, easily transportable HBO systems were sought to support deployed aeromedical evacuation operations from remote theaters of operation. The Emergency Evacuation Hyperbaric Stretcher (EEHS) system provides a ready means of quickly initiating treatment at the incident site and transporting the casualty under pressure to a rear–echelon treatment facility, reducing the risks of permanent injury to warfighters suffering from conditions benefited by treatment with hyperbaric oxygen. **Methods and Results:** Pursuant to that goal of a portable chamber system supporting deployed operations a joint service (USAF/USN) collaborative venture was initiated through the Department of Defense funded Foreign Comparative Testing Program. The Navy conducted a battery of environmental, quality assurance and operational performance evaluations of the system ultimately leading to the required American Society of Mechanical Engineer (ASME) certification for human occupancy of a pressure vessel. The Air Force component of this initiative performed aeromedical and human factors evaluations of the system leading to aeromedical approval for flight. Exhaustive evaluation of the EEHS demonstrated a robust, yet lightweight and portable chamber system capable of staged-storage, deployability, rapid treatment initiation, and transport of casualties. Current endeavors are developing instructions for deployment and integrating the EEHS into the operational community. **Summary:** Historically, during contingency operations Hyperbaric Medicine relied upon CONUS, or at best host country, hospital facilities for administration of this important treatment modality. This will no longer be the case. Since we will be able to initiate treatment for the combatant in-theater, we will *preserve the combatant's optimal mission capability* by reducing the magnitude of the injury, and shorten the duration of recovery from battlefield injuries.

Introduction

Hyperbaric Medicine (HBO), in private or civilian practice, has a well established primary role in the clinical treatment and resolution of several chronic disease conditions as well as an adjunctive role in a few acute maladies (5, 7, 15). In military medicine the historic role for HBO has long been, almost exclusively, associated with Decompression Illness (DCI) and the resolution of the physical manifestations evolved nitrogen gas produces on individuals injured by misadventures related to diving or high altitude exposure (11, 12). While this near exclusive association to DCI leveraged the preservation of this modality as a military medical care asset, the landscape of military medicine, as well as advances in science and technology, have focused attention on the greater potential role HBO can posture in military—combat casualty—medicine. The impact this medical subspecialty may have in military readiness could be significant.

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Much like the reincarnation clinical Hyperbaric Medicine in the United States experienced in the late 20th Century, through hard work of visionaries like Jefferson Davis, Dean Heimbach and others, there is a new investment in the 21st Century future of this modality in critical care medicine—even more important its advancement into the theater of operations. Research endeavors during the past five to eight years indicate HBO can have an influential role in many acute traumatic injury conditions (14, 16) sustained on the battlefield. Very recent investigative efforts are exploring the significant beneficial impact HBO has on injuries sustained from conventional projectile ordinance, and directed energy and biological, mass-effect weapons that are being developed for tomorrow's military operations.

However, to achieve the impact HBO will provide for the injured combatant, a change in the delivery technology must occur. The discipline of Hyperbaric Medicine up to now has limited operational participation due principally to a lack of treatment facilities available for in-theater/field support of combat casualty care and management. The fabrication time, size and cost of contemporary steel pressure vessels made forward deployment impossible. It is critical to the efficacy of hyperbaric oxygen that it be initiated quickly (within 4 - 6 hours) following injury. Therefore, to get HBO as close to the point of wounding as tactically possible, thus advancing our wartime readiness mission and addressing the Joint Health Service Support Plan: Vision 2010, alternate chamber technologies were pursued.

The challenge to the technology was to meet the concept of operations (CONOPS) requirements for low-cost, small cube size, modularity and flexibility needed for deployed aeromedical operations. Moreover, the candidate technology needed to provide a means to evacuate, under pressure if necessary, combatants to and from remote theaters of operation as quickly as possible. Two chamber technologies are currently in testing and/or development. First, for multiplace HBO treatment systems, a concrete/resin composite materials construction that can be quickly (~1month) placed at contingency hospital locations. Second, a modular-panel steel or composite-materials chamber that can be pallet-transported far-forward for deployment or contingency hospital placement and set-up and operating within 24 to 48 hours.

To satisfy the need for a truly portable system that provides safe aeromedical evacuation of theater casualties to a definitive medical hyperbaric treatment facility, a joint a collaborative bi-service effort—United States Air Force (USAF) and United States Navy (USN)—was funded by the Department of Defense, Foreign Comparative Testing (FCT) Program. The focus of this endeavor for both the USAF and USN was to obtain a portable and collapsible hyperbaric system. The principal USN requirement was access for emergency treatment of diving casualties including the capability for a Treatment Table 6A (8). The USN intent is to integrate this system into the Submarine Rescue Diving and Recompression System and the Transportable Recompression Chamber System as well as on-site resolution of DCI at remote dive sites and transfer of diving casualties under pressure. The USAF interest in this technology is to address the near-term need for emergency treatment of altitude induced DCI at sites where host nation or local support is not tenable. However, the USAF has a visionary interest of addressing a long-term need for a deployable system that could be quickly transported to remote, in-theater positions and quickly evacuate injured soldiers to a definitive treatment facility for continued recovery from a myriad of acute traumatic injuries. Then, stabilized patients could be transported safely while pressurized by gurney, ambulance, or aircraft, thus quickly initiating treatment close to the incident site and permitting evacuation, thus reducing the risks of permanent injury to warfighters suffering from conditions benefited by treatment with hyperbaric oxygen.

Procedures:

The FCT evaluation initially identified two candidates systems to be evaluated, one obtained from the United Kingdom, SOS Ltd., and another from Giunio Santi Engineering, Italy. During the program's early evaluation phase it became evident that the latter system would not meet DoD needs, thus the SOS, Ltd. System was the only candidate system advanced to the final testing phase described herein. The emergency evacuation/treatment hyperbaric stretcher (EEHS), a system currently commercially available, is a collapsible vessel constructed of composite materials, approximately 30 inches in diameter, and about seven feet long, when inflated. The pressure vessel proper, excluding hoses and gas supplies, weighs approximately 150 pounds and is self-contained, easily transportable, and capable of withstanding at least 3 Atmospheres Absolute (ATA). Current pressurization procedures employ available air sources (SCUBA cylinders). EEHS is easily set up and pressurized in minutes with minimal training and has a built-in breathing system for oxygen administration with overboard dumping capability during air transport.

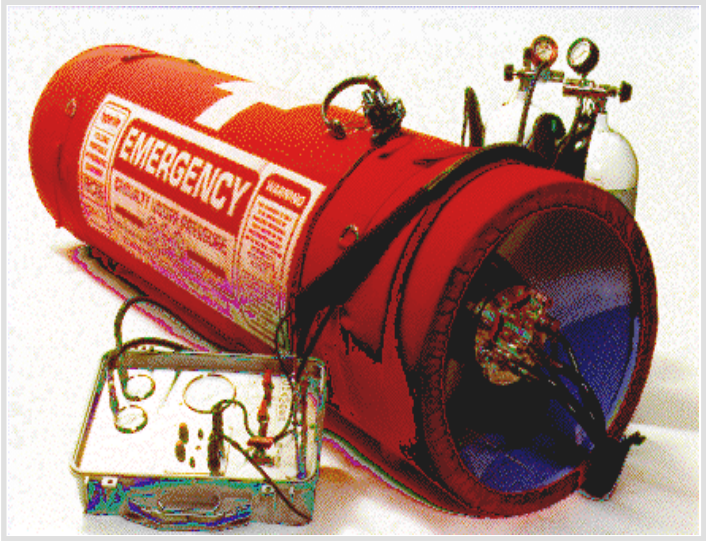

Fig. 1. Emergency Evacuation Hyperbaric Stretcher (EEHS)

Three aspects of the deployable hyperbaric stretcher were evaluated during this collaborative evaluation venture. The USN contribution to the effort was the conduct of a battery of evaluations including component system quality assurance audits, environmental and performance evaluations. The USAF complement to this venture was to demonstrate aeromedical transport compatibility assuring the EEHS and all its components were safe for transport aboard USAF, and to the extent possible, USN and US Army fixed and rotor wing aircraft. Tests by the USAF included a series of system environmental challenges, and several aircraft fit and function evaluations. Both the USN and the USAF performed operational evaluations to assure the EEHS would be usable in a deployed operational environment. The objective of these evaluations was to provide DoD with a hyperbaric stretcher system that meets the needs of the forward deployed units, as well as provide access to hyperbaric oxygen for victims of natural or terrorist caused mass casualties.

In the United States, Canada, 58 recognizing countries and for this activity the DoD, vessels wherein a human is exposed to increased ambient pressure must be manufactured and perform in accordance with a standard set by the American Society of Mechanical Engineers (ASME) (3, 13). Furthermore, to ensure that the designer and fabricator of a medical hyperbaric vessel employ a minimum safety standard for these vessels the Main Committee for Pressure Vessels for Human Occupancy (PVHO) developed rules (PVHO-1) for guiding construction (10). While the U.S. Food and Drug Administration (FDA) regulates hyperbaric vessels as Class II medical devices, any vessel meeting the PVHO-1 specifications will have an easier time achieving FDA approval. The standards cited above apply generally to metallic vessels. Recent technological advances with flexible, nonmetallic vessels—the focus of this activity—led to application of a Case exception to the rules defined for metallic chambers. So, it is to the PVHO Code Case 6 standard that the USN challenged the EEHS to meet assuring a well-constructed and safe operating system for deployable use.

Tasks performed by the USN in pursuit of Code Case approval of this system included, but were not limited to, the following tests:

1. Cyclic hydrostatic pressure test simulating repetitive usage. This evaluation assessing long term performance and endurance consisted of more than 4000 cyclic pressurizations from baseline to the design pressure of slightly more than 3 ATA.
2. Extreme temperature storage and inflation to evaluate the system's ability to tolerate environmental stress of cold (-40^{o}C) and heat (+60^{o}C). Following exposure to the respective thermal stress, the system was either warmed to –18^{o}C from -40^{o}C, or cooled to +49^{o}C from +60^{o}C, then inflated to operating pressure and monitored for performance.
3. Hydrostatically pressure tested to at least five times the rated pressure of the vessel to ensure a proper safety factor is present.
4. Solar radiation to evaluate performance following prolonged sunlight exposure (300 hrs; bandwidth 0.28 to 3.0 μm and >11 W/m2).
5. Salt fog to evaluate tolerance for exposure to high salt environment (6% sodium chloride solution with specific gravity of approximately 1.04).
6. Vibration (11-2000 Hz) to test susceptibility to component breakdown under random and sinusoidal vibration (30 min x, y and z axis).
7. Off axis drop test to evaluate integrity against damage from accidental drop (45^{o} from 3 feet elevation).

Fig. 2. Containerized EEHS and components

All the aforementioned tasks included a thorough inspection of the system at least prior to and following each challenge. Often, intermediate inspections were conducted during the challenge to assess pressure and integrity of the system to the challenge. Finally, to complete the assessment, and in compliance with PVHO-1 requirements, a free and unbiased inspection of the material quality assessment plan, manufacturing operations and quality control assurance was performed.

Supplementary to the materials and components tests, pursuant to the ASME-PVHO requirements, the Naval Experimental Diving Unit (NEDU) performed several functional and operational evaluations to assess the suitability of the system for deployment. The complete description of the tests and results are chronicled in a report of that activity (9). Briefly, the operational tests were directed at a functional assessment including: a) ease of set-up and transfer of system into a multiplace chamber, b) transport evacuation from a remote shore based location to a treatment facility, c) transport using a small (36-foot length) boat to a treatment facility, and d) transfer simulation from a primary treatment chamber into EEHS, then transfer to a remote treatment facility. In addition to these unmanned evaluations several manned exposures were performed. The focus of these manned evaluations was to identify any human factor issues needing special training provisions or component modifications prior to deployment.

The USAF contribution to this collaborative venture was the appraisal of the EEHS for air transportability certification and approval for use in-flight, thus providing access to aeromedical evacuation. Similar in consideration with regard to safety aspects of materials and fabrication defined by ASME-PVH, safety considerations are defined for air transport of medical instruments and devices. These requirements are defined in Air Force Instructions (AFI) concerning General Flight Rules (1) and Aeromedical Evacuation Equipment Standards (2). The Air Force Research Protective Systems Branch was charged with the responsibility for evaluating and determining acceptability of medical equipment to be used aboard fixed and rotor wing aircraft.

The matrix of tests conducted, some of which were similar to those performed by the USN and repeated as a part of this evaluation (i.e., vibration, hot and cold storage and system performance), to attain the air transportability certificate for the EEHS included:

1. Baseline system performance to familiarize the evaluation team with the system and to note any potential safety issues related to the aeromedical evacuation environment.
2. Electromagnetic interference evaluation of electrical components of the system to assess potential interactions generated by the system influencing the aircraft, or, conversely aircraft produced electromagnetic forces affecting operation of the system.
3. Altitude exposures at a flight level of 15, 000 feet to assure monitoring components and systems function are reliable in this hypobaric environment.
4. Rapid decompression of EEHS whilst in operation to approximate stresses imposed during an emergency or accidental decompression of the aircraft during transport of a patient. This test was operated three separate times from a base of 8,000 feet decompressed to 45,000 feet at time intervals of 60s, 7s and 1s, respectfully.
5. Vibration curves representing lifetime exposures to three different classes of aircraft signatures were performed. Random frequency profiles (20 to 2000 Hz) and sinusoidal-on-random frequency curves (10 to 500 Hz) were employed for each of the three major axes of the system. All components were active during this test and performance assessments were carried out at 15-min intervals for the 60-min test. This evaluation was conducted to assure component in-flight function and reliability, and to identify any patient safety and welfare issues related to in-flight transport.

Finally, and an equally important adjunct to the static aeromedical evaluation tests mentioned above, was the airborne performance evaluations and analysis of the EEHS for placement, security, fit and function for several airframes. Principal among these evaluations included detailing methods for in-flight security of the system for safe travel and for emergency conditions including air turbulence and in-flight emergencies. Also, another important assessment of this task was to exercise the patient/operator communications issues in the noisy aeromedical transport environment. The comprehensive results of this evaluation are contained in a Technical Report composed by the executing agency (4).

Fig. 3. EEHS Extended Ready for Patient Ingress

Discussion:

The USAF Aeromedical Evacuation has the DoD responsible mission to provide tactical and strategic aeromedical evacuation of casualties for all US military services. Currently, the USAF has no available system to address the need for safe aeromedical evacuation of theater casualties suffering from decompression illness, arterial gas embolism, carbon monoxide poisoning or gas gangrene for hyperbaric treatment. Furthermore, the USN has an identified need for a portable system to evacuate casualties from submerged disabled submarines (DISSUB) and remote dive site transfer of diving casualties under pressure. These needs led to a joint collaborative, non-developmental, evaluation of a portable hyperbaric system. The USN conducted fabrication and materials certification tests, and the USAF was responsible for achieving aeromedical transportability certification.

The combined USN ASME-PVHO and USAF air transportability certification evaluations previously described provided a rigorous baseline and detailed assessment of the capability of the candidate hyperbaric

evacuation/treatment system. The EEHS performed well in all aspects, manned and unmanned, of the testing program. Comprehensive discussion of the results of the USN and the USAF test programs are available for review. Briefly, the system met or exceeded the major benchmark requirements for ASME-PVHO-1 CODE and Aeromedical transport certification and approval. There were some minor-to-moderate adjustments made in sub-components of the system, but in summary, the system performed to required mission objectives. Notwithstanding the thorough nature of the performed tests, there are substantial implementation and procedural issues remaining to be addressed. Some of these issues are considered in a report by Latson and Flynn () concerning use of the EEHS in submarine escape and rescue. With regard to USAF aeromedical evacuation mission objectives, a draft report is being prepared.

Now that a viable transportable hyperbaric stretcher system is available for deployment, the next level of integration into the operational community is provision of technical and operational consultation to the deployed units. For DISSUB and remote site support, the USN relies principally upon master divers for operation and performance of the treatment tables for the injured individuals. The USAF, given the therapeutic mission requirements for the EEHS system, requires flight surgeon (trained in hyperbaric medicine) oversight for operation and transport accompaniment of the injured individual. Toward that objective a Concept of Operations for the Hyperbaric Care Air Transport (HCAT) Team has been drafted (6) as a Unit Type Code and is actively seeking sanction. The HCAT team would be composed of one Hyperbaric trained physician, one hyperbaric critical care nurse, and one aerospace physiology technician. Expertise of this team would carry the EEHS system (HCAT-A) when deployed. In general, the HCAT team would assist the aeromedical evacuation mission providing a limited, rapidly deployable resource to oversee hyperbaric care and offer expert counsel for the management of injured patients in transit to the definitive care target destination. Presently three HCAT Teams are being recommended.

Summary:

Historically, during contingency operations Hyperbaric Medicine relied upon Continental United States (CONUS) or at best host agency hospital facilities for administration of this important modality. This will no longer be the case. Since we are able to initiate treatment for the combatant, in-theater, we will *preserve the combatant's optimal mission capability* by reducing the magnitude of the injury, and shortening the duration of recovery from many battlefield injuries. Moreover, HBO will become an important player in DoD humanitarian efforts in support of casualties sustained by individuals from natural disaster and terrorist activities.

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The Relevance of Hyperbaric Oxygen to Combat Medicine

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At the Davis Hyperbaric Laboratory, Brooks AFB, TX we have embarked on a series of research protocols designed to determine the efficacy of hyperbaric oxygen treatment (HBO) in combat wounds. Our research has been directed towards finding ways to minimize the extent of combat injury, reduce the consumption of medical resources, speed healing of combat wounds, and improve the result in the healed wound. In this presentation the basic science related to the use of HBO in treating combat wounds will be presented and our current research efforts will be discussed.

Actions of HBO

Several of the cellular and molecular actions of HBO make it an attractive adjunct to combat wound treatment. Hyperbaric oxygen therapy has been shown to expedite wound healing by hastening angiogenesis, increasing or restoring the bactericidal properties of polymorphonuclear lymphocytes and macrophages, speeding the migration of macrophages, and hastening wound epithelialization and contraction[1,2,3]. These effects have been clinically useful and proven for diabetic wounds, poorly vascularized tissue, infected tissue, osteomyelitis, and irradiated tissue[4,5]. In full thickness, skin grafts and flaps, hyperbaric oxygen has been shown to speed healing and enhance flap take and graft survival, especially when compromised[6,7,8,9,10,11]. In burn patients undergoing grafting procedures, hyperbaric oxygen has been shown to shorten hospital stay, enhance donor site and graft healing, and reduce the number of grafting procedures required for wound closure[12,13,14]. The salvaging effect of hyperbaric oxygen on failing flaps and full thickness skin grafts has been demonstrated in numerous studies[15,16,17].

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HBO is capable of favorably influencing a number of cytokines and growth factors integral to wound healing. When administered after wounding, HBO up-regulates collagen synthesis through pro-al (I) mRNA expression[18]. In rabbit ear wounds HBO has been shown to up-regulate mRNA for the PDGFβ receptor[19]. This effect has been further born out in clinical studies. In ischemic flaps HBO up-regulates fibroblast growth factor (FGF) causing an increased effect over that seen with fibroblast growth factor alone[20]. In situations where FGF is ineffective, HBO can render it highly effective[21]. This is an effect different than up-regulation. In patients with Crohn's disease IL-1, IL-6, and TNFα levels were diminished during HBO treatment[22]. TNF levels in normal rats became elevated after a single exposure to HBO[23]. Perhaps under different physiologic conditions HBO may cause up or down regulation of cytokines. Vascular endothelial growth factor (VEGF) is up-regulated by hypoxia, yet HBO also up-regulates this factor[24]. Transforming growth factor-β (TGF-β1) and platelet-derived growth factor ββ (PDGF-β) are synergistically enhanced by HBO[25].

The HBO paradox: up-regulation of events stimulated by hypoxia:

HBO thus acts in a paradoxical manner. Many of the processes that are stimulated by hypoxia are accelerated by the administration of HBO. The following biologic processes and factors are stimulated or up-regulated by hypoxia, and by HBO: angiogenesis, collagen synthesis, and osteoclastic activity. One known mechanism is that by which fibroblasts are stimulated to make collagen through peroxides, which occur, in the hypoxic wound and during HBO treatment[26]. Therefore the peroxides generated by HBO mimic one of the stimuli found in hypoxia. Another mechanism is the stimulation of cytokines by hypoxia and further upregulation of these cytokines under the hyperoxia, which occurs during HBO treatment. This is the case for some interleukines and for tumor necrosis factor (TNF). There is some confusion on the exact timing of the release of growth factors and cytokines; in one study VEGF, TNF-α, and TGF-β occurred in hypoxic wounds after they had been released in normoxia. VEGF, TGF-β, and PDGF-β have bi-phasic release patterns; their release is stimulated by hypoxia and hyperoxia, but is lowest during normoxia[27,28]. Furthermore, the activity of released VEGF is further enhanced during hyperoxia, especially in the presence of lactate[29]. It is clear that biologically active chemicals such as cytokines and growth factors have a complex array of stimuli to up and down regulate activity. Oxygen, cytokines, and biologically active chemicals and metals appear to have key roles in the expression of healing. As we learn more about the role of oxygen its role appears to be much more detailed than in a simple mass-action equation.

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In reperfusion injury, HBO diminishes tissue damage caused by leukocyte activation. In muscle this effect of HBO is mediated by inhibiting synthesis of guanylate cyclase (cGMP) and subsequent leukocyte β–2 integrin dependent adhesion[30,31]. This adhesion of leukocytes to vessel walls initiates the reperfusion injury inflammatory cascade[32,33]. In cardiac muscle the action of leukocytes is thought to be largely responsible for the reperfusion injury of myocardial infarction[34]. When the activation of leukocytes is blocked, they do not adhere to the β–2 integrin receptor on the surface of vascular endothelium and reperfusion injury is prevented[35,36]. HBO acts to prevent this activation and adhesion[37].

In addition to the above mechanisms the primary reason for administration of HBO is the oxygenation of poorly vascularized tissue – a situation present in at least a small way in nearly every wound. In addition to the provision of tissue oxygenation levels many times the normal level, oxygen is a potent vasoconstrictor and is capable of reducing the edema in injured tissue, facilitating blood flow and further oxygenation.

Uses of HBO for combat wounds

With these cellular and molecular effects in mind we have been looking at ways of applying HBO to the clinical situations encountered in combat. We developed a rat skin graft – open wound model which allowed us to test the effectiveness of HBO in treating open wounds which had been partially covered with mesh grafts. We saw no difference other than a slight increase in granulation tissue in the HBO treated group at one week, probably due to technical problems with the model and the short time period to evaluation.

We have hypothesized that HBO will shorten the time to healing of split thickness skin grafts by increasing the tensile strength of these grafts. This would allow for earlier mobilization and discharge of grafted patients. In the pig model we have developed we will also be able to test a number of treatments for open wounds designed to shorten epithelialization times.

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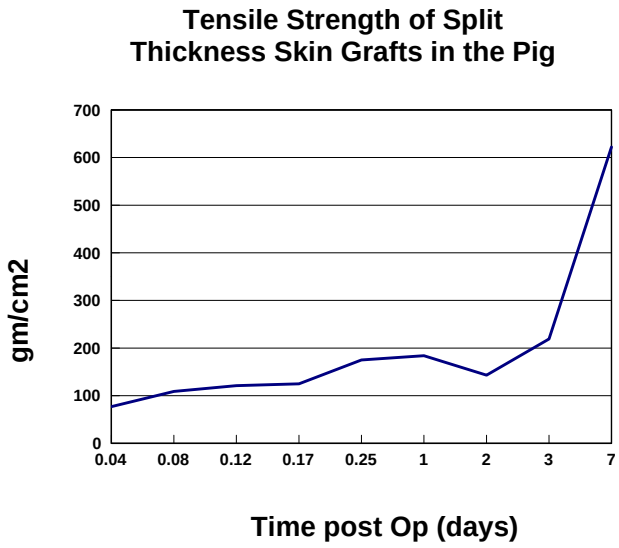

We have begun two protocols testing the effect of HBO on the healing of fractures in long bones. In our clinical protocol we are testing the effect of HBO on the time to fracture healing in patients with lower extremity fractures. It is too early to assess results but we are hypothesizing that we will see a 20% reduction in healing time with a lessened need for secondary procedures and a lower complication rate in the HBO treated group. In a rabbit study we are testing the tensile strength of the rabbit tibia after osteotomy and compression plate fixation in control and HBO treated groups.

We have postulated that HBO will reduce the recovery time in nerve injuries and possibly improve the end result based on animal studies showing that nerves subjected to division, ischemia, and crush injury recover faster when treated with hyperbaric oxygen, axonal growth is stimulated, and the end result of nerve injury is superior to those animals not treated with HBO[38,39,40,41]. We have developed a post radical prostatectomy protocol investigating the incidence and rate of recovery of impotence following the procedure in HBO and control groups. In addition we have carpal tunnel syndrome and nerve laceration protocols under consideration.

In our facility we see a large number of chronic open wounds from a variety of causes – diabetes, peripheral vascular disease, and radiation are the major contributors. HBO has a role in accelerating the healing of these wounds, but we have very little knowledge on the interplay of cellular and biochemical events in wound healing and how these are affected by HBO. We have designed a human study and two rodent studies to evaluate the role of growth factors and biomarkers in wound healing and their ability to predict a favorable result. In our human work we have found that individual patients have slow and fast healing phases, sometimes alternating, and that the appearance of nitric oxide by products in the urine is a reliable predictor of wound closure.

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HBO has long been known to favorably affect the result of muscular compartment syndrome, lessening the degree of muscle necrosis and even eliminating the need for fasciotomy[42,43,44,45]. We have proposed a rabbit compartment syndrome study evaluating biomarkers of compartment syndrome, the effect of HBO in oxygenating ischemic muscle, and the end result of HBO treated animals with compartment syndrome. We hope that the judicious and prompt use of HBO following injury may eliminate the need for surgery in some cases and improve surgical results.

HBO can be lifesaving in extreme blood loss where resuscitation with blood products is not possible. We have wondered if HBO could be useful in less severe blood loss, perhaps eliminating or reducing the need for blood transfusion. The reduction of blood use in the field has particular appeal because of the logistical problems in supplying blood to a forward location and the ability to avoid contaminated blood. We have designed a rabbit study in which animals with a 50% blood loss are given HBO to determine if the recovery from blood loss is accelerated over the control group.

It is our hope that in time we will be able to position hyperbaric chambers in the forward medical facility and reduce the severity of wounds, hasten healing times, reduce the need for blood and surgical procedures, and lessen complication rates. Our current work is directed to understanding the events in injury and wound healing and identifying the parameters where HBO may be of use.

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3-Nitrotyrosine Predicts Healing in Chronic Diabetic Foot Wounds Treated with Hyperbaric Oxygen

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INTRODUCTION

The medical art of healing the chronic diabetic foot wound is to a great extent empirical. Current methods rely on visual examination of the wound. For example the appearance of granulation tissue and the formation of new epithelium are often noted as signs of positive treatment effect whereas increasing size of a wound may indicate treatment failure. Since changes in the chronic wound may occur over a period of several weeks, determining the effect of treatment can be problematic. Extensive documentation including photographs can contribute to the objectivity to this process. However extensive documentation adds to the time and cost of treatment and may not be feasible in many health care models. Wound treatment, including amputation, topical growth factors and HBO are also expensive. Finally, and most importantly, time and effort spent on ineffective treatment is time lost to the patient and perhaps a window of opportunity lost to the physician if the wound progresses and amputation is the only remaining treatment option. When these aspects of wound treatment and evaluation are considered, diagnostic methods that rapidly and objectively determine the effect of wound treatment are of considerable economic and therapeutic importance.

Our main hypothesis is that treatments that are effective will increase the production of NO in the chronic non-healing wound. In addition, increased NO production is an early event that could serve as a rapid indicator of treatment effect. In other words effective treatments will cause increased NO production whereas treatments that have little effect will not increase NO. There is significant evidence suggesting that NO does plays an important role in healing of the chronic wound. NO is produced by a variety of cells including wound resident macrophages, epithelial cells, and neutrophils (1). NO promotes angiogenesis (2), keratinocyte proliferation (3), and collagen deposition (4,5,6), properties that are essential to wound repair. When other radicals such as superoxide are present, NO reacts to form an especially toxic radical, peroxynitrite, which is thought to be important in the reduction of bacterial colonization (7,8,9). NO has a half-life that is measured in seconds, however stable end-products of NO including nitrate and 3-NT have been used as an indirect measure of NO production.

The correlation between healing and increased NO production has been demonstrated in the non-healing diabetic wound. Non-healing diabetic wound exudate fluid nitrate levels have been shown to be decreased relative to wound exudate from surgical wounds of normal subjects suggesting that NO production is deficient in diabetics (10). In a recent report, we have shown that when non-healing diabetic foot wounds are treated with topical platelet derived growth factor (PDGF, Regranex), urine nitrate levels are 2-fold lower ($P<0.01$) for patients whose wounds still fail to heal compared to those whose wounds respond and heal (11). Plasma levels show a similar relationship with a four-fold difference on average though this difference was not found to be statistically significant due to inter-patient variance. These data show that increased NO production is correlated with wound healing and a favorable treatment outcome with topical PDGF. Taken together these results suggest that nitrate determination could be used to objectively evaluate the clinical response of the diabetic wound to treatment. However, systemic nitrate levels are problematic since substantial amounts of NO and consequently nitrate are produced during maintenance of vascular homeostasis and during disease processes characterized by inflammation. Thus systemic nitrate levels may be elevated in some patients, despite the absence of healing. In addition non-invasive sampling of wound exudate and subsequent determination of nitrate can be problematic if the wound produces little exudate. Another end-product of NO production, 3-NT, was therefore considered as a healing marker.

3-NT is produced *in situ* by the reaction of nitrating agents and free or protein associated tyrosine. Peroxynitrate is produced by the reaction of NO and superoxide, though other chemistries have also been

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identified (12). The non-healing diabetic wound is composed macrophages and other immune effector cells that are inactive (13), but have the capacity to produce peroxynitrite. We hypothesized that an early event in healing is increased NO and consequently peroxynitrite, and as a result, increased cellular accumulation of 3-NT. In an earlier report we demonstrated that 3-NT accumulation occurs in activated murine macrophage-like cell line and that cellular accumulation can be measured using immunocytochemical methods in conjunction with flow cytomtery (14). These previous findings suggested to us that cellular accumulation of 3-NT in cells collected from the wound could be used as an objective marker of healing during treatment with HBO.

METHODS

PATIENT SELECTION AND OUTCOME EVALUATION

Diabetic patients with non-healing wounds that had failed antibiotic therapy and meeting the criteria for treatment with HBO were enrolled in the study. Further, only those patients where the objective of treatment was wound healing were selected. In some cases HBO therapy is given to define viable tissue prior to amputation, thus in these cases healing is not the objective of therapy. In this study, subjects meeting these criteria were selected consecutively until a total of 12 total patients were acquired. One patient that was initially included was later excluded because he failed to return for treatments after initial evaluation. Patients inspired 100% oxygen for 90 minutes with 5 minute intervals of air every 30 minutes at a pressure of 2.4 atmospheres absolute once a day until their wound showed significant signs of healing or until treatment was determined to be ineffectual. A favorable outcome was determined by observing the formation of granulation tissue and re-epithelization of the wound bed, called herein progressive healing (PH), whereas those patients that showed little or no improvement during treatment are called herein minimal improvement (MI).

TRANSCUTANEOUS OXIMETRY (TCOM)

Transcutaneous oximetry (TCOM) values were obtained on all patients prior to initiation of their HBO treatment series. Several TCM3 TCOM units by Radiometer (Copenhagen, Denmark) are currently used to gather this baseline data on all patients for our facility database. These values are obtained in the standard fashion after the skin sites are prepared by shaving, cleansing, and dabbing with adhesive tape. The monitor leads are attached after the ionic TCOM solution is placed in the membrane/ring electrode. The chest was used as the site for control values and the other values were obtained from skin near the wound.

DETERMINATION OF 3-NT IN WOUND CELLS

Wound dressings were collected during wound care. Portions containing exudate were cut from the dressing and placed in 25ml of Dulbecco's phosphate buffered saline with a ph of 7.4 (DPBS), shaken for 3 minutes, and then centrifuged. The supernatant was aspirated and then the pellet was suspended in 10 ml DPBS. The cell suspension was then filtered through a 60 μm nylon mesh to remove threads and other large debris. The filtered suspension was centrifuged, the supernatant aspirated, and the pellet suspended in fixative (FACS Lyse Solution, Beckton-Dickenson, San Jose, CA). Fixed wound exudate cells were washed twice in 10 ml DPBS and then blocked for non-specific binding of secondary antibody for 30 min with 10% normal goat serum. Cells were then suspended in 10 μl of rabbit polyclonal IgG anti-3-NT antibody solution (Upstate Biotechnology, Lake Placid, NY), diluted 20-fold in DPBS in 10% normal goat serum, and incubated overnight in the dark at 4ºC. Cells were then washed 2 times with 1 ml DPBS and suspended in 10 μl of phycoerythrin-conjugated goat anti-rabbit Fab fragment solution (Sigma, ST. Louis, MO), diluted 20-fold in DPBS and then incubated for 1 hr at room temperature. Following incubation, the cells were suspended in 400 μl DPBS. Processing for the 3-NT negative control was identical to the above with the exception that IgG collected from normal rabbit serum (DAKO, Cupertino, CA) was used instead of anti-3-NT IgG antibody. The concentration of rabbit IgG in the negative control was identical to anti-3-NT antibody. Flow cytometry was performed on a FACS Caliber instrument. The epithelial and PMN cells that we sought were separated from exudate debris using a dot-plot of linear side scatter and linear forward scatter of light, which

corresponded respectively to the size and roughness fingerprint of these known standard cell types. The identity of cells was confirmed by sorting the gated population and evaluating morphology using conventional light microscopy. The fluorescence intensity associated with phycoerythrin was measured using the peak height measured for each cell in the FL-2 band pass filter. The same instrument settings were used during all runs reported. The geometric mean of the population of FL-2 signals was computed using Cell Quest software (Becton-Dickinson) and used in subsequent statistical comparisons. A minimum of 10,000 cells was used for population statistics.

RESULTS

Of the 12 patients considered in this study 6 showed progressive healing (PH) and 6 showed minimal improvement (MI) during treatment with HBO. Table 1 shows that demographic characteristics of PH and MI patients are similar. The table also shows that in all MI patients, neutrophils were recovered from the wound sample, whereas none were recovered from PH patients.

Our main hypothesis is that HBO increases the production of oxidative radicals and that this increase is essential for healing and will be revealed by increased cellular accumulation of 3-NT in healing wounds compared to non-healing wounds. In addition, we have postulated that production of oxidative radicals is a relatively early event in the healing process, thus cellular accumulation will decline in the later stages of healing. In contrast MI patients are expected to show no change in cellular accumulation of 3-NT during treatment with HBO. Figure 1 shows that the data collected during this study supports this hypothesis. PH and MI patients show similar levels of epithelial cell accumulation of 3-NT during the first week of HBO treatment, however by week two trends in accumulation diverge with PH patients showing significantly greater accumulation than MI patients. By week 5 3-NT levels decline in PH patients. Figure 2 shows that accumulation of 3-NT in epithelial cells is approximately 3 times greater in PH compared to MI patients ($p<0.001$, Tukey-Krammer multiple comparison test)

Another hypothesis that has been addressed during the current investigation is that patients with lower Tcom's will respond less favorably to HBO. Table 2 shows that PH and MI patients are similar with respect to Tcom's. Correlation analysis of 3-NT accumulation and Tcom data did not reveal any association.

Table 1- Demographic, TCOM, cellular accumulation of 3-NT and outcome. Race: B=Black; W=white; H=Hispanic. Tcom values: first row are values when breathing air, chest reference/wound, second row when breathing 100% oxygen, chest reference/wound. Outcomes, PH- progressive healing; MI- minimal improvement.

Patient	Age	Race	Gender	Tcom Air C/W; O2 C/W	Cell Type Collected	Mean 3-NT (SD), Min, Max	Healing Outcome
A	62	W	M	85/89; 410/359	Epi	12.8 (9.1),0.8, 22.2	PH
B	77	W	F	69/4; 324/69	Epi	25.7 (12.2),15.3, 47.3	PH
C	63	H	M	83/29; 457/260	Epi	16.7 (10.5),5.3, 37.8	PH
D	44	B	M	59/53; 330/113	Epi	15.8 (6.3),2.9, 23.1	PH
E	72	W	M	63/47; 363/168	Epi	15.8 (16.0),-1.9, 49.3	PH
F	69	H	F	40/6; 355/16	Epi	3.5 (3.0), -1.0, 9.6	PH
G	63	W	M	54/35; 293/91	PMN	3.7 (1.1),3.0, 4.5	MI
H	53	H	M	69/57; 384/109	Epi /PMN	5.9 (5.9), 0.9, 14.1	MI
I	58	B	M	37/0; 232/143	Epi /PMN	2.5 (3.2), -0.6, 5.7	MI
J	56	W	M	51/28; 420/140	Epi /PMN	10.5 (2.9), 7.8, 15.3	MI
K	73	H	M	79/60;399/153	Epi /PMN	3.4 (1.5), 1.9, 5.7	MI
M	50	H	M	67/32; 477/229	Epi /PMN	4.5 (0.6),3.8, 5.0	MI

Table 2- Relationship of Tcom values to outcome. Mean (SD).

Tcom	MI	PH
Chest, Air	60 (6)	67 (7)
Wound, Air	35 (9)	38 (13)
Chest, Oxygen	368 (36)	373 (21)
Wound, Oxygen	144 (19)	164 (52)

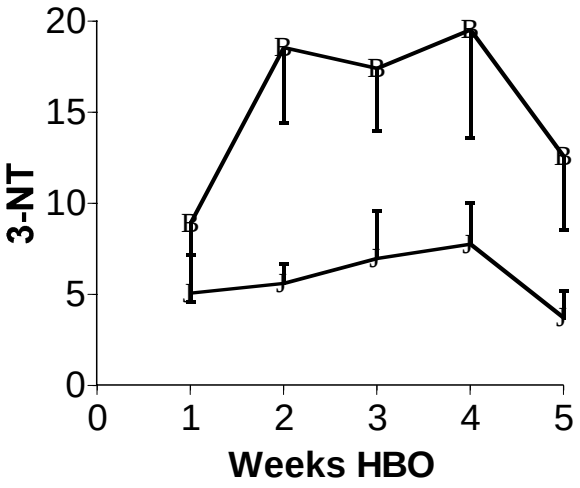

Figure 1- 3-NT in wound exudate cells in healing and non-healing patients. Black squares mean 3-NT of six PH patients during the period; Black circles mean 3-NT of six MI. Error bars are SEM.

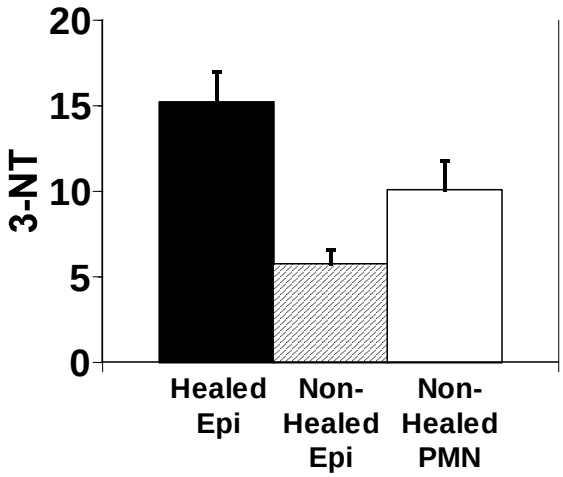

Figure 2- 3-NT cellular accumulation in healing and non-healing cells. PMN polymorphonuclear cells, i.e. neutrophils. Difference between epithelial cell accumulation of 3-NT in MI and PH patients highly significant, (Tukey-Kramer Honest Signficant Difference test, $p<0.001$) other differences not significant.

CONCLUSIONS

A non-healing wound in a patient with diabetes requires aggressive intervention to prevent the loss of a limb (15). HBO treatment is an approved intervention that has been shown to be effective (16) and is sometimes used as an adjunct to antibiotics (17). Since the cost of HBO treatment is high, $14,000 for 30 treatments at one treatment center (18), diagnostic methods that reduce treatment time and cost are beneficial. We reasoned that a biomarker linked to early events during healing could be used to determine if a patient is responding to treatment, or if another treatment modality should be employed. Early determination of treatment effect would result in improved resource management and improved patient care.

Although patient numbers are small in this study, some clear trends are observed. Identification of neutrophils in the cell suspension obtained from the wound predicts unfavorable treatment outcome with HBO. Since neutrophils are associated with the acute response to bacterial infection one explanation is that antibiotic therapy was insufficient and that normal healing could therefore not proceed. HBO has been shown to selectively inhibit neutrophil adhesion (19) in healthy subjects, thus another possible explanation is

that in these diabetic subjects, neutrophil response was inappropriate leading ultimately to wound failure. Both explanations deserve additional investigation.

3-NT accumulation in epithelial cells is increased in PH but not MI patients during treatment with HBO. This supports our primary hypothesis that increased oxygen partial pressure in the wound will lead to increased production of oxidative radicals such as peroxynitrite that in turn nitrate proteins, including those found in epithelial cells. In all PH patients epithelial cell accumulation of 3-NT was near 0 at the beginning of HBO treatment and then increased by at least 3 fold during the next several weeks. We did not find any relationship between Tcom values and wound healing outcome or 3-NT accumulation suggesting that oxygen increase above some threshold is sufficient to cause increased production of nitrating radicals and also healing. These findings suggest that changes in epithelial cell accumulation of 3-NT could be used to determine if patients are responding to HBO treatment. Patients that fail to show an increase in 3-NT during the first 2 weeks of treatment should receive another treatment besides HBO.

The chemical kinetics governing the accumulation of 3-NT in wound exudate cells is unknown. Both epithelial cells and neutrophils are capable of producing nitrating species. However the processes governing the accumulation of nitro adducts, including 3-NT, in cells is only poorly understood. Recently denitrase-like activity has been identified in some organs (20) and hypochlorous acid produced by neutrophils may cause the removal of the nitro group from 3-NT (21). There is evidence that HBO inhibits transcription of inducible nitric oxide synthase gene in murine peritoneal macrophages suggesting indirectly that HBO may inhibit formation nitrating species (22). Clearly more research is required to definitively identify the mechanisms which govern 3-NT accumulation. Cellular accumulation occurs when the rate at which adducts are formed exceeds the rate at which they are removed. We have hypothesized that in the healing wound production of nitric oxide increases leading to increased nitrating species and increased nitro adduct formation. Given our current understanding of the chronic non-healing diabetic wound it appears that increased oxygen partial pressure can facilitate increased nitric oxide synthesis rate and in turn increase healing rate.

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Role of a Clinical Hyperbaric Chamber in Support of Research and Military Hyperbaric Operations

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Summary

The DERA Hyperbaric Systems Group is the DERA focus for the research and project support programme for diving, escape and rescue from submarines and for provision of hyperbaric oxygen therapy. The Institute of Naval Medicine is responsible for training military Diving Medical Officers to support MOD Diving operations, submarine escape and rescue operations and Special Forces operations. Jointly they operate the Sir James Watt Hyperbaric Medicine Unit based at the Royal Hospital Haslar. The unit provides:

- Clinical treatment
- Clinical research
- Equipment evaluation
- Training for physicians, nursing and technical staff

Background

The Hyperbaric Systems Group (HSG) is part of the DERA Centre for Human Sciences (CHS). The group is based at Alverstoke, close to the Institute of Naval Medicine (INM) the Royal Hospital Haslar (RHH), the Defence Diving School and the Submarine Escape Training Tank (SETT). The Hyperbaric Systems Group is the DERA focus for the research and project support programme for diving, escape and rescue from submarines and for provision of hyperbaric oxygen therapy.

The Institute of Naval Medicine, Diving and Hyperbaric Medicine Department provides operational medical support to Royal Navy diving activities and provides specialist training in diving and hyperbaric medicine.

The Sir James Watt Hyperbaric Medicine Unit is based at the Royal Hospital Haslar; it is available at 20 minutes notice throughout the year. The unit provides:

- Clinical treatment
- Clinical research
- Equipment evaluation
- Training for physicians, nursing and technical staff

The hyperbaric chamber is an RN ‘Type A’ chamber modified by a large 'rectangular' door. It is 2.4 metres in diameter and has 2 compartments. The main compartment is 6 m long and the man lock is 2.4 m long. The maximum working pressure is 9 bar (80 msw). The chamber is fitted with a 'medical lock' and electrical and gas penetrations for medical equipment. It can accommodate 6 seated or 2 critically ill patients on trolleys together with appropriate medical and nursing staff and chamber attendants.

The patient breathes oxygen (O_2) at pressures above 1 atmosphere (bar) from the Built in Breathing System (BIBS), hood or ventilator depending on their medical condition.

The chamber is provided with most of the equipment that can be found in a typical Intensive Care Unit (ICU). This includes:

- ventilators
- vital signs monitors

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- syringe drivers
- infusion pumps
- transcutaneous oxygen monitors
- defibrillator.

All of this equipment has been assessed and certified as fit for use in the chamber.

History of the Hyperbaric Medicine Unit

The unit was established in 1996 as a partnership between:

- DERA, which:
  own and run the chamber,
  provide technical staff, including a 24 hour 'on call' team of operators,
  provide 2 ‘hyperbaric’ nurses and fund the secondment of a nurse from the local civilian hospital.

- Institute of Naval Medicine (INM), that provides:
  the Medical Director who has medico-legal responsibility and hyperbaric expertise,
  a roster of experienced qualified medical officers.

- Defence Secondary Care Agency (DSCA), that:
  ran the Intensive Care Unit (ICU) and other medical specialties,
  owns the current building,
  provides support services and a military nurse.

Each of the stakeholders benefits from the relationship:

Benefits to DERA

The benefits to DERA include a significant non-MOD income. In common with other nations, the UK MOD research budget is declining. There is a requirement to maintain the capability (facilities and staff) required to conduct the MOD work programme but which the MOD cannot afford. The HMU is financially self-supporting and it employs the team required to conduct the MOD work programme. Many of the skills gained in HMU are transferred to other parts of the MOD work programme. The experience gained in the HMU gives our independent ethics committee the confidence that the staff conducting the current diving and submarine escape programme can do so safely.

The establishment of a clinical research programme (e.g. collaboration with Royal Marsden Hospital) broadens the links with academic institutions.

Benefits to INM

The Institute of Naval Medicine is responsible for training military Diving Medical Officers capable of supporting MOD operations including:

Diving operations aboard forward deployed ships (Mine Countermeasures Diving),
Submarine escape and rescue operations (such as 'KURSK'),
Special Forces operations (including newly evolving capabilities).

INM also supports local area commands engaged in underwater and altitude activities; these include:

Submarine Escape Training Tank (SETT),
Defence Diving School,
Fleet Diving Headquarters,
RN Air Medical School,
DERA Alverstoke diving and submarine escape and rescue research programme.

INM also provides diving and hyperbaric treatment advice to UK forces worldwide.

Only by having access to a caseload that includes a significant number of critically ill patients can these medical officers obtain and maintain the skills that they require.

Benefits to the Defence Secondary Care Agency

The HMU provides the Defence Secondary Care Agency with the ability to treat military personnel and train its medical officers and nursing staff.

The DSCA received an income as a result of patients being transferred from HMU to the Intensive Care Unit and other wards at the Royal Hospital Haslar.

DSCA also received payment from DERA for services provided under the terms of a Service Level Agreement.

Benefits to Patients

The Hyperbaric Medicine Unit treats both civilian and military patients. The catchment area for civilian patients is the entire southeastern region of England.

Military patients have been treated for:

Diving injuries (decompression illness)
Necrotising fasciitis
Crush injuries
Re-vascularisation of soft tissue flaps

Conditions which benefit from HBO therapy

The Undersea and Hyperbaric Medical Society endorses the use of Hyperbaric Oxygen for 13 medical conditions:

- Air or gas embolism
- Carbon monoxide poisoning with or without smoke inhalation and cyanide poisoning
- Gas gangrene
- Crush injury
- Decompression illness
- Healing problem wounds
- Necrotising soft tissue infections
- Osteomyelitis
- Radiation tissue damage
- Skin grafts and flaps (where patient is ‘compromised e.g. diabetics)
- Thermal burns
- Some intra cranial abscesses
- Exceptional blood loss

The majority of these are of military relevance.

The role of the Hyperbaric Medicine Unit

The HMU has an integrated role providing support for the Royal Navy, Army and Royal Air Force, National Health Service and Defence Evaluation and Research Agency. Its initial objective was to provide training for Diving Medical Officers, an enhanced research capability for DERA, and patient care not readily available in the southeast of England.

Clinical treatment

The HMU provides acute treatments on short notice for injured divers, carbon monoxide intoxication and necrotising fasciitis.

Injured divers from throughout the United Kingdom, English-speaking Commonwealth countries and UK military divers call the Duty Diving Medical Officer (DDMO) who then provides advice and refers the patient to the closest hyperbaric unit with appropriate capabilities. The DDMO carries a cell phone and is manned by INM medical specialists. Specialist trainees may carry the phone under supervision of a consultant specialist. If HMU is the closest appropriate chamber, the DDMO will then see the patient, evaluate the case and treat as indicated. The DDMO is backed by the tertiary care capabilities of Queen Alexandra Hospital in Portsmouth and Royal Hospital Haslar in

Gosport. These capabilities include Intensive Care Unit, accident and emergency department, radiology, anaesthetic and ENT specialists. The DDMO is support by on-call nurses who hold Certified Hyperbaric Registered Nurse (CHRN) and 'intensive care' qualifications. The technicians and dive supervisors supporting chamber operations are exceptionally experienced owing to constant exposure to hyperbaric operations gained from the HSG research programme. Injured divers are usually treated and then admitted for observation and support, with re-treatments provided as clinically indicated. Treated divers are followed in association with their respective general practitioners. Each case is entered into a diving accident database. INM keeps the British Hyperbaric Association diving accident database, receiving additional cases from other member chambers. The database provides a research tool for HMU and INM.

Cases of carbon monoxide intoxication are referred to HMU by area hospital accident and emergency departments. If another appropriately skilled chamber is closer, the patient is directed there. Often, patients are transported to HMU by air or ground from an appreciable distance away, due to area shortages of intensive care beds. These cases are treated twice in the first twelve hours after admission and then further therapy provided depending on recovery. The number of treatments received by any patient are always less than five and rarely more than three.

Cases of necrotising fasciitis are referred from area intensive care units due to Royal Hospital Haslar's unique combination of military plastic surgeons and a hyperbaric facility. The nature of military operations results in as many cases coming from the Ministry of Defence as from the civilian community.

Caseload July 1996 to July 2000

Since the unit opened at RH Haslar, it has treated a total of 478 patients consisting of:

198 Divers,
81 Wound Care patients,
164 patients with Carbon Monoxide poisoning
35 Research volunteer patients

This has involved a total of 1344 treatments, which has resulted in 2990 hours under pressure of which 1076 hours were outside 'normal office hours'.

52 patients were referred to ICU; occupying 290 bed days.
Over 120 patients were referred to general wards; occupying 180 bed days.

To provide the standard of care required to treat critically ill patients (and hence the experience needed by medical officers) a hyperbaric unit must be located in a hospital with an Intensive Care Unit

Clinical research

The academic and research experience within DERA and INM, along with experience gained from treating both NHS and military patients allows for collaborative research funded by both MOD and non- MOD sources. In the UK research funds are frequently tied to studies requiring collaboration of two or more agencies, DERA / INM collaboration with a university or hospital fulfills that criterion.

Typical research projects

A study was designed to assess the hypothesis that early HBO therapy would be of benefit in the treatment of acute ankle injuries suffered by military personnel. This was to be a randomised, blinded sequential clinical trial. Subjects were to be assessed according to well-defined inclusion and exclusion criteria and then randomly assigned to one of three groups. These were; 1) standard medical treatment only; 2) standard medical treatment plus four hyperbaric oxygen treatments at 0.96 bar oxygen partial pressure; and 3) standard medical treatment plus four hyperbaric oxygen treatments at 2.4 bar oxygen partial pressure. Hyperbaric treatments were to follow a standard treatment protocol consisting of 90 minute 2.4 bar exposures. Measurements of functional improvement were to be compared between treatment groups to determine the statistical significance of HBO treatment versus control and 0.96 bar treatment groups. The relevant ethics committees approved the protocol and technical preparations were completed. These included the provision of 2 independent breathing gas systems that allow subjects to breathe either oxygen or a placebo. The allocation of the subject to the active or control groups would be known only to the chamber supervisor who is able to switch the appropriate breathing gas to that subject.

The study has been deferred due to funding/recruitment issues, but the technical preparations were used to advantage in a study conducted in collaboration with the Royal Marsden Hospital.

That study aimed to assess the value of hyperbaric oxygen in the treatment of Radiation-Induced Brachial Plexopathy (RIBP). i.e. radiation damage induced during the treatment of breast cancer.

The study involved 36 volunteer patients who were randomly assigned to an 'active' or 'control' group. Because of the design of the treatment chamber, none of the patients or investigators was aware of which group patients were assigned to. This is believed to be the first large-scale double-blind randomised trial of the effectiveness of HBO conducted in the UK. All of the patients received 30 'treatments' over a period of 6 weeks. Each treatment involved exposure to pure oxygen or to the 'control' gas mixture for 90 minutes at a maximum pressure of 2.4 bar.

There were no statistically significant differences in outcome between the active and control groups, however four patients unexpectedly experienced significant reduction in arm oedema. Two of these patients have sustained this reduction to date (20 months).

A further study has been jointly funded by the MOD and the UK Medical Research Council to investigate effect of HBO on post-irradiation arm lymphoedema in 21 patients. The trial is due to start in November 2000

Training and education

Training programmes for post-graduate physicians and nursing staff evolved naturally as a result of the unique military training opportunities provided by HMU, its relationships with academic and military institutions, the active research programme and the high level of clinical activity.

Diving Medical Officers (DMO) are trained for 3 months under the auspices of the Institute of Naval Medicine. The course is tailored to the individual, as throughput is approximately three to five trainees per year. Training includes; standing duty as the Duty Diving Medical Officer (DDMO), supervising routine and acute treatments at HMU, participating as the Independent Medical Officer for HSG trials work, medical support to the Submarine Escape Training Tank, participating in the Standard Underwater Medicine Course at INM and 'training runs' at HMU, where medical procedures are practiced at pressure up to 6 bar (50msw).

Medical students usually attend HMU for a one-month rotation, participating in patient care and completing a short research topic paper.

Two or three Research Fellowships for Anaesthetic Registrars are to be offered offered each year. Research projects will be sponsored by the Environmental Medicine Unit at INM in collaboration with the University of Portsmouth and by DERA.

Nurses are trained either by completing a Hyperbaric Nursing course at the National Hyperbaric Centre in Aberdeen or the 'Hyperbaric Team Training' course at San Antonio Texas. They are encouraged to qualify for the Certified Hyperbaric Registered Nurse qualification. A minimum requirement for employment at HMU is an intensive care nursing qualification. Continuation training is provided by a one week in three rotation in the local civilian hospital Intensive Care Units and attending academic conferences. HMU nurses also provide medical support to DERA HSG trials. Nursing students are assigned to HMU for one to eight week rotations, depending on their training programme and interest. A training course for Hyperbaric Nurses is currently being developing as a UK /European alternative to that provided in San Antonio.

HMU provides education to the medical community in the form of study days and courses. These are provided in two fora. The first is a HMU funded study day designed specifically to train anaesthetic Consultants, Registrars (Residents) and Senior House Officers in hyperbaric operations. This is tailored to groups of less than fifteen and includes a chamber acquaint dive. All lectures are provided by INM and DERA staff. The second forum is a sponsored study day or course. This study day provides Continuing Medical Education hours to local interested medical professionals. It includes national and international specialists lecturing on hyperbaric topics and presenting research. It is intended to provide weeklong courses under auspices of the Undersea and Hyperbaric Medical Society (UHMS) which will include international speakers such as Eric Kindwall. These courses are designed to attract international participants.

Evaluation and development of medical equipment

The demand for medical equipment for use in hyperbaric chambers has increased with the increasing need to support critically ill patients. This demand is normally from clinicians, who naturally have a preference for the equipment that is available to them on the wards, theatres and Intensive Care Units.

These devices were not originally designed to operate at raised pressure or in the presence of high concentrations of oxygen. If they are to be used in a chamber they must be assessed and modified if necessary.

Ventilators, thermometers, transcutaneous blood gas monitors, patient monitors, defibrillators, infusion pumps and laryngoscopes have all been assessed for use in the HMU.

It was soon apparent that a process was required in order to properly evaluate these devices and document the results. A procedure evolved as the result of work carried out on a patient ventilator for use to 50 metres in HMU.

The procedure was given the acronym '**SELECT**' and it involves:

Specifying the requirement; the clinical requirement will normally be specified by experienced clinical or nursing staff,

Evaluating the risks; these include implosion, explosion, fire, electrical shock or altered performance,

Liaising with the user and the equipment supplier,

Eliminating the risk; this may be by modifying the equipment or by specifying procedures or conditions for its safe use.

The process should be under the control of a **C**ompetent person who has the necessary skill and experience. There may be legislative requirements

On completion of the process, the equipment should be '**T**agged' to show that it has been assessed as suitable for use in the hyperbaric chamber. Some equipment will have required modification and because it will outwardly look the same as any other item of the same type; it must be clearly marked 'for chamber use'.

The dangers of not using properly evaluated and modified equipment should need no further amplification.

The future

The Royal Hospital Haslar is closing; essentially to be replaced by a MOD Hospital Unit at the local civilian hospital (Queen Alexandra Hospital). This is part of a larger development due to be completed in 2006. Meanwhile this closure has resulted in the loss of the ICU and Emergency Room at RH Haslar with consequent effects on patient management and logistics. As an ‘Interim’ measure the HMU will open a chamber at the local civilian hospital towards the end of 2000 to treat patients requiring HBO and intensive care. This is a standard RN 'Type B' chamber housed in an ISO container and is on loan from the MOD. Ancillary equipment including compressors, gas storage and distribution system are housed in a second smaller container. The facility will be incorporated into an existing building that provides a clinical reception area and access to the rest of the hospital. The unit will be integrated with the Critical Care Directorate and will be supported by all of the services normally found in a major hospital.

The current chamber will continue to be used for ambulatory patients and will remain at RH Haslar until scheduled to be moved and integrated into the newly constructed civilian hospital as the UK MOD focus for Defence Hyperbaric Medicine.

Incidence of Decompression Illness and Other Diving Related Medical Problems Amongst Royal Navy Divers 1995 – 1999

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ABSTRACT

Background: The Diving Accident Database held at the Institute of Naval Medicine (INM) contains details of all Royal Navy, and the majority of UK recreational diving accidents, that have occurred since 1990. Details of all Royal Navy dives completed since 1995 are recorded on the Dive Database, also held at INM.
Aim: To determine the incidence of decompression illness (DCI), and other diving related medical incidents, amongst Royal Navy divers.
Methods: The number and type of dives completed by Royal Navy divers (including Ships Divers, Mine Clearance and Special Forces divers) between 1995 and 1999 was extracted from the Dive Database. Details of all cases of DCI, and other medical incidents, were extracted from the Diving Accident Database. The data was analysed and incident rates calculated for DCI and other medical conditions.
Results: During the 5 year period 106,487 dives were completed. 21 cases of DCI occurred (18.8/100,000) and 8 cases of pulmonary barotrauma (7.5/100,000). The incident rate for DCI following military air dives was 16/100,000, nitrox dives 19.4/100,000 and heliox dives (1.3 bar constant pO_2) 58.4/100,000. The incident rate for DCI amongst recreational divers using air was estimated at 7.58/100,000.
Discussion: The incidence of DCI following military air dives is approximately twice that of DCI amongst the recreational diving community. However, there is believed to be significant underreporting of recreational DCI. The incidence of DCI following heliox dives is much greater than that associated with air dives. This increased incidence of DCI is probably a factor of depth and increasing decompression stress rather than that of difference in gas mix.

BACKGROUND

The Institute of Naval Medicine holds paper records of most, if not all, Royal Navy diving accidents that have occurred since the early 1940's. Some of the earliest records relate to 'incidents' which occurred during Professor Donald's historic research into oxygen toxicity. Details of all dives are recorded in both the divers personal dive log and unit master dive log. Because of the large number of paper records analysis of the data contained within them would be difficult if not impossible. To assist in future analysis of data, and also to collect information as to the epidemiology and natural history of the decompression disorders, a computer database was developed at the Institute of Naval Medicine (INM) in 1990. This database was designed to record detailed information on all Royal Navy diving accidents, and with the assistance of the British Hyperbaric Association (BHA) all civilian cases of decompression illness treated by member chambers. As the BHA represents all of the major therapeutic recompression facilities in the UK it is estimated that over 80% of all civilian cases of decompression illness treated within the UK are recorded upon this database.

Details of numbers of accidents are of limited use without information as to the number, and type, of dives completed. To enable this information to become accessible in 1994 a second computer database was developed at INM to record details of all Royal Navy dives. The year 1994 was used to trial the reporting system and to ensure that all diving units were aware of the requirement to report their diving activities to INM. Data from the year 1994 is thus incomplete, with 1995 being the first complete data year. By combining the data from these two databases it has been possible to perform detailed analysis of both number and type of dives carried out as well as the incident rates for medical incidents including decompression illness.

During the period of the study there have been major changes in the type of diving apparatus used with the semiclosed Diving Set Self Contained Clearance Diving (DSSCCD) being replaced by the closed circuit Clearance Diving Breathing Apparatus (CDBA). DSSCCD used oxygen in nitrogen breathing mixtures and had a maximum operating depth of 54 metres whereas CDBA is used with oxygen in helium breathing mixtures and supplies the diver with a constant partial pressure of oxygen (1.3bar) down to a maximum depth of 80 metres. The closed circuit Long Endurance Breathing Apparatus (Mixed Gas) (LEBA (MG)) diving apparatus, which uses oxygen in nitrogen breathing mixtures, was also

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introduced during the later part of the study period. LEBA(MG) permits diving to a maximum depth of 24 metres and supplies the diver with a constant partial pressure of oxygen (1.4bar).

AIM

To determine the incidence of decompression illness, and other diving related medical incidents, amongst Royal Navy divers.

METHODS

For the 5 years between 1995 to 1999 the number and type of dives completed by Royal Navy divers (including Ships Divers, Mine Clearance and Special Forces divers) was extracted from the Dive Database. Details of all cases of DCI, and other dive related medical problems, were extracted from the Diving Accident Database. Incident rates for DCI were calculated as were incident rates for other dive related medical conditions. Because the Diving Accident Database also contains details of recreational diving accidents, but not number of recreational dives, it has been possible to estimate incident rates amongst UK recreational divers and so make comparison with comparable military dives.

RESULTS

During the 5 year period 1995-99 a total of 106,487 dives were completed by Royal Navy divers, an average annual total of approximately 21,297 dives. The majority of these dives, 74,677 (70%), used air as the breathing gas although with the introduction of CDBA the number of dives using heliox has increased from 104 (0.5%) in 1995 to 3227 (15%) of all dives in 1999. Analysis of the depth range of dives reveals that the majority of dives (65%) are shallow dives to depths between 0 and 11 metres with only 4,379 (4.1%) of dives exceeding a depth of 44 metres.

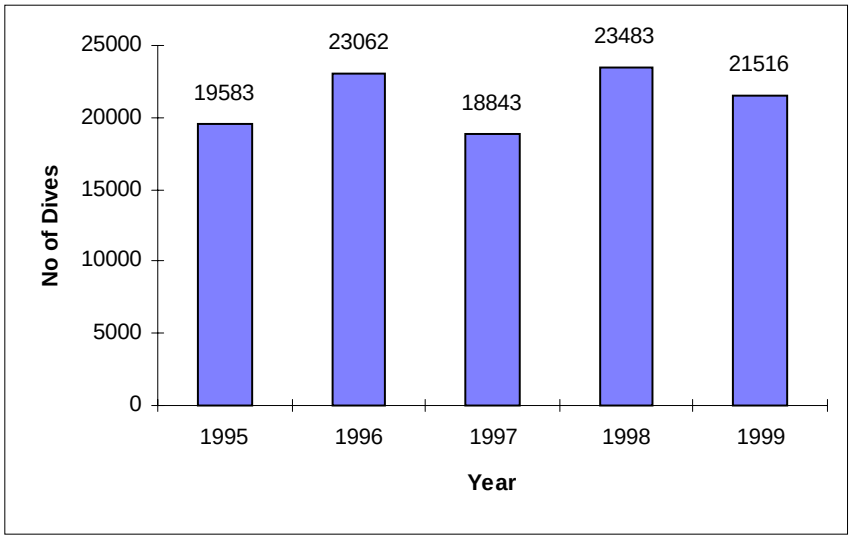

Figure 1: Number of dives per year 1995-1999

Moving to incidents, during the 5 year period there have been 20 cases of DCI. This does not include a case of arterial gas embolism that resulted from a diver accidentally opening the by-pass of the DSSCCD he was using when exiting the water. The overall incident rate for decompression illness is thus 18.8/100,000 dives. More detailed analysis of the 20 cases of DCI reveals that 5 occurred following dives in the range 0-11 msw (7.1/100,000), 4 in the 12-24 msw depth range (16.5/100,000), 4 in the 25-43 msw depth range (50.6/100,000), 6 in the 44-69 msw depth range (137/100,000) and 1 following a dive deeper than 70 msw (621/100,000). Looking in detail at the dives to depths in excess of 44 msw, 2 cases of decompression illness were reported following air dives (147/100,000) with the remaining 5 occurring after heliox dives (351/100,000). Of the 5 cases of decompression after heliox dives 2 occurred following dives using surface supplied open circuit 20% oxygen in helium (855/100,000) with 3 cases occurring after 60 msw dives of short duration using CDBA (252/100,000).

Table 1: Number of Diving Incidents and Incident Rate 1995-1999

Incident type	N	Incident rate/100,000
Decompression illness	20	18.8
Pulmonary barotrauma	8	7.5
Oxygen toxicity	4	3.8
Hypoxia	4	3.8
Hypercapnia	1	0.9
Omitted decompression	2	1.9
Near Drowning	3	2.8
Inner ear barotrauma	1	0.9
Fatality	2	1.9
Total	**45**	**42.3**

In addition to the 20 cases of decompression illness there were also 8 cases of pulmonary barotrauma, incident rate 7.5/100,000. Four cases of hypoxia and 4 cases of oxygen toxicity were reported with an incident rate of 3.8/100,000 per condition. However, as both hypoxia and oxygen toxicity are primarily associated with rebreather use if only dives using rebreathers are considered the incident rate increases to 19.2/100,000.

Two fatalities occurred during the study period giving a fatality rate of 1.9/100,000 dives.

Between 1995 and 1999 BHA recompression chambers treated 758 recreational divers with DCI. It is estimated that the approximately 80,000 recreational divers in the UK complete an average of 25 dives per diver per year. This gives a figure of 2,000,000 dives per year. Using this estimated figure the incident rate for DCI amongst UK recreational divers is estimated at 7.58/100,000.

DISCUSSION

Depth of dive appears to be associated with an increased incidence of decompression illness with an incident rate of only 7.1/100,000 for dives between 0-11 msw increasing to 137/100,000 for dives in the 44-69msw range. For dives to depths in excess of 44msw the incident rate for dives using air (147/100,000) is lower than that for dives using heliox (352/100,000). However, the maximum permitted depth for military air dives is only 50msw compared to the 80msw for heliox dives and as such direct comparison of risk can not be made. Indeed once the small number of dives (n=234) to depths in excess of 44msw using surface supplied open circuit 20% oxygen in helium, which accounted for 2 cases of decompression illness, are excluded the incident rate for decompression illness associated with deep (in excess of 44msw) dives using constant partial pressure 1.3 bar oxygen in helium falls to 252/100,000. Furthermore, all 3 cases of decompression illness associated with constant partial pressure 1.3 bar oxygen in helium have occurred following the same short duration (6 minute bottom time) 60msw dive profile. A possible explanation for this small cluster of cases following this particular dive profile is that divers are descending at a greater rate than called for by the table. With such a short duration dive even an extra 20-30 seconds actually spent at depth would be sufficient to change a ‘safe’ profile to one with an increased risk of decompression illness. The new 1.3 bar oxygen in helium tables, currently under evaluation, have been calculated with a faster descent rate to allow a margin of error if the diver should exceed the standard descent rate.

The incident rate for DCI at 7.58/100,000 for recreational divers appears to be less than half that for military divers at 18.8/100,000. However, almost all of the recreational dives will be carried out using air. Once all heliox and nitrox dives are excluded from the military figures then the incident rate for decompression illness following military air dives drops slightly to 16/100,000. Furthermore, the figure of 7.58/100,000 for recreational DCI is almost certainly an under estimate as it is known that not all chambers report cases to the Diving Accident Database. In addition to this underreporting from chambers there is also the fact that denial of symptoms and self-treatment with normobaric oxygen is not uncommon amongst recreational divers. The true figure for recreational divers may thus be some 20-50% greater than that estimated.

As well as decompression illness other significant diving related incidents have occurred during the study period, in particular 8 cases of pulmonary barotrauma confirmed by clinical examination and X-ray. All of these cases occurred after shallow dives, primarily training dives. In addition to the 8 cases of pulmonary barotrauma with no neurological deficit there were 5 cases of neurological decompression illness following shallow dives (0-11msw). Although there was no radiological confirmation of lung rupture in any of these 5 cases, lung rupture and arterial gas embolism is the most probable mechanism of causation, the depth time profiles of the incident dives being such that inert gas release on

decompression is considered highly improbable. These incidents illustrate the potential dangers associated with shallow water diving in which only small depth transitions, either due to poor buoyancy control or swell, can result in large and damaging pressure changes.

Evaluation of Treatment Tables for Severe Decompression Accidents

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Introduction

This paper describes the requirement for an in-depth analysis of the treatment of a severe decompression accident following a rapid, uncontrolled ascent during deep diving operations using the "Canadian Underwater Minecountermeasures Apparatus" (CUMA).

Background

The risk of a serious decompression accident is of great concern for divers using a self-contained, mixed-gas breathing apparatus such as the CUMA. While such incidents are rare, more dives are being conducted worldwide by military, commercial and technical divers using similar apparatus. Dives can be conducted at deep depths (greater than 50 metres of seawater, maximum 81 metres of seawater (msw)), breathing helium and oxygen mixtures. Unlike surface-supplied divers, CUMA divers are untethered, free swimming and subject to more variables which can effect buoyancy and ascent rates.

If a rapid or uncontrolled ascent to the surface occurs, or omission of a significant part of the required decompression (decompression obligation), a severe decompression accident (SDA) may occur. Serious permanent disability and a high risk of fatality is expected in the event of an SDA. It is not known whether existing treatment tables can adequately deal with the expected outcome from such an accident.

In the event that an SDA does occur, survival will depend largely upon the severity and adversity of the physiological and structural changes which are incurred by the diver as a result of the dive profile, rate of ascent and treatment responses on the surface.

While immediate or rapid recompression on the surface is expected to provide the greatest benefit and relief in conjunction with standard accepted procedures, such as the administration of surface oxygen and intravenous fluid, it is not well known whether or not it is necessary or important to recompress the diver to a depth equal to, or greater than the depth of the incident dive.

Recompression to depths greater than the incident dive and the use of breathing gas mixtures other than those specified by in-service Canadian Armed Forces (CF) treatment tables may be required to adequately treat the diver. The current accepted belief among some diving medicine professionals is that uncontrolled, rapid ascent must be treated by recompressing the diver to the depth of the incident dive plus one atmosphere of pressure. Thus, a CUMA dive to the maximum depth or 81 msw would require recompression to 90 msw for effective treatment. Most CF treatment facilities, on the other hand, are capable of treating to a maximum depth of only 69 msw. In addition, these deep treatment procedures may require more gas, personnel and supplies than existing treatment facilities can supply.

Whether or not it is necessary to recompress to a depth which exceeds the maximum depth of the dive plus one atmosphere of pressure for the treatment of SDA is unknown. It may be possible to recompress to a

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lesser pressure, administer raised partial pressure of oxygen, and apply adjunctive agents to effectively and efficiently treat serious decompression accidents. A review by the US Navy of the use of USN Treatment Table 6 and USN Treatment Table 6A for suspected arterial gas embolism did not demonstrate a greater benefit in the use of the deeper table (1).

Present Option

CF Treatment Table 8 for "deep blow up" may begin as deep as 225 feet of seawater and lasts for 56 hours and 29 minutes. The use of this table places high demands on the treating facility for personnel, equipment and breathing gases. In addition, many chamber personnel are unfamiliar and inexperienced in the use of this treatment option.

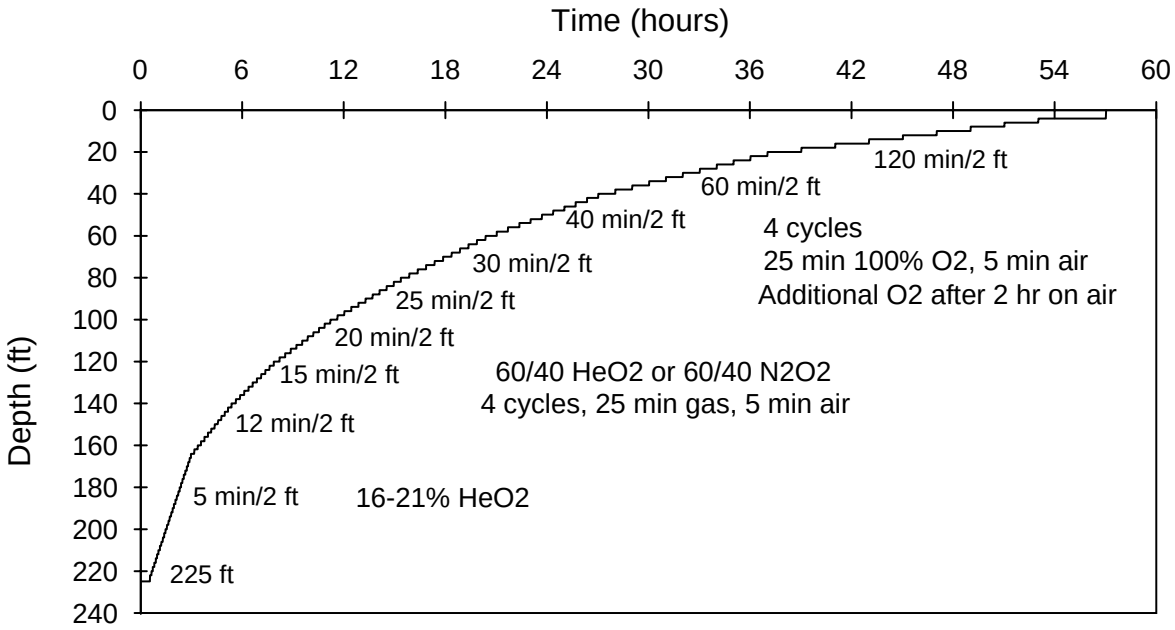

Figure 1. CF Treatment Table 8 for blowup from deep HeO_2 dives

Evaluation of Treatment Options

The risk of serious and permanent injury following SDA precludes the experimental use of divers in the evaluation of treatment table option. Therefore, it is necessary to explore other useful options for the evaluation of treatment tables. A mathematical model of human physiology, gas dynamics and bubble growth in response to pressure changes provides one means by which treatment table effectiveness in reducing and clearing inert gases may be evaluated. Although the presence of bubbles in a physiological model does not represent decompression illness *per se*, it is generally accepted by most diving medicine researchers and clinicians that the presence of more bubbles, especially of greater dimension and higher volume, can correlate with a higher incidence of decompression illness.

A preliminary study of CF Table 8 showed that it is inappropriate for use in SDA; although it removed bubbles from SDA very quickly, it also generated bubbles in the slowest tissues later on, thereby creating an additional decompression problem towards the end of the treatment schedule. Subsequent evaluations of other alternative treatment tables suggested that shallower, shorter tables such as USN Treatment Table 6 (CF TT6, maximum depth 18.2 msw, total elapsed time of 4 hours and 46 minutes) and USN Treatment

Table 6A (CF TT6A, initial recompression to 50 msw, total elapsed time of 5 hours and 54 minutes) did not inherently generate more inert gas, and yet were effective in reducing bubbles generated by SDA.

A review of case studies (SDA) may provide some insights into the effectiveness of treatments used. Databases were reviewed at DCIEM (representing CF diving incident and accident cases over the previous ten years) and from NEDU, Panama City, Florida (representing treatments provided from 1985 to 1995). Also, a limited number of commercial and civilian cases were reviewed. Fewer than ten cases could be identified as representing SDA from these databases. Information derived was not deemed sufficiently specific enough in most cases to provide any useful conclusions in evaluating the effectiveness of treatment options used.

An important modality for evaluating the effectiveness of treatment options involves the use of a suitable animal model. Animal studies were conducted using live, anaesthetized pigs at the SINTEF Unimed Norway in association with Unimed Scientific Limited. Treatment Tables 6 and 6A were selected for evaluation since the theoretical work had suggested that they might be the best tables for SDA. In addition, they are already well known internationally and represent standard treatment tables which can be readily carried out on-site during minecountermeasures (MCM) operations. Effective treatment of SDA with either of these tables represents a considerable advantage by reducing required treatment hours and pressurization, thereby reducing the overall volume of required treatment gas, manpower and need for specialized equipment. This represents a significant operational advantage for the Canadian Armed Forces and international diving communities.

Conclusions

The Canadian Armed Forces use of CUMA for deep helium-oxygen diving in MCM and other operational diving missions, such as “Operation Persistence,” the recovery of SwissAir 111 in 1998, requires that treatment options be reviewed in the event of Severe Decompression Accidents (SDA).

It may be possible to effectively treat SDA with shallower, shorter treatment tables such as USN TT6 or USN TT6A.

The evaluation of treatment table options in this study consists of a mathematical model of inert gas dynamics and the use of a pig model to provide a live, physiological model of SDA and treatment table effectiveness.

Further studies, using the animal model, may include testing of more treatment tables (e.g., RN 67), the use of adjunctive therapies such as intravenous rehydration with saline or perfluorocarbons, the use of a “drogue” device to slow the rate of ascent, pathological analysis of the pig model to investigate pulmonary and neuroanatomical sequelae, monitoring of jugular vein bubbles using doppler probes, and the review of in-water recompression options.

References

Howsare CR, Rocca AF, Morrison LJ, Jackson RL. Comparison of TT6 vs TT6A for the treatment of AGE in the US Navy, a retrospective study. Undersea Hyperbaric Med 1997; 24(Supplement): 33.

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Modelling and Validation of Treatment Tables for Severe Decompression Accidents

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INTRODUCTION

This paper addresses the question of suitable treatment of dysbarism following a severe decompression accident during the use of self-contained breathing apparatus such as the Canadian Underwater Minecountermeasures Apparatus (CUMA) using 1 ata oxygen in helium to a maximum depth of 81 metres. The work involved a dual approach; a theoretical analysis of the problem followed by experimental work designed to follow up specific aspects arising from the theoretical analysis.

THE MATHEMATICAL MODEL

The physiological model of decompression is based on the eight compartment model of gas dynamics described in Mapleson (1963) combined with the model of bubble dynamics described by Van Liew and Burkard (1993). Table 1 lists the compartments together with the time constants which are the factor governing gas uptake.

TABLE 1
Characteristics of each compartment. Time constant in minutes.

Compartment	Tissues	Time constant
1	Adrenals, kidneys, thyroid	0.86
2	Heart, brain grey matter	1.87
3	Liver plus portal system, other small glands and organs	3.07
4	Brain white matter	5.31
5	Red marrow	12.25
6	Muscle and skin	50.62
7	Nonfat subcutaneous	69.14
8	Fatty marrow and fat — nitrogen — helium	211.3 78.3

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The complete hyperbaric exposure is simulated by making iterative calculations using appropriate time increments. The output for each compartment includes the total volume of inert gas which forms into bubbles; the partial pressures of the inert gases in the tissue, the venous blood and the bubble; the change in bubble radius from an assumed initial size usually taken as 2 mm. These are calculated for each time interval. Venous blood is assumed throughout to be in equilibrium with the tissue which it drains. Gas exchange at the lungs is assumed to be complete on each passage of blood through the lungs. In addition to calculating these parameters for each tissue, weighted means of each are used to calculate the values for central mixed venous blood. This is required for comparison of predicted bubbles with precordial bubble counting.

The conversion from the volume of gas carried as bubbles in the mixed venous blood to predicted pulmonary artery bubble counts is made using the relationship derived from experimental hyperbaric exposures and is shown in figure 1. The bubble counting technique is described in Eftedal et al (1993). The experimental data contributing to the points in figure 1 include over 100 experiments using 14 different types of hyperbaric exposure. The average bubble counts for each series of experiments range from zero to over 6 bubbles/cm^2, the most severe exposure included animals which died during or shortly after decompression. This relationship has now been used for comparison of model prediction with pulmonary artery bubble counts or grades for many kinds of hyperbaric exposures from a wide range of sources. The relationship between bubble counts and Doppler K-M grades has been taken as that reported by Eftedal et al (1998). Although there are several assumptions implicit in making these conversions the model has performed well. It has also been used to help design decompression trials to give a selected average bubble count (Flook 1999). The work described here represents the most severe test so far in that the model was used to predict both bubble counts at the end of a primary dive and the fate of the bubbles during and following the use of decompression treatment tables; predictions which were then tested in experimental conditions.

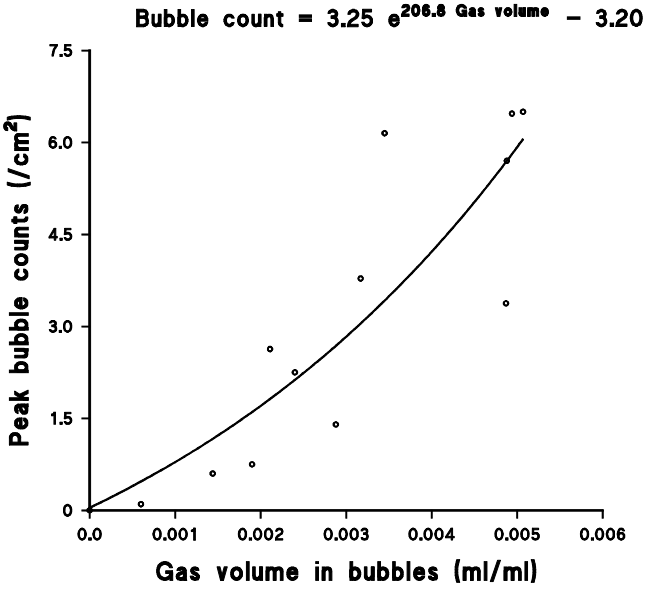

Figure 1 The relationship between average precordial bubble counts in experimental hyperbaric exposures and predicted volume of gas carried as bubbles in the mixed venous blood. See text for details.

THE THEORETICAL STUDY

The theoretical study focused on 81 metres as the depth of the primary exposure with the most severe exposure being 20 minutes at depth followed by uncontrolled decompression at 10 metres/minute. The start of a treatment recompression was preceded by a surface interval of either 10 minutes or 60 minutes breathing either air or oxygen. Ten minutes was considered the minimum time in which the diver could be recovered and

moved to the treatment chamber. Five treatment tables were considered USN6, USN6A on either air or heliox, RN67 and ECO7A.

The main conclusions from that study were that:

even after only 2 minutes at 81 metres an uncontrolled ascent might be expected to give Doppler grade IV or higher in the average diver;

after a 20 minutes exposure the predicted volume of gas in bubbles exceeded the highest bubble count on figure 1 and exceeded any existing scale of measurement;

recompression on any treatment table resulted in removal of the bubbles;

all treatment tables studied allowed sufficient time for subsequent removal of the gas liberated from the bubbles;

treatment tables which used inert gas as part of the breathing mixture generated new bubbles at some stage in the treatment.

The predicted peak volume of gas carried in bubbles in the mixed venous blood after the 2 minute exposure was 0.010ml/ml with air breathing on the surface, 0.006 ml/ml with oxygen breathing on the surface. After the 20 minute exposure the corresponding numbers were 0.021 ml/ml and 0.015 ml/ml. Given that 20 minutes at 81 metres is an allowed CUMA exposure that was chosen for the experimental study. It was not unreasonable to doubt the model predictions at this stage in the work and to assume that it had over-estimated the amount of gas in bubbles.

Treatment tables USN6 and USN6A using air are readily provided on site during mine counter measure operations. The experimental work was planned using these for treatment after a 10 minute surface interval during which either air or oxygen was used as the breathing gas.

Table 2
CUMA81 20 minute blow-up
Time (minutes) to disappearance of bubbles following treatment by USN6 or USN6A

Compartment	USN6		USN6A	
	Oxygen	Air	Oxygen	Air
1		4.9		10.6
2	3.4	8.9	4.1/40.2	11.6/42.1
3	7.4	9.4	11.1/44.1	22.9/44.1
4	18.4	13.9	15.9/48.1	31.4/48.1
5	43.4	39.9	33.4/62.1	62.6
6	25.4	26.9	6.0/47.1	6.5/88.9
7	31.3	38.9	10.1/99.4	10.6/103.9
8	1.45	N/A	1.4	N/A

Table 2 shows the predicted time to disappearance of bubbles for treatments started after a 10 minute surface interval breathing either oxygen or air. Where 2 numbers are shown bubbles, having disappeared after the recompression, are predicted to reappear on the first move. This is predicted to happen only on USN6A.

Figure 2 shows the predicted bubble size for compartment 7 during USN6 (figure 2A) and USN6A (figure 2B) following a 20 minutes CUMA 81 with a 10 minutes surface interval breathing air. Two things are of interest; the greater pressure used for the first stage of USN6A results in much faster compression of bubbles, and in this tissue bubbles are predicted to reform on the move from the maximum depth during the USN6A but not during the move from maximum depth on USN6.

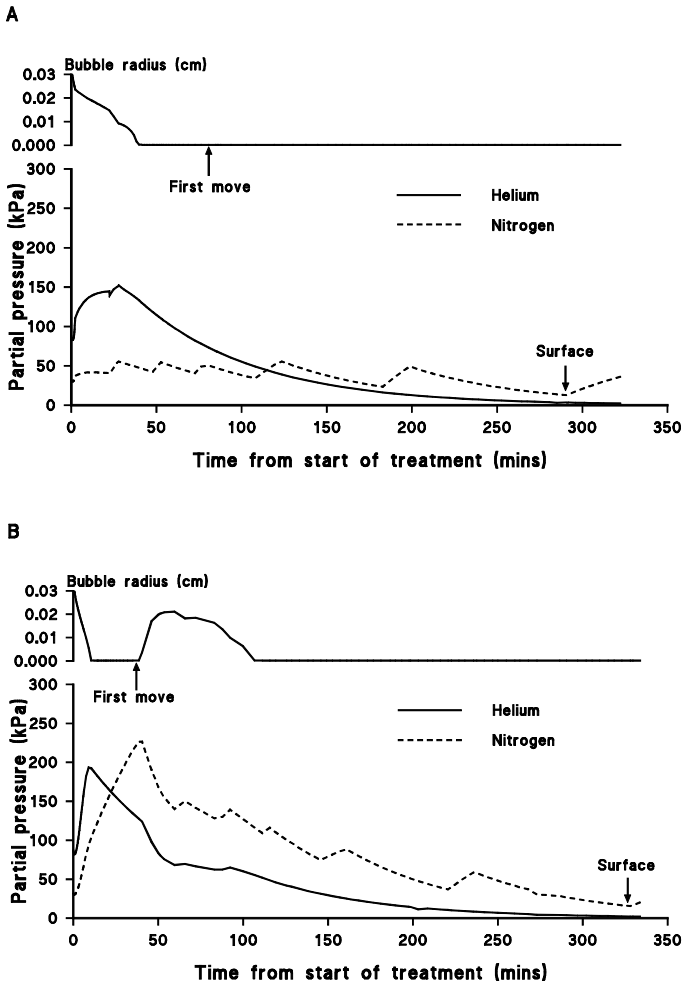

Figure 2 Showing the predicted reformation of bubbles in a tissue following the first move on USN6A and the absence of reformed bubbles following the first move during USN6.

Figure 3 shows the predicted volume of gas in bubbles for the mixed venous blood during the first 100 minutes of treatment by USN6A. This shows quite clearly that bubbles should be detected after the move from maximum depth, though the free gas volume at that time is considerably less than that at the start of treatment.

Thus the experiments were designed to answer the main question; are either of these treatments suitable for the treatment of bubbles following this severe primary exposure? The secondary questions to be answered are; are bubble numbers after the uncontrolled decompression really as high as the model predicts and can bubbles reform after the first move on USN6A?

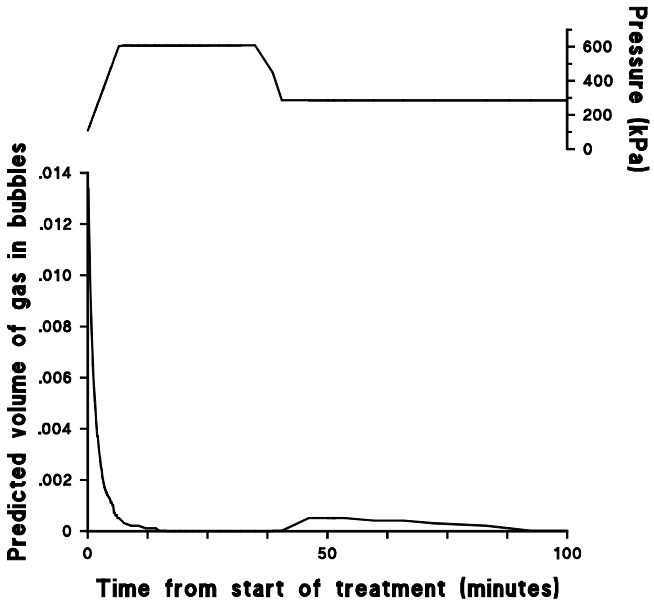

Figure 3 The predicted gas in bubbles in the mixed venous blood during the first 100 minutes of USN6A.

THE EXPERIMENTAL STUDY

The experiments were carried out in the laboratories of SINTEF Unimed in Norway with anaesthetized, spontaneously breathing pigs as the experimental model. The primary exposure was taken as 20 minutes at 81 metres. Ten animals breathed air during the ten minute surface interval, ten animals breathed oxygen.

Details of the normal laboratory routines are described in Reinertsen et al 1998. All experiments were approved by the Norwegian Committee for Animal Experiments. Chamber pressure, rate of change of pressure, breathing gases and gas switches were all controlled automatically using a system designed in the laboratory, (Kleven 1991). Bubble counts were recorded at one minute intervals; inspired and mixed expired gases were recorded at half minute intervals as was inspiratory flow, by Fleisch V pneumotachograph. No blood pressures were recorded as the decision was taken to minimise surgical intervention because of the possibility that such intervention and insertion of catheters could perhaps influence bubble numbers. The level of anaesthesia and general well being of the animals was monitored by blood gas analysis carried out on venous blood drawn from the ear. This was done during the stabilisation hour which preceded the primary compression and then not again until the first move of the treatment table was completed and after confirmation that bubbles had or had not reformed as a result of that move.

In addition to transoesophageal echocardiographic bubble detection (at 7.5 MHz) a femoral vein was exposed and a 10 MHz ultrasonic probe placed to allow detection of bubbles which must mainly derive from the large muscles of the leg.

THE EXPERIMENTAL RESULTS

Having minimised the extent of surgical intervention there are few physiological parameters available to indicate the well being of the animals before decompression. Table 3 shows the average mixed expired oxygen and carbon dioxide values for the two series during the last five minutes at 81 metres, before the primary decompression. Average inspired oxygen was 11.1%.

TABLE 3

Expired gases prior to primary decompression

	Expired oxygen (%)	Expired carbon dioxide (%)
Air on surface interval	10.5 ± 0.26	0.25 ± 0.07
Oxygen on surface interval	10.46 ± 0.11	0.25 ± 0.03

The two groups are essentially the same, the variance within each group is low and the gas values are as expected in healthy animals.

The experimental results following decompression are difficult to present as a group not least because the model prediction proved to be correct; an uncontrolled decompression from 20 minutes CUMA81 is a very severe, often fatal, experience. Even so some animals had few detectable bubbles during the ten minute surface interval. This variability is a common feature not only in animal experiments but also in experimental and operational exposures in humans.

Table 4 gives details of the outcome for the animals which breathed air during the surface interval. The number in brackets indicates the time of maximum bubble counts, decompression is completed at 84 minutes. The experiments marked ***** do not record the true maximum bubble counts. These animals died very quickly after surfacing at a time when bubbles counts were increasing rapidly. Not only do we fail to record the maximum because of the one minute interval between recordings but also, once the animal goes into circulatory failure, the number of bubbles appearing under the probe is determined by the blood flow. This means that there is not a meaningful value for the average maximum bubbles but the average of the values listed in Table 4 is 9.4 bubbles/cm^2, very much higher than the highest values shown in figure 1.

Table 4
Maximum recorded bubbles counts in pulmonary artery and femoral vein

	PA Bubbles (/cm^2)	Femoral bubbles	Outcome
Expt 1	0	0	No bubbles
Expt 5*	5.74	1203	Died before treatment
Expt 9*	5.57	474	Died before treatment
Expt 10	8.54 (94)	436	Completed USN6
Expt 11*	9.35	702	Died before treatment
Expt 12	0.11 (95)	0	Completed USN6
Expt 13	15.17 (89)	596	Died after USN6A compression
Expt 14*	7.41	1818	Died before treatment
Expt 15	22.56 (91)	1821	Died during USN6A
Expt 16	19.16 (94)	701	Died after USN6A compression

Table 5 shows the same information for the animals which breathed oxygen during the surface interval. In this series all animals survived to be recompressed and therefore the average maximum bubble counts is a more meaningful number though should still be interpreted with caution as, for example, animal 2/8 was recorded in the laboratory log as being in circulatory failure, very high heart rate reduced blood flow, at the time the maximum value was recorded. The bubbles counts are referred to as "maximum" rather than "peak" because in 2 animals this value was recorded after the treatment recompression had actually started. Figure 4 shows the time course of bubble numbers for one experiment with the arrow marking the start of recompression. Bubble numbers may not have reached a true peak before recompression started. Once again there is a very wide range of maximum counts in these experiments.

Table 5
Maximum recorded bubble count in pulmonary artery and femoral vein

	PA Bubbles (/cm^2)	Femoral bubbles	Outcome
Expt 7	5.6 (94)	0	Completed USN6A
Expt 8	0.07 (99)	386	Completed USN6
Expt 2/1	20.52 (96)	1175	Died during USN6
Expt 2/2	0.04 (86)	0.146	Completed USN6
Expt 2/3	16.01 (86)	1964	Died after USN6A compression
Expt 2/4	22.1 (85)	1928	Died during USN6
Expt 2/5	21.07 (92)	1642	Died after USN6A compression
Expt 2/6	16.74 (94)	1694	Completed USN6
Expt 2/7	0.04 (86)	0	Completed USN6A
Expt 2/8	20.94 (89)	1825	Died after USN6A compression
Average	**12.3 ± 9.7**		

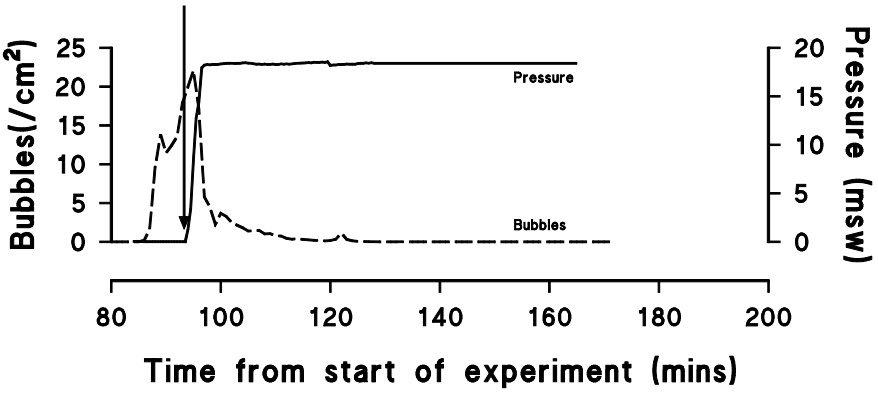

Figure 4 Time course of bubble numbers relative to pressure profile

The failure to record true peak bubble counts means that it is impossible to evaluate the effect of oxygen breathing during the surface interval though it does seem that the oxygen allowed more animals to survive to begin treatment.

Table 6 lists the experiments in which the animals survived to, at least, beyond the first move of the treatment decompression. Both air breathing and oxygen breathing experiments are included. Time to resolution of bubbles is measured from the start of the recompression and relates to the bubbles which resulted from the primary exposure.

TABLE 6

Bubble history for animals which survived beyond first move of treatment

	PA Bubbles (/cm^2)	**Time to resolution of bubbles**	**Later bubbles**	**Table**
Expt 10	6.5	43.5	None	USN6
Expt 12	0.11	11.5	None	USN6
Expt 15	22.6	26.5	0.77	USN6A
Expt 7	5.6	31.5	0.03	USN6A
Expt 8	0.07	7.5	None	USN6
Expt 2/2	0.04	before treatment	None	USN6
Expt 2/6	16.74	54	None	USN6
Expt 2/7	0.04	before treatment	None	USN6A

The wide range of bubble counts from the primary exposure, and the small number of animals which completed treatment to beyond the first move, make it difficult to quantify the results. However some tentative conclusions can be drawn. All animals in Table 6 except #15 completed the treatment. None showed any evidence of reformation of bubbles at the end of the treatment. Both USN6 and USN6A are shown to get rid of the bubbles and to do so well before the end of the treatment. These treatments continue long enough for the liberated gas to be cleared from the body. The most useful experiment from this point of view is #2/6 in which bubbles from the primary dive were certainly high enough to come within the range in which animals frequently die. This is the strongest evidence that USN6 is an adequate treatment table for this kind of accident.

With the exception of #15, which died during treatment and therefore could have been in circulatory failure, there is a relationship between primary bubble count and time to resolution of bubbles with some evidence that USN6 takes longer than USN6A to resolve the bubbles.

Of the three animals which started USN6A two had a recurrence of bubbles after the first move. None of the four which had USN6 had a recurrence of bubbles.

CONCLUSIONS

Although it would have been preferable to have a more homogenous set of experimental results, and more definitive conclusions, the experimental results are much as predicted. The first conclusion is that an uncontrolled decompression from 20 minutes CUMA81 is more likely than not to be a fatal experience. Secondly both USN6 and USN6A can resolve the bubbles and appear to do so with sufficient treatment time left to clear the liberated gas. The highest bubble count for which USN6 was successful was in experiment 2/6, a peak bubble count of 16.7/cm^2, well in excess of K-M score IV. Thirdly there is some evidence that the presence of inert gas in the breathing mixture at the maximum depth on USN6A can cause bubbles on the first move, whereas there is no evidence of reformation of bubbles on USN6.

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Respiratory Changes and Consequences for Treatment of Decompression Bubbles Following Severe Decompression Accidents

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INTRODUCTION

Earlier papers describe the theoretical and experimental work carried out to determine the best treatment strategy following severe decompression accidents during use of self-contained breathing apparatus such as the Canadian Underwater Minecountermeasure Apparatus (CUMA). The previous paper has described the extent to which decompression bubbles were formed in anaesthetised animals subjected to controlled primary and treatment hyperbaric procedures; the range of bubble counts was from zero to fatal. Treatment recompression apparently removed the bubbles quickly but in many cases this was not followed by an improvement in the condition of the animal and death occurred during the treatment. The experiments were designed to require minimal surgical intervention prior to the experiments to reduce the possibility that bubble numbers were influenced by surgery and indwelling catheters. There is therefore relatively little information available from which to draw conclusions about the immediate cause of death. Respiratory gases were monitored and a study of the information contained in those data sheds some light on this and allows a tentative conclusion to be drawn.

EXPERIMENTS

As described in the previous paper the experiments used either air or oxygen as the breathing gas during the 10 minutes surface interval between the end of the rapid primary decompression and the start of the treatment recompression. The experiments in which oxygen was breathed are the most useful for present purposes as all animals survived to start treatment including those with very high bubble counts. Five animals completed treatment. Table 1 summarises the outcome of these ten experiments.

Inspiratory and expiratory gas bags are used to enable use of controlled inspired gas mixtures and measurement of expired gases (Reinertsen et al 1998). Oxygen concentrations are measured in both. The volume of each bag is about 1 litre, equivalent to 5 or 6 tidal volumes, and therefore reflect gas switches fairly rapidly at normal respiratory rates. In addition a fast response carbon dioxide analyzer draws gas from the trachea so that end tidal carbon dioxide levels can be determined.

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Table 1
Maximum recorded bubble count in pulmonary artery and femoral vein

	PA Bubbles (/cm^2)	Femoral bubbles	Outcome
Expt 7	5.6 (94)	0	Completed USN6A
Expt 8	0.07 (99)	386	Completed USN6
Expt 2/1	20.52 (96)	1175	Died during USN6
Expt 2/2	0.04 (86)	0.146	Completed USN6
Expt 2/3	16.01 (86)	1964	Died after USN6A compression
Expt 2/4	22.1 (85)	1928	Died during USN6
Expt 2/5	21.07 (92)	1642	Died after USN6A compression
Expt 2/6	16.74 (94)	1694	Completed USN6
Expt 2/7	0.04 (86)	0	Completed USN6A
Expt 2/8	20.94 (89)	1825	Died after USN6A compression
Average	**12.3 ± 9.7**		

RESULTS

It is possible to derive some indication of respiratory function from the amount of oxygen extracted by the lungs, the inspired-expired oxygen partial pressure difference. This gives a crude measure of overall ventilation:perfusion balance though it is necessary to exercise some care in interpreting results in animals which have decompression bubbles. For example though a relative hypoventilation, ventilation lowered to an inappropriate extent compared to pulmonary blood flow, will give an increased inspired-expired oxygen difference; reduction in both ventilation and pulmonary blood flow can give a completely normal inspired-expired difference. An inspired-expired difference of zero can probably be safely taken as an indication that the animal is dead but the values can go from grossly abnormal to being apparently normal shortly before death as the failing circulation drops to a level which matches the reduced ventilation. An extremely low breathing rate results in a delay in the effect of a gas switch being transmitted to the expiratory bag which can result in negative values for the oxygen difference.

Table 2 shows oxygen difference before the primary compression and before the primary decompression for the experiments listed in Table 1, the animals breathing oxygen during the surface interval. Maximum bubble counts are also listed. Up to the start of the primary decompression all animals appeared to be similar, there is no indication of those animals which will have the highest bubble numbers.

Table 3 shows the same parameter:- at the end of the surface interval; on completion of the treatment compression; after a period of oxygen breathing at 18 metres; on completion of treatment. The five animals which survived to complete treatment did not have greatly changed oxygen differences after the primary decompression and returned almost to pre-experimental values after the treatment. Three had bubbles; #7 had 5.6 bubbles/cm^2 (equivalent to Doppler grade IV- according to Eftedal et al 1998), # 2/2 had 1.14 bubbles/cm^2 (Doppler grade III) and # 2/6 had 16.7 bubbles/cm$_2$. Experiment 2/6 is of particular interest as that level of bubbling proved fatal in other animals. With the exception of # 2/5 the animals which did not survive had abnormally high oxygen differences at some point during the experiment. Again animal 2/6 is different, being characterised by apparently normal oxygen extraction throughout despite the very high bubble count.

Table 2
Inspired-expired oxygen difference (kPa)

	Pre-compression	Pre-decompression	Bubble count
Expt 7	1.67	5.55	5.6
Expt 8	1.41	4.77	0.07
Expt 2/1	2.63	7.42	20.5
Expt 2/2	1.97	4.64	1.14
Expt 2/3	2.32	5.11	16.0
Expt 2/4	1.90	5.52	22.1
Expt 2/5	0.33	6.33	21.1
Expt 2/6	1.89	5.24	16.7
Expt 2/7	2.05	5.52	0.04
Expt 2/8	2.01	4.94	20.9
Mean ± St Dev	**1.82 ±0.62**	**5.50 ± 0.83**	

Table 3
Inspired-expired oxygen difference (kPa)

	Surface Interval	Post Treatment Compression	After oxygen breathing	After Treatment
Expt 7	6.58	1.85	1.75	1.64
Expt 8	2.80	2.51	3.24	2.01
Expt 2/1	11.94	122.0		
Expt 2/2	3.62	2.28	2.43	1.94
Expt 2/3*	27.0	-0.05		
Expt 2/4	4.99	107.1		
Expt 2/5*	2.92	-0.87		
Expt 2/6	2.82	3.54	3.88	2.52
Expt 2/7	3.96	2.64	2.53	2.08
Expt 2/8*	18.54	-0.13		
Mean ± St Dev			**2.77 ± 0.82**	**2.04 ± 0.32**

* animal dead at the end of treatment compression

DISCUSSION

Animal 2/6 survived the procedures against the odds. A bubble count of 16.7 /cm^2 would usually prove fatal. This animal's gross pulmonary function appeared not to be deranged by that extent of bubbling. A similar level of bubbling in experiment 2/3 led to early death following an abnormally high oxygen extraction. What is the difference? Were there any critical differences in the lungs of these animals? Should we be considering some kind of pulmonary therapy during treatment in this kind of accident?

There is a clue to the cause of the differences between these animals in the pattern of respiration. Tidal ventilation of the lungs can be seen on the trace which records end-tidal carbon dioxide concentration. For this purpose a useful comparison can be made between number 2/4 and 2/6 both of which had USN6 as treatment, 2/4 died 30 minutes after disappearance of the bubbles, well into the treatment. Figures 1 shows the breathing rate for experiment 4 together with the pressure profile and the bubble counts; the respiratory rate for experiment 6 is displayed as a box enclosing all values. The very low respiratory rate of animal 4 explains the high oxygen extraction; the rate dropped as bubble count increased but did not rise again as the bubbles were reduced during treatment. There appears to have been some kind of irreversible change in animal 4 which was not experienced by animal 6.

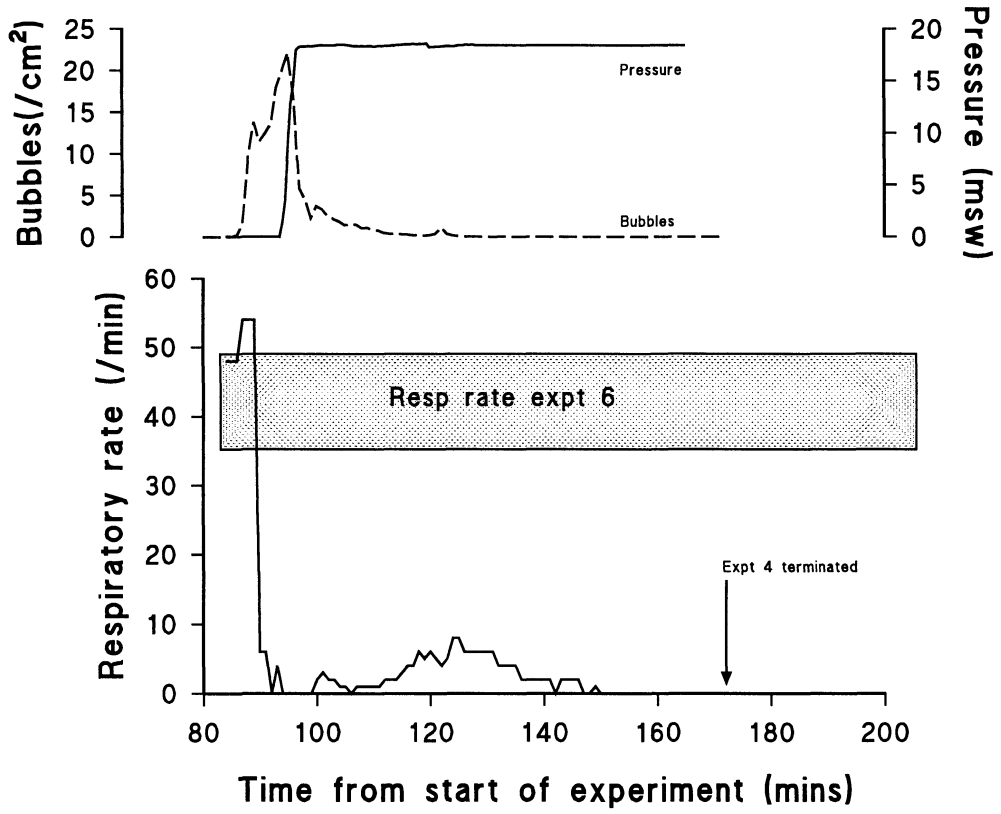


Figure 1 Respiratory rate, pressure profile and bubble counts for experiment 2/4.

Figure 2 shows pulmonary artery bubble counts and end tidal carbon dioxide levels for animal 4 over part of two consecutive minutes as bubbles developed. Figure 3 continues with end tidal carbon dioxide half a minute after the second trace in figure 2 and also 30 minutes later. These figures illustrate the complete abolition of a regular respiratory pattern within the space of about 2 minutes. The final respiratory pattern is prolonged expirations with irregular single inspiratory efforts, apnoea.

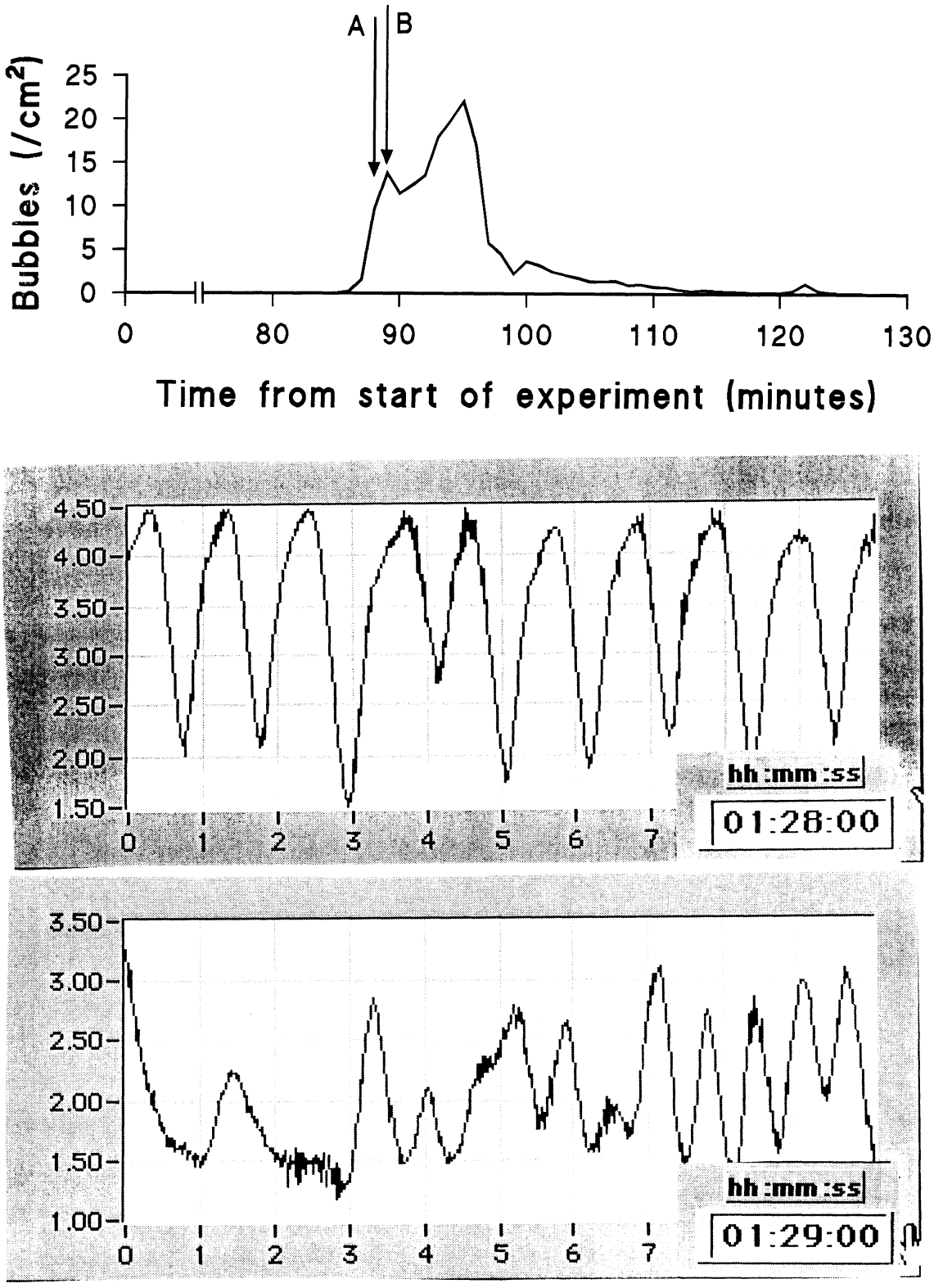
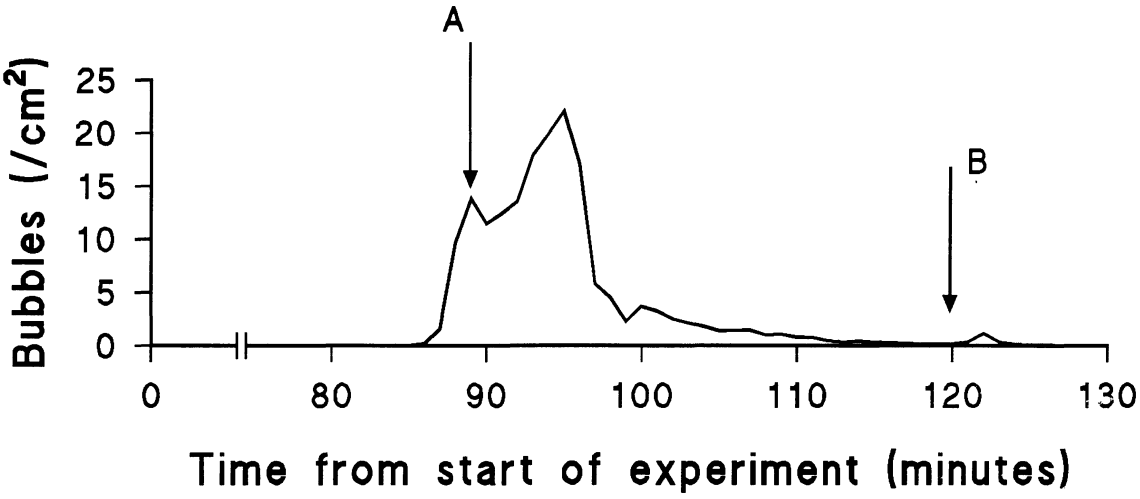


Figure 2 Respiratory patterns, experiment 2/4. See text for details



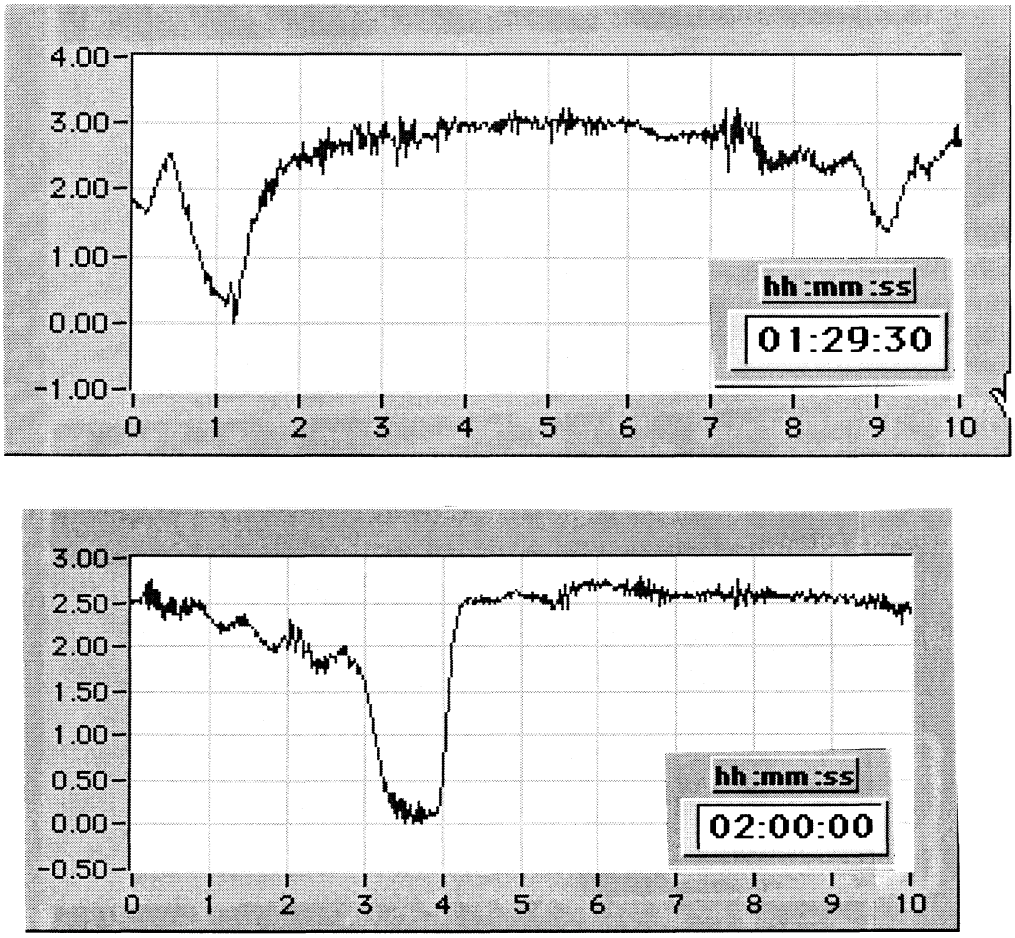


Figure 3 Respiratory patterns, experiment 2/4. See text for details

Apnoea is characteristic of herniation of the respiratory centre through the foramen magnum which is usually a consequence of increased intracranial pressure. The fact that a regular respiratory pattern was not restored after resolution of the bubbles supports this hypothesis, such herniation usually requiring intervention if it is to be reversed.

Theoretical calculations suggest that volume of the free gas phase in the brain is equivalent to a volume increase of 3 - 4%. The time course of the change in respiratory pattern is rather too quick to explain the initial change as resulting from anything other than a pressure increase due to the increase in volume as the free gas phase forms. However there is the possibility that the bubbles caused endothelium damage with resultant increase in extravascular fluids, leading to further increase in intracranial pressure over and above that caused by the increased free gas volume. Pou et al (1993) have shown that the exudation of lymph from the pulmonary vasculature continues after the resolution of gas bubbles; it is probably safe to assume a similar pattern in the brain. This would suggest that even though the free gas volume itself may not be enough to cause herniation the removal of free gas by treatment compression will not arrest progress towards the irreversible change, intracranial pressure continuing to increase after the removal of bubbles as fluid leaves the leaky vasculature.

The respiratory pattern seen in experiment 4 matched the patterns seen in the other animals which did not survive treatment.

CONCLUSION

The primary exposure used in this work was extreme and has apparently resulted in changes beyond those usually reported in the decompression treatment literature. In a severe decompression accident the focus of effort would normally be on initiating hyperbaric treatment as rapidly as possible. This work suggests that, in addition to working to reduce bubble formation and free gas volumes, attention should also be given to clinical procedures to reduce intracranial pressure. If so then the first stage must be to draw up guidelines to define the type of decompression accident which could cause a large enough free gas phase. In addition to the type of hyperbaric exposure used in this work free ascent, as used for submarine escape, is another possible situation in which increased intracranial pressure should be considered a likely cause of death. The same theoretical model as used in the current project also predicts the brain to be the main "target organ" for bubble formation in the submarine escape procedures (Flook 1997).

In decompression accidents of a severity similar to that described here the need to prevent increased intracranial pressure may shift the priority in the first 10 to 15 minutes away from hyperbaric treatment. Ideally both treatment to minimise the increase in intracranial pressure and the treatment to reduce bubbles would start without delay but in practice it may be necessary to consider holding off recompression for a few minutes to allow other treatment to be started.

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Effect of Exercise on Bubble Activity during Diving

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Exercise is intrinsic to military and commercial diving, and exercise may either increase or decrease the risk of decompression sickness (DCS) after diving. Vann and Thalmann (1) explained the relation between exercise, diving, and the risk of DCS using the parameters of: exercise intensity, exercise duration, and the phase of diving during which exercise is performed. Before diving, intense, vigorous or ballistic exercise which induces muscular soreness may also create microscopic intramuscular gas nuclei which increase the risk of DCS. During diving, the increased metabolic rate of exercise can enhance the rate of inert gas absorption, rapidly causing tissue supersaturation and subsequently increasing the risk of DCS (2-4). After diving, vigorous exercise or forceful straining which involve the Valsalva manoeuver is associated with cavitation, bubble formation, and the coalescence of micro-bubbles all of which increase the risk of DCS (1,2,4,5). Thus, although exercise is integral to diving, exercising before, during, and after diving, for several different reasons, may be associated with an increased risk of DCS. Exercising appropriately during decompression, however, may facilitate inert gas elimination and reduce the risk of DCS. While this hypothesis originated with Boycott, Damant and Haldane (6) in 1908, several investigators studying both divers and astronauts have since suggested that exercise may facilitate inert gas elimination and therefore reduce the risk of DCS after diving or during spaceflight (1,2,4,7-11)). Rather than study DCS symptomatically, bubble activity may be measured directly using Doppler ultrasonic monitoring for venous gas emboli (VGE) (12). The purpose of this investigation was to test the hypothesis that bubble activity can be reduced by performing moderate intermittent exercise during decompression.

MATERIALS AND METHODS

This investigation was approved by the Human Research Ethics Committee of the Defence and Civil Institute of Environmental Medicine (DCIEM), Department of National Defence, Canada, and conducted in the water-filled portion of the Diving Research Facility. Thirty-nine healthy males, 11 Canadian military divers and 28 commercial diving students, voluntarily performed a total of 100 simulated dives in the hyperbaric chamber during the study. Each experimental dive (Fig. 1) was to a pressure of 450 kPa equivalent to 45 metres of seawater (msw) for 30 min followed by a 55 minute staged decompression according to the DCIEM Standard Air Diving Table (13). Some divers elected to make a 300 kPa (30 msw), 12 min no-decompression "work-up dive" no less than two days before their first experimental dive. A minimum of five days was required between the beginning of any two consecutive dives for all subjects. Subjects were assigned to one of four trials:

inactive during both the bottom period and during the decompression – (*I/I*),
inactive during the bottom and active during decompression – (*I/A*),
active during the bottom and inactive during decompression – (*A/I*), and
active during the bottom and active during decompression – (*A/A*).

Active subjects performed five minutes of moderate arm or leg exercise beginning at minute 5, 15, and 25 of the compression, and/or minute 7, 15, 25, 35, and 45 of the decompression (Fig. 1). Each exercise period was followed by five minutes sitting at rest. Leg exercise was performed on submersible electrically braked bicycle ergometers (Warren E. Collins, Braintree, Ma.) installed in the dive chamber. The ergometers were waterproofed

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in the manner described by Thalmann et al (14). Arm exercise was performed on an specially constructed paddle ergometer or by lifting light weights. The intensity of both the arm and leg exercise was maintained at approximately 50% of each subject's previously determined arm or leg VO_2 max by monitoring heart rate (7,15,16) via an unorthodox precordial electrocardiograph lead obtained by using three chest electrodes hard wired through the data acquisition unit of the dive chamber and connected to standard clinical electrocardiograph recorders equipped with digital cardiotachometers (MultiCare Model 304, Rigel Research Ltd., Morden, Surrey, England). No attempt was made to correct the heart rates for the effects of immersion or increased PO_2.

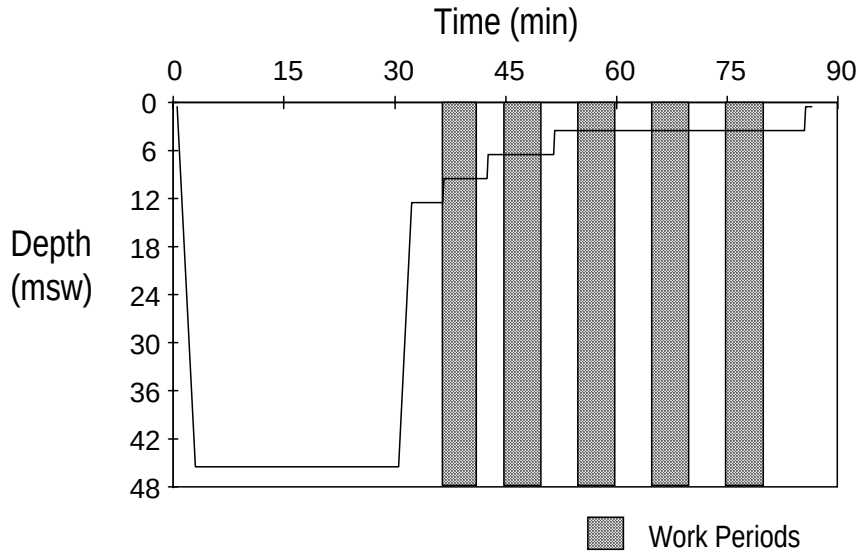

Figure 1. Dive profile used (45 msw for 30 minutes) showing activity periods during decompression stops.

VGE monitoring was conducted at approximately 21, 61, 100, and 147 minutes after the decompression ended by experienced Doppler technicians using ultrasonic bubble detectors (TSI DBM 9008, Techno Scientific Inc. Woodbridge, Ont.). Each subject's precordium was monitored with the subject standing at rest. Both the left and right subclavian veins were also monitored and assessed at rest. Rather than treating the left and right subclavian scores of each subject independently, the highest of the two scores was used as the most meaningful indicator of VGE status and DCS risk. The auditory output from the bubble detector was scored manually, using the Kisman-Masurel (KM) code and simultaneously recorded on audiocassettes. The KM code was converted to a single bubble grade using a 12 point ordinal bubble grade from 0 to IV (0,1-, 1,1+... IV-, IV, IV+). The bubble grade at rest was subsequently used to calculate the Kisman integrated severity score (KISS) according to the following formula (17,18).

$$KISS = \frac{100}{4^{\alpha}(t_4 - t_1)} \sum_{i=1}^{3} \frac{(t_{i+1} - t_i)(d_{i+1}{}^{\alpha} + d_i{}^{\alpha})}{2}$$

where: $\alpha = 3$ (α accounts for the fact that the bubble grade is not a linear measure of bubble quantity)
t = time of observation in minutes after reaching the surface and
d = Doppler grade (0 to IV) observed at time t.

The KISS is an index derived from integrating the bubble scores over the observation period; hence it takes into account not only the bubble grade but also the time distribution of observed VGE. It is related to the volume of released gas and gives a better representation of overall VGE activity than the maximum bubble grade observed after a dive.

In addition to the KISS analysis, the precordial bubble grades observed in the precordium were also converted to bubble count estimates (BCE) (bubbles/cm^2) using a scale (Table 1) developed by Eftedal *et al*. (19,20). The BCE was derived from an analysis of simultaneous transesophageal echocardiography and Doppler monitoring in pigs.

Table 1. Correspondence between KM Bubble Grades and Bubble Count Estimates (bubbles/cm^2)

K.-M. grade	0	I-	I	I+	II-	II	II+	III-	III	III+	IV-	IV
Bubbles/cm^2	0	0.01	0.05	0.1	0.15	0.2	0.3	0.5	1	2	5	10

A preliminary analysis of these data revealed that the effects of arm and leg exercise were quite similar and, in fact, not significantly different from each other ($p>0.05$). Consequently, these data were pooled and activity (*A*) data include both arm and leg exercise.

Subject populations in the four groups were as follows: *I/I* and *I/A* groups – 12 subjects each; *A/I* and *A/A* groups – 13 subjects each. Although some subjects did more than one dive in each group, only the first dive done by a subject was selected for analysis. Furthermore, when a subject participated in both the groups being compared, the results of only one experiment were selected (i.e., if a subject initially participated in group *I/I* and later in group *I/A*, only the data from the *I/I* dive were used). Finally, subjects in *I/I* were different from those assigned to *I/A* and those in *A/I* were different from those assigned to *A/A*.

Both the KISS and BCE values can be treated as scores or indices and their values can be considered non-parametric. The appropriate test statistic of such data between independent groups is the Mann-Whitney U or rank sum test (21). This test is one of the most powerful non-parametric tests to test whether or not two independent groups have been drawn from the same population. Essentially this test determines whether the median scores between the groups is statistically significant, in this case at $p < 0.05$.

Based on the hypothesis that physical activity during decompression reduces bubble activity, the following groups were tested: *I/I* vs. *I/A* and *A/I* vs. *A/A*, with the expectation that bubble activity should be higher in the former group of each pair.

RESULTS:

Figure 2 shows the comparison between the means of the KISS values for the *I/I* and *I/A* groups and the *A/I* and *A/A* groups. The median precordial and subclavian KISS's for the divers were consistently significantly lower for *I/A* compared to *I/I*. For the *A/I* vs. *A/A* trials, the resting precordial KISS was significantly lower for the *A/A* condition. Although there was a decrease for the subclavian veins for the *A/A* trials, the decrease was not significant at the 0.05 level.

Figure 3 shows a comparison of the mean BCE observed at times 21, 61, 200 and 147 minutes after the end of decompression. The BCE can be considered to be a "snapshot" of VGE activity at discrete times after a dive. The median BCE's for trial *I/A* at minutes 61 and 100 at rest were significantly lower compared to trial *I/I*. The median BCE's for trial *A/A* at rest at minutes 100 and 147 were significantly lower compared to trial *A/I*.

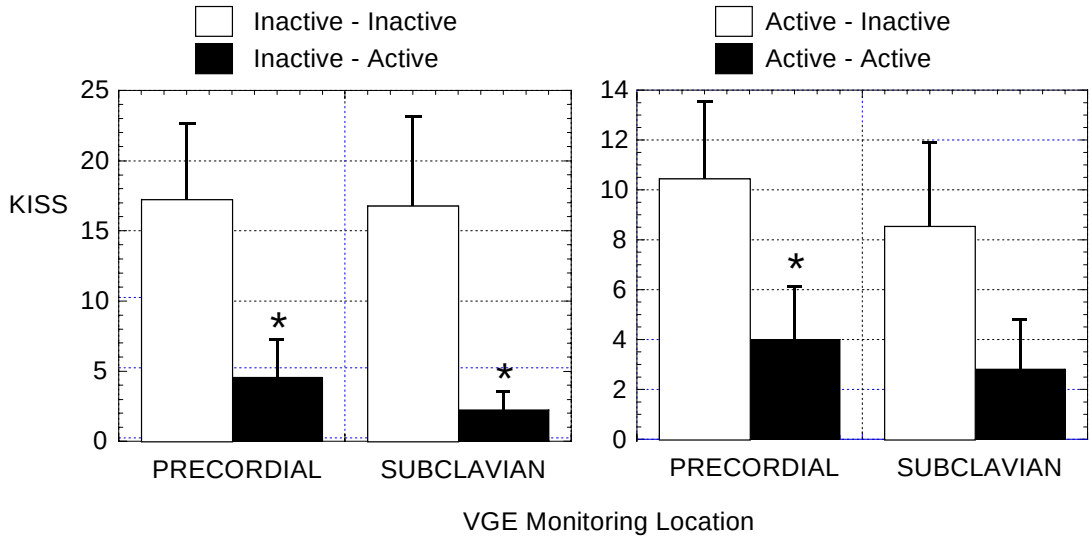

Figure 2. Mean and standard error for Kisman Integrated Severity Scores in the precordium and subclavian veins for the diver at rest.

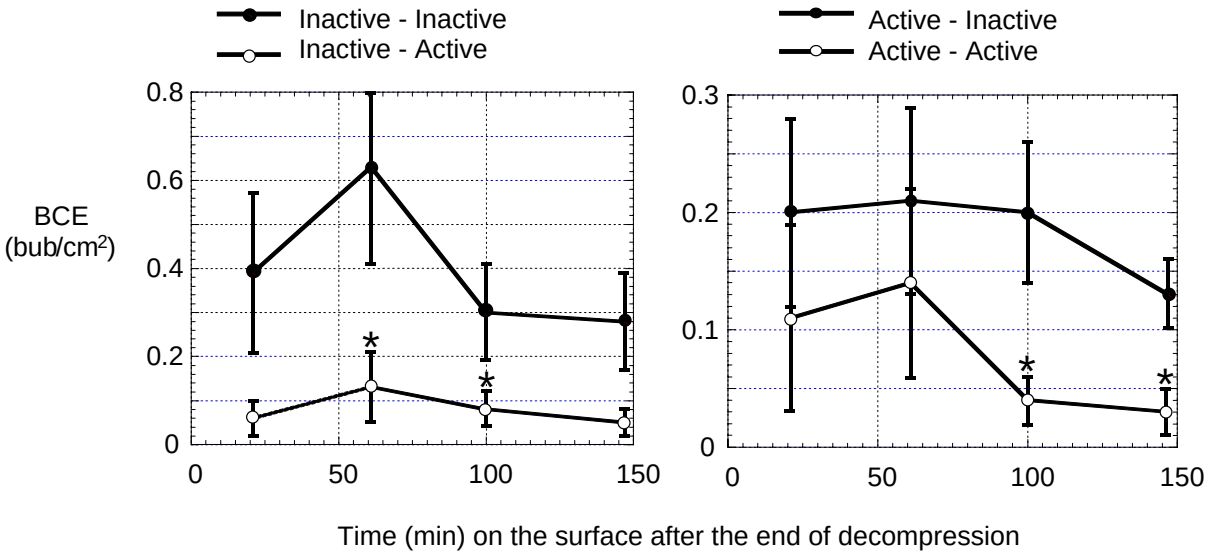

Figure 3. Bubble Count Estimates (bubbles/cm2) at 21, 61, 100 and 147 minutes after decompression.

DISCUSSION:

In all group comparisons of KISS and BCE, scores tended to be higher with inactive compared to active decompression, and these differences were significant in 3 of the 4 KISS comparisons and in half of the BCE comparisons. On the strength of the trends exhibited by these observations, it would seem reasonable that statistical significance would be achieved with greater numbers of subjects, and so it would be logical to conclude support of the hypothesis that physical activity during decompression decreases Doppler-monitored bubble activity. This suggests that mild exercise during decompression enhances inert gas elimination and, by extension, may reduce the risk of decompression sickness and enhance diver safety. It has not determined whether or not mild exercise may enhance inert gas elimination to the point of reducing the times required for inactive decompressions.

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Thermography - A Method for the Evaluation of the Resistance of Military Pilots, Parachutists and Divers at Hypo and Hyperbaric Exposure

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Summary: A mixed team from the AMI and the NIAR has developed a long - term activity in the field of the hypo and hyperbaric exposure of aeronautical staff and divers - relevant to the topics of the HFM Symposium in the field of "Selection and Training". The subject of the work refers to the evaluation of the efficiency of thermography (a non-invasive and not often used investigation method) in the study of the circulatory system answer to the pressure variation during the exposure of the human body to hypo and hyperbaric conditions. Using the thermography, we tried to build-up a monitoring system of the physiological and circulatory system parameters changes at hypo and hyperbaric exposure.

Keywords: thermography, hypo and hyperbaric exposure monitoring system, resistance of military personnel.

Introduction.

Analysing the trend in medical research, it is clear that every year, more and more expensive and sophisticated devices are introduced to achieve the goals of the researchers. Only a few countries or research centres can follow that way, others, not being able to afford themselves such science policy, they have to try to find something different. Our multi-year activity tried to establish how thermography (n non-invasive paraclinic method) is able to contribute in simulated flight or dive conditions to the vascular system parameters monitoring. We showed that thermography, combined with informatics and statistics can offer valuable data to the medicine.

What we obtained is a method - an early warning system - that needs minimum investments and which could cut future costs involving the selection of flight candidates and the eventual loss of flying material by filtering the high risk candidates.

Objective of research

Thermography is. a method of research enabling to record the thermal data for different anatomical regions. The temperature is function of different stress applied to the subjects. We tried to analyse the thermal answer of specific professional groups:

- of pilots - to a dynamic stress - hypobaric hypoxia due to the exposure and physical test in a pressure chamber,
- of parachute jumpers simulating the conditions of a real jump in a pressure chamber,
- of divers in hyperbaric conditions due to the exposure in a pressure chamber or real diving in the Black Sea.

The result was the build-up of a system, which could be used to evaluate the risk groups of subjects, offering a method to screen-out the flight candidates.

Design and setting

The scope of the study was to record with thermographic means, the changes in circulatory system during pressure variations due to exposure in a pressure chamber:

- simulating flight conditions at 5500 m altitude and equivalent pressure and oxygen conditions (for pilots and parachute jumpers) and
- conditions for wet or dry depth at 10 m, 20 m or 50 m (for divers).

We used the AMI ÖKG -type pressure chamber with controlled pressure and temperature conditions for the hypobaric conditions and the Medical Naval Centre - Constanta pressure chamber for hyperbaric conditions. The thermal images were recorded with an IRTIS - 200 Russian built system and subsequently analysed with our own dedicated programs.

Paper presented at the RTO HFM Symposium on "Operational Medical Issues in Hypo- and Hyperbaric Conditions", held in Toronto, Canada, 16-19 October 2000, and published in RTO MP-062.

The results were correlated with the physiological and physiopathological data of subjects.

Protocol and subjects of the study

The study was extended on a three-year period and comprised the analysis of pilots, parachute jumpers and divers. Subsequently we will refer to each group.

1-st group - flying crews. We studied 54 subjects having professions linked to flight (pilots and flight engineers). Statistically they represent a homogenous group having similar background: flight training.

All the subjects were exposed for 15 minutes to hypobaric hypoxia in the pressure chamber. The exposure was between 9.30 and 12.00 AM, two hours after a light breakfast.

age	pilots	flight engineers
20-30	9	6
30-45	29	10
Total	38	16

We performed the following recordings:

- before exposure - EKG recording
  - blood pressure (BP) and pulse readings
  - thermographical recording.
- during exposure (duration - 15 minutes) - effort test in the 7th minute of the exposure
  - EKG recording - at ground level
  - at 5500 m altitude (before and after the effort test)
- after exposure - EKG recording
  - BP and pulse readings,
  - thermograpical recording
- 15 minutes after exposure - thermographical recording.

2-nd group - parachute jumpers. We studied 20 parachute jumpers within the same age group and with similar military training. The following recordings were performed

- before exposure - EKG recording
  - blood pressure (BP) and pulse readings
  - thermographical recording.
- after exposure - EKG recording
  - BP and pulse readings,
  - thermograpical recording
- 15 minutes after exposure - thermographical recording.

3-rd group - divers. The study extended on a group of 16 trained submarine sailors and 9 trainees in a diving school (a homogenous group from the point of view of age and training).

The conditions of thermographical recordings were those required by the European Association of Thermography: approximately 21°C and normal pressure, with restricted air ventilation and controlled humidity. Each of subjects had three series (before, immediately after the exposure and 15 minute after the exposure) of four thermograms (head, arms and hands, feet and legs with frontal and back views). The thermal images of the subjects form an archive, subsequently read and analysed by the dedicated program.

Physiological and physiopathological data

Due to the fact that the recording conditions, phyisiology, physiopathology and the interpretation of results are different in case of hypobarism and hyperbarism, in the present paper we will refer to the first case - hypobaric hypoxia.

Hypobaric hypoxia - represents the decrease of the atmosphetic pressure and implicitly of the partial pressure of oxygen in the breathed air, it appears in the flight at high altitude.

The most important factor in providing the necessary oxygen to the organism is its partial pressure.

level	atmospheric pressure	O_2 partial pressure
sea level	760 mm Hg	160 mm Hg
5500 m altitude	405 mm Hg	85 mm Hg

At high altitude the human body is subject to the hypoxic stress, its resistance differs from subject to subject. The healthy ones resist to the absence of oxygen at an altitude of 5500m, well trained subjects resist well above - up to 8000 m. The adaptation of the human body is achieved by compensatory physiological mechanisms to provide the necessary oxygen to the principal organs and systems.

These mechanisms are: **a. respiratory**
b. circulatory
c. enzymatic (biochemical)

a.) Respiratory mechanism

The stimulus starting this mechanism is represented by hypoxia. The receptors are:

- specialised nervous cells localised in the lateral reticular formation
- sinocarotidian and cardioaortic chemoreceptors.

The afferent and efferent paths are complex and localized at the level of central and peripheral nervous system. The effectors are the respiratory muscles. The compensatory answer mechanism is represented by the increase in quantity of breathed air

- by increasing the volume of air breathed in a single breathing,
- by increasing the respiratory frequency (hyperventilation).

b.) Circulatory mechanism.

This mechanism is started by the same stimulus - the hypoxia, and is compensating the diminution of the partial pressure of oxygen, by compensating the repartition of blood in different organs, achieving a vasodilatation in the vital ones: brain, heart, kidneys, and a vasoconstriction in rest.

Also it achieves the acceleration of blood flow, by increasing the heart rhytm.

c.) biochemical-enzymatical mechanism

It compensates the low partial pressure of oxygen by:

- increasing the capacity of blood to transport the oxygen from the lungs to the tissues
- adaptation of tissues to less oxygen, using the anaerobe cycle to obtain energy with an oxygen.debt, compensated lately, when external conditions return to normal.

The changes in the circulatory system draw changes in local temperatures, visualised, recorded and quantified in the changes ot the thermal images.

Results

We divided the two groups: pilots and parachute jumpers in subgroups versus the following three criteria:

A. heredo - colateral antecedents

B. variations of pulse and blood pressure (BP)

C. thermographic abnormalities (not following the theory) due to hypoxic exposure

A. The first classification depends upon the heredo - colateral antecedents of subjects (parents with cardiac diseases: hypertension, vascular cerebral accidents, etc.). We established two groups::

group A.I - subjects with antecedents

group A.II - subjects without antecedents,

considering that the belonging to the group **A.I** represents a risk factor.

B. The second classification of the subjects was versus their clinical parameters (pulse and blood pressure - BP)

group B.I - constant BP and pulse, emphasizing excellent health and an excellent adaptation mechanism,

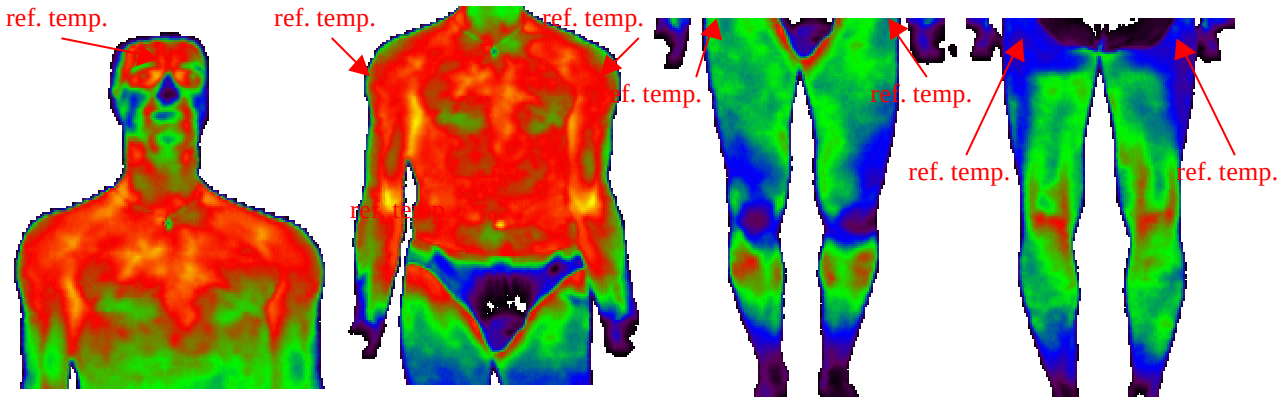
group B.II - moderate increase of values of BP and pulse denoting a good adaptation mechanism.

group B.III - decreased values of BP and pulse meaning a deficit in the adaptative physiological answer.

The belonging to the group **B.III** represents a risk factor

C. The third classification was versus the thermographical results:

We determined the maximum, mean and minimum temperature for each anatomical region and also a reference temperature for each region (a point without blood vessels - forehead, shoulders and hips). (fig.1)



cephalic extremity | upper extremities | lower extremities frontal view | lower extremities back view

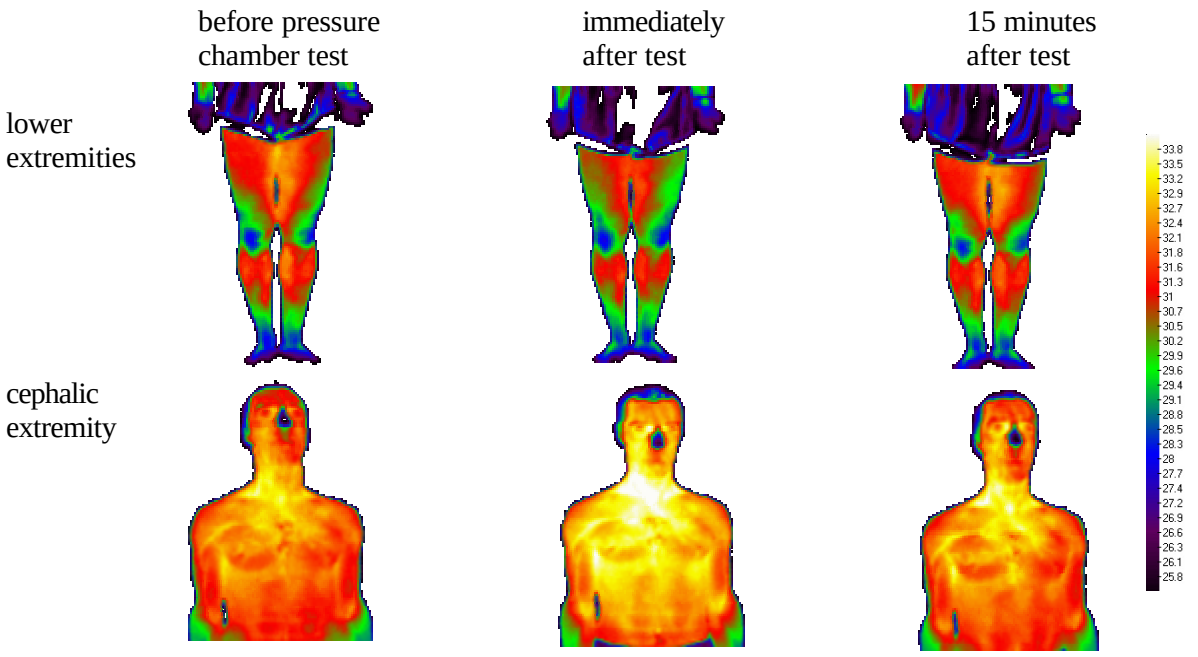
We evaluated the difference between the maximum temperature and the reference temperature (the same for the mean and minimum temperature) for each anatomic region before, immediately after and 15 minutes after the pressure chamber test. Analysing the results we obtained the thermographic classification as fpllows:

group C.I - normal thermographical recordings.

- decrease of the temperature up to 1,5°C of upper and lower extremities after the hypoxic exposure

- increase of the temperature of the cephalic extremity immediately after the test and its return to the initial values after 15 minutes.

This denotes an excellent adaptation to hypoxia.

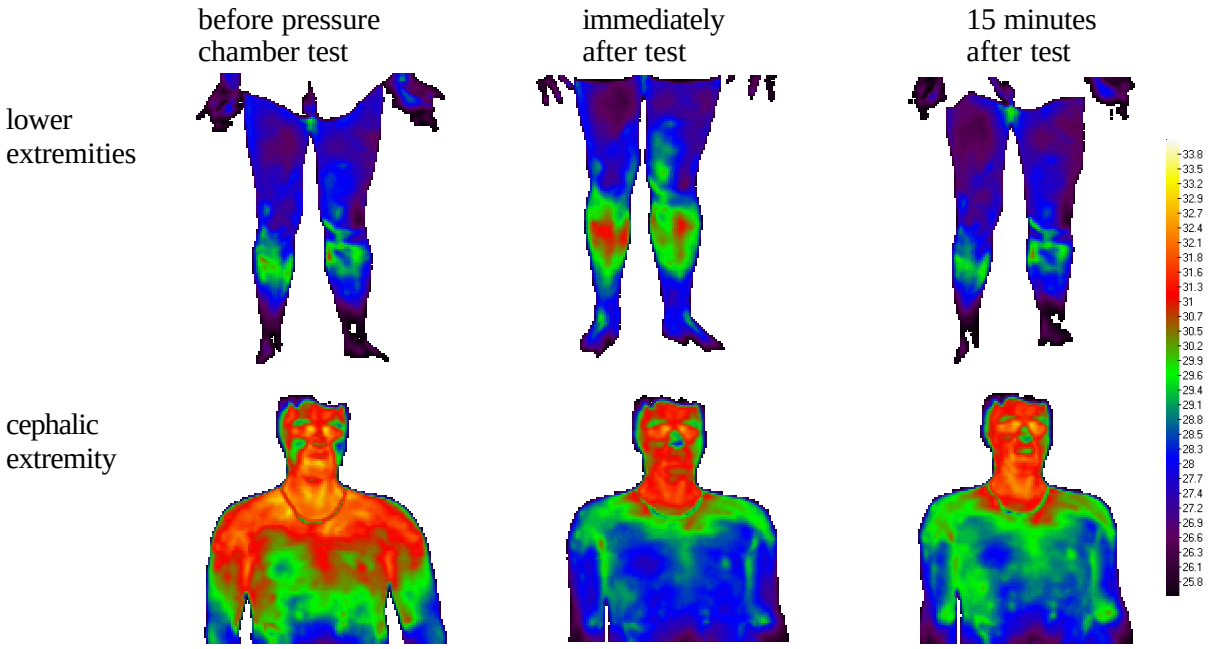


group C.II - inversed thermographical recordings.

- increase of temperature up to 1°C of upper and lower extremities after the hypoxic exposure and its decrease after 15 minutes,

- decrease of the temperature of the cephalic extremity immediately after the test and its increase after 15 minutes.

This denotes a good adaptation to hypoxia.

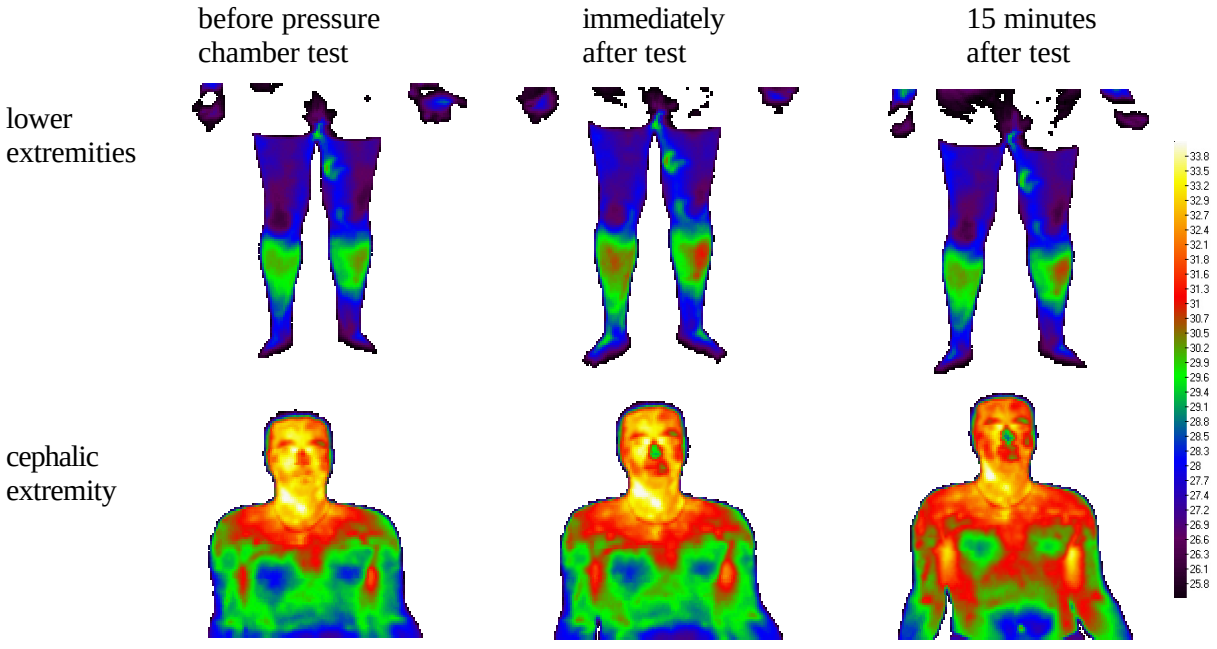


group C.III - thermal inertia

- increase of the temperature of upper and lower extremities after the hypoxic exposure, remaining constant after 15 minutes,

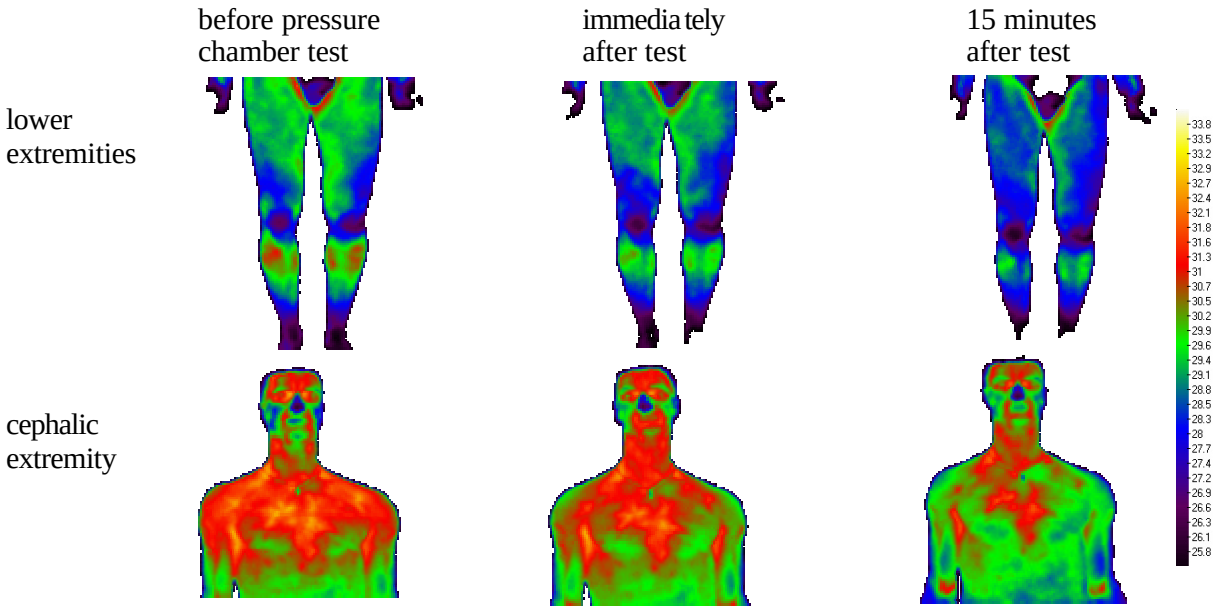
- decrease of the temperature of the cephalic extremity immediately after the test, remaining constant after 15 minutes,

This denotes a less efficient adaptation mechanism.



group C.IV - thermal amputation - there is a thermal amputation in a segment or more, in the extremities.

- denotes circulatory problems evident in hypoxia and latent in normal conditions.



The groups **C.III** and **C.IV** represent risk groups in hypoxia.

To analyse the thermographical images, we used a routine in our dedicated program to evaluate the temperature of the analysed anatomical regions.

- cephalic extremity
- upper lower extremities
- lower extremities - frontal view
- lower extremities - back view

Discussion of results

From the point of view of risk factors we have the following groups:

R.I - the existence of heredo-collateral antecedents (**A.I**)

R.II - AT and pulse decrease at hypoxic stress (physiological group **B.Ill**),

R.III - thermographical modifications due to hypoxic stress (thermographical group **C.III** and **C.IV**). Concluding these criteria we obtained a new classifications of subjects as follows:

0 degree risk factor group:

- subjects presenting no risk factors, subjects with excellent health and very well trained, with a perfect adaptation mechanism to hypoxic stress..

I-.st degree risk factor group

- subjects presenting one risk factor (supposing only a general subsequent medical supervision of the subjects).

2-nd degree risk factor group

- subjects presenting two risk factors (supposing careful subsequent medical supervision)

3-rd degree risk factor group

- subjects presenting three risk factors (supposing careful medical supervision, more frequent testings, shorter professional life).

We are presenting the results reffering to the hypoxic-hyperbaric tests (pilots and parachute jumpers)

1-st group - flying crews

We divided the 54 subjects as follows:

degree of risk factor group	risk factor	number of subjects	%
0	no	7	13.0
1	**R.I**	6	11.1
	R.II	3	5.6
	R.III	10	18.5
2	**R.I+R.II**	2	3.7
	R.II+R.II	9	16.7
	R.II+R.III	5	9.3
3	**R.I+R.II+R.III**	2	3.7
	*	10	18.5

Note:

* means a group of subjects who were accidentally exposed to psychic stress (conflictual situation) before the pressure chamber test - not included in our statistics.

The concordance between this classification and thennography is 87.5% in the 2-nd risk group and 100% in the 3-rd risk group.

2-nd group - parachute jumpers.

The 20 subjects were grouped as follows

degree of risk factor group	risk factor	number of subjects	%
0	**no**	3	15.0
1	**R.I**	10	50.0
1	**R.II**	1	5.0
2	**R.I+R.II** or **R.I+R.III** or **R.II+R.III**	4	20.0
3	**R.I+R.II+R.III**	2	10.0

From the point of view of the thermographic classification we had the following classification:

- 9 subjects (45%) with normal answer of both cephalic extremity and upper and lower extremities, denoting excellent adaptation to the hypoxic stress.
- 5 subjects (25%) with normal answer of the cephalic extremity and thermal inertia of upper and lower extremities, denoting relatively good adaptation to the hypoxic stress.
- 4 subjects (20%) with normal answer or thermal inertia of the cephalic extremity and thermal inertia of upper and lower extremities, denoting less efficient adaptation to the hypoxic stress.
- 2 subjects (10%), one with thermal inversion of the cephalic extremity and thermal inertia of upper and lower extremities, the other with thermal inertia of the cephalic extremity and thermal inversion of upper and lower extremities denoting bad adaptation to the hypoxic stress.

The concordance between this classification and thennography is 100% in both 2-nd risk group and 3-rd risk group.

NOTE:

We observed similar concordance in the case of divers in hyperbaric conditions.We hope we will be able to present these results in a future occasion.

Conclusions

· Excellent concordance between clinical risk criteria probes and thermographic abnormalities.
· Thermography reveals circulation system defaults not decealed by normal clinical methods.

Thermography can be (must be) used in:
- selection uf candidates for professions supposing hypoxic conditions,
- testing and training of flying crews and of parachute jumpers,
The answer to hypoxic stress depends on: - genetical background,
- training in hypoxic conditions.

Medical and thermographic watching reduce the risk factors and warn on the possibility of their accidental apparition.

Perspectives

· Introduction of thermography as usual method to the above mentioned fields.
· The use of the method in cosmic flight conditions

Altitude Decompression Sickness Risk Prediction Research

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ABSTRACT

High altitude exposure in aircraft, hypobaric chambers and with extravehicular activity (EVA) in space results in an inherent risk of altitude decompression sickness (DCS). In the past, general guidelines for safer altitude exposures have been developed through costly, time-consuming studies, each specific to unique scenarios of altitude exposure. Rapidly changing technology in aircraft design and mission requirements demand improved capabilities in predicting DCS risk during mission planning and execution. In 1990, a new bubble growth algorithm and a statistical model based on the existing USAF DCS Database were initiated at Brooks AFB. The first version of this combined model was completed in 1996. A model validation study using human subjects was completed in 1999. An updated version of the model based on the validation results has been produced and the software is being developed.

INTRODUCTION

Decompression sickness (DCS) is caused by exposure to significant reductions in environmental pressure. These situations are encountered during diving, high altitude exposures or artificially induced pressure changes in hyperbaric or hypobaric chambers. For large and rapid pressure reductions, supersaturation occurs as a result of the slow tissue gas exchange processes for expelling excess nitrogen. These gases, which come out of solution when tissues are sufficiently supersaturated, collect as bubbles in the tissue. The size and location of these bubbles are thought to have a significant effect on the resulting DCS symptoms. The risks can be minimized or prevented with sufficient denitrogenation by prebreathing pure oxygen (preoxygenation) before such exposures.

The risk of DCS increases with extended exposure times, very high altitudes, and greater physical activity during the exposure. The assessment of DCS risk for both civilian and military personnel under specified flight protocols is a critical problem that the USAF deals with on a regular basis. To provide answers to these questions, and also to obtain a clearer understanding of the effects of denitrogenation, the High Altitude Protection Function of the Air Force Research Laboratory has developed a model to predict DCS risk using physical and physiological principles.

Reports of altitude DCS from the field are rare (1). However, data from chamber studies show varying rates of DCS incidence for simulated operational profiles. With proper procedures (e.g., preoxygenation (Preox), suit/cabin pressurization, etc.), the risk of DCS can be significantly reduced. Countermeasures for preventing DCS are thus not the problem. Rather, the problem facing aircrews is how to quantify the risk of DCS and then select an appropriate combination of available countermeasures compatible with the constraints of a given mission. To quantify the risk of DCS the AFRL has developed an Altitude DCS Risk Assessment Computer (ADRAC), based on a DCS risk prediction model. A model based on the loglogistic distribution was used to predict the probability/risk of DCS over time as a function of altitude, Preox time, exposure time, exercise, and the time of onset of maximum venous gas emboli (VGE) grade. Before this theoretical model can be transitioned to operational application, it must be validated in the laboratory.

METHODS

There are several methods of DCS risk assessment. The simplest is to find the answer in the literature. However, data on a specific exposure profile is usually not available. The next obvious approach is to conduct an altitude chamber study to determine the DCS risk for that specific profile. However, such studies are expensive and time consuming. People with experience in the field may extrapolate from available data and make a “best guess”. The scientifically sound approach is to develop and validate an altitude DCS model that can accurately predict the DCS risk. This model can then become the “chip” in a DCS risk assessment computer, i.e. ADRAC. Potential applications for ADRAC include:

- Mission Planning
- Systems Design
- Real-time Cockpit Display

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- Education and Research
- Pressure Suit Control
- Cabin Pressurization Control

Following a lengthy feasibility study, the first version of the ADRAC DCS model was completed at AFRL in 1996. A prospective series of human trials to validate this model were completed in 1999 (4,7). This model validation was successful and the model was modified to include these new data resulting in greater accuracy. Detailed descriptions of the ADRAC model can be found elsewhere (2,3,6). The following is a short outline of the model and its capabilities.

The major components of the ADRAC model include (a) the AFRL Altitude DCS Research Database, (b) statistical models, and (c) a deterministic (bubble growth) model. AFRL at Brooks AFB has conducted experiments on human subjects in a hypobaric chamber for many years, creating a unique database of approximately 2500 altitude exposures with a variety of flight profiles. The subjects were exposed to different altitudes, various preoxygenation times, various exercise levels, and various exposure times. The subjects were monitored continuously and were required to report any pain or other symptoms. If the symptoms were indicative of DCS, the experiment was terminated and the subject repressurized to ground level. During each exposure, venous gas emboli were recorded by precordial 2-D Doppler/echocardiography.

To quantify the risk of DCS, survival models using the loglogistic distribution were developed to predict the probability of DCS incidence and onset time as a function of the following risk factors (2).

- Altitude / Pressure
- Exposure Time
- Preoxygenation Time
- Exercise
- Time to Maximum Bubble Grade (Bubble Growth Model)

The bubble growth model consists of a program that numerically solves a system of equations describing bubble growth due to a hypobaric decompression (3). It returns a single value; the onset time of maximum bubble radius. The model consists of an advection-diffusion equation coupled with two ordinary differential equations, and the conservation of mass and momentum equations. The system is in spherical coordinates and it describes the growth of a single bubble surrounded by a limited amount of tissue. Since blood leaving the capillaries removes nitrogen gas from the system, a sink term in the diffusion equation was added to account for loss of tissue nitrogen.

RESULTS

To evaluate these models, validation data were collected at AFRL (6). The profiles in the validation study were selected to fill in gaps in the database where little or no data was available. Five profiles were selected for the validation study (n=30/profile). Data from these exposures were not used in the development of the initial model being validated. The endpoint for each exposure was the onset of DCS symptoms. The actual incidences of DCS (A_{DCS}) and VGE (A_{VGE}) from these exposures were compared to those predicted by the model (P_{DCS}). To assess the goodness of fit of the model, we used the 95% confidence band.

For these 5 profiles, the actual DCS incidence was within the 95% confidence intervals of that predicted by ADRAC model (Table 1).

Results from these and other studies required new stratified models to be developed and adjusted for interactions between pressure and exercise (5). The database used to develop the initial model contained no information on heavy exercise, whereas three of the five validation profiles above used heavy exercise.

Table 1. Results of validation

Profile	Preox (min)	Alt (ft)	Exercise	P_{DCS} (%)	A_{DCS} (%)
1	90	35,000	Mild	94	94+/-9
2	30	25,000	Heavy	62	61+/-17
3	75	30,000	Rest	50	58+/-17
4	0	18,000	Heavy	17	13+/-12
5	15	22,500	Heavy	38	30+/-16

We have been able to adjust the model to account for the heavy exercise, and this has allowed us to better predict the onset of symptoms for shorter exposures at the higher altitudes. Also, at the lower altitudes, very little data on zero preoxygenation was available when the initial model was developed. The validation data and additional low altitude exposure data have allowed us to modify the model to account for these low altitude predictions. This new version of the model is the basis for the Altitude DCS Risk Assessment Computer (ADRAC) currently under development at AFRL.

SOFTWARE DEVELOPMENT

Following the validation of the model, we developed a software application that uses the described model to predict altitude decompression sickness. The software has been written in Java, so that it can run on any operating system. In the software, the user can create/modify/delete scenarios. A scenario is a set of parameters that the user specifies, consisting of 4 inputs to the model:

- Altitude – The user can specify 18,000 to 40,000 feet
- Exposure Time - From 0 to 360 minutes
- Exercise Level – Either rest, mild, or heavy
- Pre-Breathe Time – From 0 to 240 minutes

After creating the scenario(s), the user can obtain the risk associated with it. The risk is calculated and displayed. A table view shows the detailed risk at the different times, and a graph view plots these values. While viewing the output, the user can dynamically modify the scenario and, “on the fly”, view the subsequent changes to the risk. The effect on the graph and table is immediately seen. The old values in the graph will not be erased, and the new plot will be superimposed, so the user can quickly see the differences by the changes in his parameters. Scenarios are saved to disk so that the user can maintain information from session to session.

CONCLUSIONS

The predictive ability and accuracy of the ADRAC model has been validated by a total of 5 profiles using human subjects exposed in an altitude chamber. The data from these profiles has been added to the model database and the model modified to improve its predictive capability.

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Altitude Decompression Illness – The Operational Risk at Sustained Altitudes up to 35,000 ft

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Summary

Altitude decompression illness (DCI) is generally considered to be a risk at altitudes in excess of 18,000 ft. UK military aircrew are therefore not routinely exposed to altitudes in excess of this, however, there are circumstances such as loss of cabin pressure, parachute operations, and high cabin altitudes in future aircraft, when exposure to altitudes in excess of 18,000 ft may be necessary. A series of experiments were carried out at the DERA Centre for Human Sciences to investigate the risk of venous gas emboli (VGE) and DCI symptoms at altitudes up to 35,000 ft. Subjects were exposed, for a maximum of four hours, to i) simulated altitudes between 20,500 ft and 25,000 ft breathing an oxygen/nitrogen gas mixture, ii) 25,000 ft breathing 100% oxygen with and without one hour of prior denitrogenation and iii) simulated altitudes up to 35,000 ft with one hour prior denitrogenation. It was concluded that VGE formation will occur at cabin altitudes that will be encountered by aircrew of future agile aircraft although only 7% of subjects developed symptoms. Exposure to 25,000 ft breathing an oxygen/nitrogen gas mixture resulted in VGE and symptoms significantly earlier than during exposures to 20,500 ft and 22,500 ft. Furthermore, exposure to 25,000 ft for four hours breathing either gas mix or 100% oxygen, without prior denitrogenation, incurred a substantial risk of developing symptoms of DCI. Denitrogenation, however, for one hour prior to decompression provided effective protection against development of symptoms of DCI at 25,000 ft for subjects at rest. Finally, subjects exposed to 35,000 ft developed VGE and symptoms of DCI significantly earlier than subjects exposed to 25,000 ft.

Introduction

A method of using compressed air to prevent mine shafts beneath water and submerged ground from flooding was first described in 1841 (Triger 1845). The first application of this technique took place in 1841 in France, and although it was considered a complete success, symptoms consistent with decompression illness (DCI) were described by the workers. A brief note suggests that two of the workers who had been compressed for seven hours suffered pain, one in the left arm and the other in the left shoulder and both knees, half an hour after the exposure (Pol & Watelle 1854). Later, during the building of the St Louis Bridge in the 1870s one hundred and nineteen caisson workers developed neurological symptoms and fourteen workers died (Woodward 1881). Paul Bert showed that decompression from a raised pressure gave rise to the evolution of bubbles in tissues and fluids and postulated that these were the cause of the clinical syndromes seen in caisson workers and divers (Moon *et al* 1995). The possibility of bubble formation on ascent to altitude, however, was not considered until 1901 when von Schrotter reported symptoms including difficulty of breathing, despite the use of oxygen, during a 15 minute exposure to 30,000 ft. Von Schrotter attributed the incident to bubble formation in accordance with Paul Bert's theory for the aetiology of symptoms experienced by caisson workers and divers (Fryer 1969).

Aviators ascending to altitude, like divers ascending from depth, are exposed to a reduction in pressure. When the pressure of the gases dissolved in the body tissues exceeds that of the atmospheric pressure the tissues become supersaturated with gas and there is potential for the formation of bubbles within the tissues. These bubbles are thought to be the cause of a myriad of clinical disorders from mild limb pain or paraesthesia through to more serious neurological or respiratory symptoms, and ultimately to complete circulatory collapse and death. The manifestation of symptoms may be caused simply by the physical presence of gas causing direct mechanical disruption of a tissue, tissue compression, or obstruction of a blood vessel. In contrast, symptoms may be caused

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by a tissue response to the presence of bubbles which may stimulate activation of endothelial cells, platelets or biochemical pathways (Francis & Gorman 1993).

The minimum altitude at which bubble formation is sufficient to result in symptoms is not known, although 18,000 ft is generally considered to be the threshold for decompression illness (DCI). This threshold of 18,000 ft came from a theory put forward by J.S. Haldane who proposed that a pressure drop of one half of the original gas pressure, whatever the value, would be safe - ie: sea level to 18,000 ft. Altitude decompression illness however, was not considered when this theory was presented (Boycott *et al* 1908). This 2:1 rule is commonly held today despite the demonstration of decompression illness, albeit rarely, below this altitude. With this in mind UK military aircrew are not routinely exposed to altitudes in excess of 18,000 ft in order to minimise the risk of decompression illness. There are circumstances, however, when altitudes in excess of 18,000 ft will be encountered by UK military personnel. For example, following loss of cabin pressure a maximum altitude of 25,000 ft is recommended and some aircraft have the facility to remain at this altitude for longer than four hours. Parachute operations may expose individuals to altitudes in excess of 18,000 ft, and high altitude high opening operations will provide the greatest risk of decompression illness. Finally, future fast jet aircraft, such as Eurofighter (EF) will attain cabin altitudes in excess of 18,000 ft when the aircraft reaches its operational ceiling.

The reported incidence of DCI in RAF aircrew to date has been extremely low. Harding (1992) stated that only two cases of DCI had been reported by aircrew in the RAF between 1980 and 1990, although there have been several anecdotal incidents of unreported limb pain by Canberra crew members. A recent survey of Canberra aircrew found that more than 20% of respondents had experienced limb pain that was considered to be consistent with symptoms of DCI (Mitchell & Lee 2000). Similarly, a large discrepancy between the number of reported cases of DCI in aircrew (USAF) and the incidence of DCI in experimentally similar profiles has been highlighted by Pilmanis & Bisson (1992). These authors reported that while only 1- 2 cases of DCI are declared each year in pilots that fly at cabin altitudes between 28,000 ft - 30,000 ft (U-2 & TR-1), 73% of research subjects exposed to a similar altitude profile reported DCI. Furthermore, in an anonymous survey, this same population of pilots reported that 62% had experienced DCI at least once during a high altitude flight. These data suggest that reported cases of DCI are unlikely to reflect the true incidence during flight.

This paper describes a series of experiments that were carried out at the DERA Centre for Human Sciences to investigate the risk of developing venous gas emboli (VGE) and symptoms of DCI at altitudes up to 35,000 ft.

Methods

Fifteen male subjects were exposed, with Local Research Ethics Committee approval, to each of the profiles shown in Table 1 for a maximum period of four hours.

Altitude (ft)	Denitrogenation	Breathing Gas Composition
20,500	No	56% oxygen 44% nitrogen
22,500	No	56% oxygen 44% nitrogen
25,000	No	63% oxygen 37% nitrogen
25,000	No	100% oxygen
25,000	Yes	100% oxygen
30,000	Yes	100% oxygen
35,000	Yes	100% oxygen

Table 1. Experimental profiles indicating the simulated altitude, the use of denitrogenation with 100% oxygen for one hour prior to decompression, and the composition of the breathing gas from the initiation of decompression.

The subjects were fitted with an aircrew coverall, a cloth G type flying helmet and a modified RAF P/Q type oronasal oxygen mask. The mask was modified with the addition of a drinking facility, and subjects were encouraged to drink fluids throughout the experiment. Subjects were supplied with breathing gas from a Type

17 oxygen demand regulator with a positive pressure, of about 5 mmHg, to ensure no inward leaks of ambient air into the mask during inspiration.

No subject had been exposed to a hyper- or hypobaric environment within the 48 hours prior to participating in this study. For profiles that did not employ denitrogenation, subjects started to breathe the appropriate gas mixture as decompression to simulated altitude was initiated. For profiles employing denitrogenation subjects breathed 100% oxygen (preoxygenation) for exactly one hour before decompression to simulated altitude, and subjects remained at rest throughout the period of preoxygenation. Subjects were decompressed to simulated altitude in the CHS's hypobaric chamber, at a rate equivalent to 5,000 ft min^{-1}. Subjects remained at the required altitude for a maximum duration of four hours and remained at rest throughout the exposure to altitude.

On reaching the simulated altitude the subjects were monitored, every fifteen minutes, using 2D and Doppler echocardiography (SONOS 1500 or 2500 Hewlett Packard with a 2.5MHz transducer) for the presence of VGE (Olson *et al*; 1992). A four chamber view of the heart was obtained (Figure 1), with the subject in the seated position. Any VGE that were detected in the right cardiac chambers were graded by the investigator outside the hypobaric chamber on a 0 - 4 scale based on that described by Spencer (1976). During each echocardiograph the subject moved each limb in turn in such a manner that the limb joints were rotated and flexed to allow any bubbles present around the joint to be dislodged.

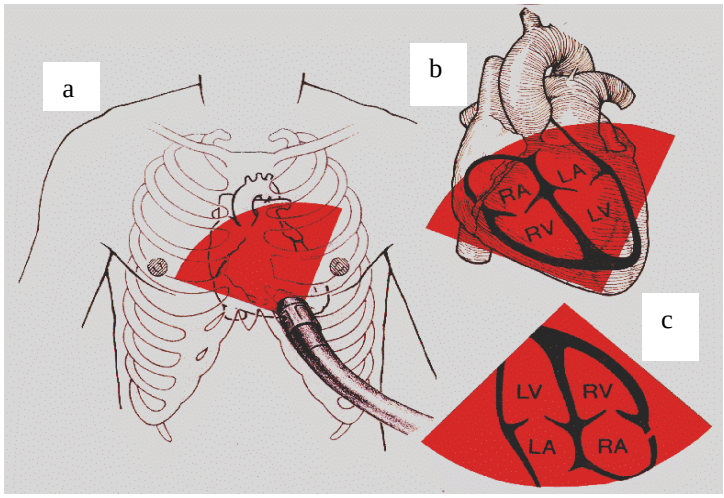


Figure 1. Diagram showing a) orientation of the echocardiograph transducer on the chest wall, b) plane of the echocardiograph through the cardiac chambers and c) view of 2D echocardiographs used for data analysis.

Subjects were briefed prior to exposure to altitude on the symptoms of decompression illness and instructed to report any symptoms or sensations experienced at altitude that were not present at ground level. In an attempt to avoid the reporting of spurious symptoms the subjects were encouraged to watch films throughout the exposure and, beyond the pre-exposure brief, subjects were not reminded again about symptom reporting.

If the subject reported limb or joint pain that was constant - Grade II pain according to Webb & Pilmanis (1992) - they was asked to rate the level of pain on a scale from 1-10 (0 being no pain and 10 being worst pain imaginable). The subject was then immediately recompressed to ground level at a rate of 5,000 ft min^{-1} (unless a different rate was indicated). The subjects were also recompressed to ground level immediately if any other symptoms resulting from exposure to simulated altitude were reported by the subject or observed by the investigators, or if gas emboli were detected in the left cardiac chambers. During recompression, the simulated altitude at which the subject no longer experienced symptoms was recorded. All subjects were required to breathe 100% oxygen for a further two hours on reaching ground level unless their symptoms indicated that hyperbaric oxygen therapy was required.

The latency from reaching the final altitude to exhibiting any VGE, grade 4 VGE and reporting symptoms was calculated. These onset times were analysed using analysis of variance. Where no VGE or symptoms were exhibited during exposure to the final altitude it was assumed, for the purposes of statistical analysis, that VGE

or symptoms could have developed at 240 minutes. This does however, have the effect of biasing the results towards shorter, or worst case, mean onset times.

Results

Figures 2 and 3 show an example of an echocardiograph from a subject at 30,000 ft without and with VGE respectively. Table 2 shows the percentage of subjects that exhibited any VGE, and grade 4 VGE, with mean times to onset from reaching the final altitude. Table 2 also shows the percentage of subjects that reported symptoms consistent with DCI that resulted in recompression to ground level, and the mean time to initiation of recompression. Figures 4, 5 and 6 show the cumulative number of subjects, during each 30 minute period of each profile, exhibiting any VGE, grade 4 VGE, and symptoms, respectively.

Venous gas emboli, grade 4 VGE, and symptom development at 20,500 ft, 22,500 ft and 25,000 ft were compared (Figs 4(a), 5(a) & 6(a) respectively). Subjects exposed to 25,000 ft exhibited grade 4 VGE significantly earlier than subjects exposed to 20,500 ft and 22,500 ft ($p<0.05$) (Fig 5(a)). Similarly, subjects exposed to 25,000 ft breathing a nitrogen/oxygen gas mixture exhibited symptoms significantly earlier than subjects exposed to 20,500 ft and 22,500 ft (Fig 6(a)).

Venous gas emboli, grade 4 VGE, and symptom development at 25,000 ft employing a nitrogen/oxygen breathing gas, 100% oxygen breathing gas, and 100% oxygen breathing gas with one hour prior denitrogenation have also been compared (Figs 4(b), 5(b) & 6(b) respectively). There was no significant difference in the onset time of VGE or symptoms between subjects exposed to 25,000 ft breathing either gas mix or 100% oxygen. However, subjects breathing the nitrogen/oxygen gas mixture at 25,000 ft exhibited grade 4 VGE significantly earlier than subjects breathing 100% oxygen ($p<0.05$). Subjects who denitrogenated prior to exposure to 25,000 ft exhibited VGE, and grade 4 VGE, and symptoms significantly later than subjects exposed 25,000 ft without denitrogenation ($p<0.001$, $p<0.01$ & $p<0.001$ respectively) (Figs 4(b), 5(b) & 6(b) respectively).

Venous gas emboli, grade 4 VGE, and symptom development at 25,000 ft, 30,000 ft and 35,000 ft with one hour prior denitrogenation have been compared (Figs 4(c), 5(c) & 6(c) respectively). Subjects exposed to 35,000 ft exhibited VGE and symptoms significantly earlier than subjects exposed to 25,000 ft with denitrogenation ($p<0.01$ & $p<0.01$ respectively). However, there was no significant difference in the onset of grade 4 VGE between 25,000 ft, 30,000 ft and 35,000 ft with denitrogenation (Figs 4(c), 5(c) & 6(c)).

Altitude (ft)	Preox	Breathing gas (% O_2)	% with VGE	Mean time to onset (mins)	% with G4 VGE	Mean time to onset (mins)	% with symptoms	Mean time to recompression (mins)
20,500	N	56	80	77 ± 70	53	95 ± 30	7	192
22,500	N	56	67	54 ± 38	47	82 ± 37	7	172
25,000	N	63	100	51 ± 58	93	83 ± 49	53	138 ± 39
25,000	N	100	87	52 ± 60	60	89 ± 43	60	125 ± 35
25,000	Y	100	33	123 ± 53	20	162 ± 23	0	-
30,000	Y	100	60	111 ± 78	33	108 ± 68	40	148 ± 46
35,000	Y	100	93	102 ± 69	53	116 ± 51	53	106 ± 46

Table 2. Percentage of subjects undergoing each profile exhibiting any VGE, grade 4 VGE and symptoms, together with times (mins) to onset of VGE and times to recompression following symptom development (mean ± SD).

During these altitude exposures a number of subjects exhibited gas emboli in the left ventricle, (Figure 7 shows an echocardiograph from a subject with gas emboli in both the left and right ventricles). Gas emboli in the left ventricle will pass directly into the arterial circulation. Therefore, these subjects were immediately recompressed to ground level as the potential for development of neurological symptoms is considered to be greater in individuals with arterial gas emboli. Table 3 shows the conditions under which subjects developed arterial gas emboli (AGE) and times to onset. Five out of the six subjects exhibiting AGE were also exhibiting maximum grade (grade 4) VGE.

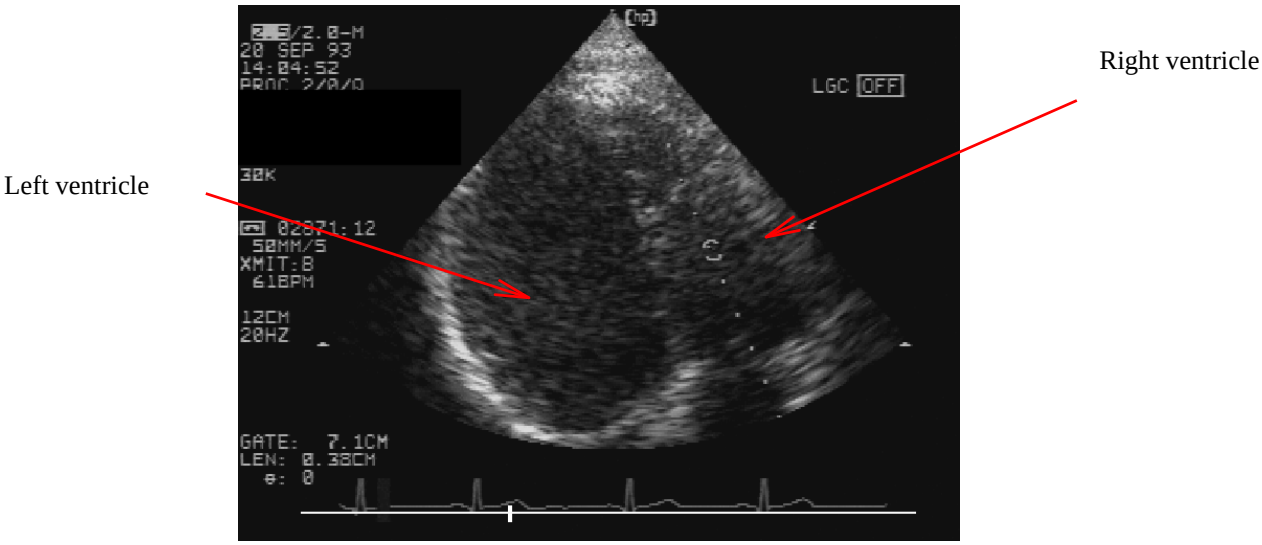


Figure 2. Echocardiograph from a subject at 30,000 ft breathing 100% oxygen following denitrogenation – no gas emboli are evident in this image.

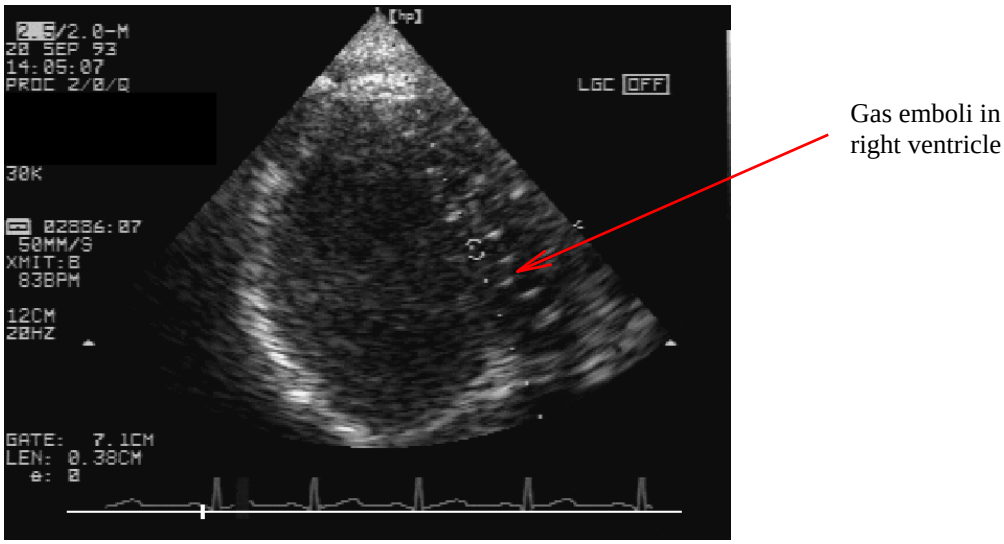
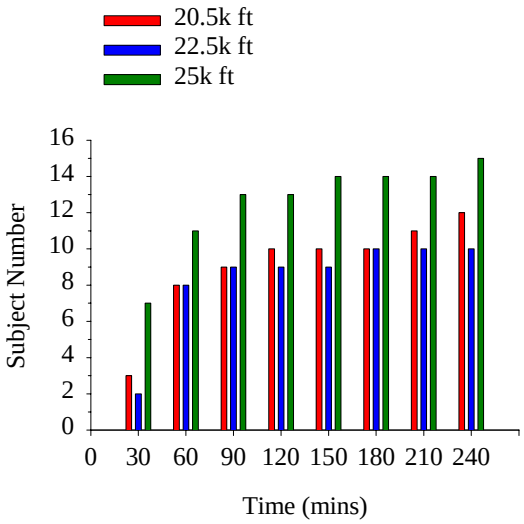
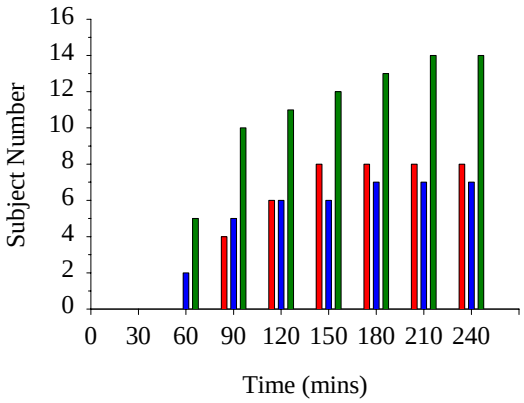
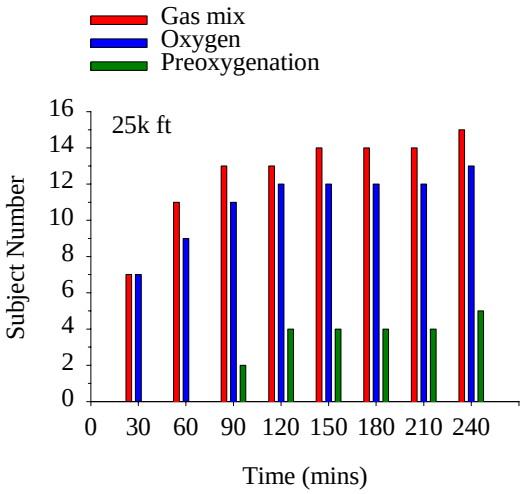
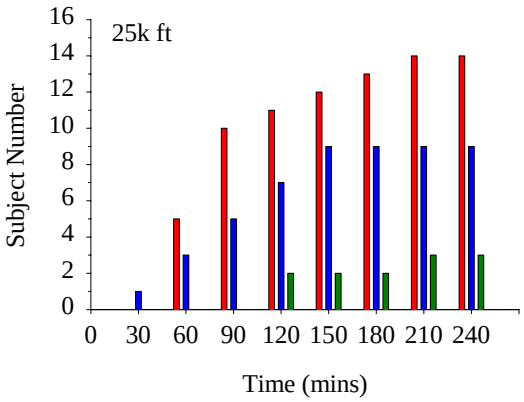


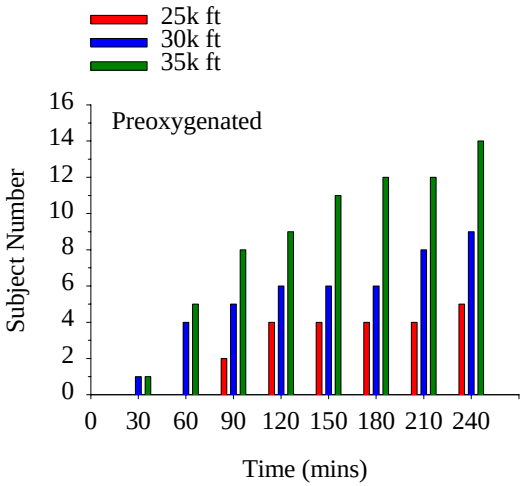
Figure 3. Echocardiograph from a subject at 30,000 ft breathing 100% oxygen following denitrogenation – several gas emboli are present in the right ventricle of this subject.











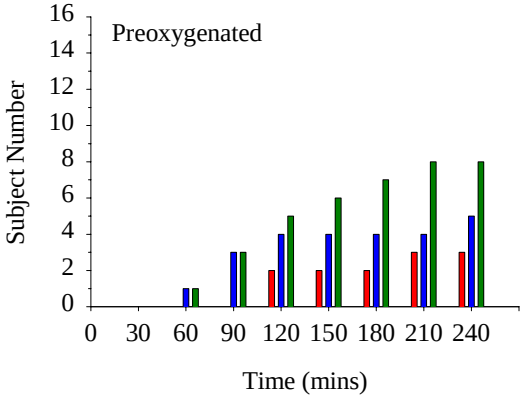


*Figure 4. Showing the cumulative number of subjects developing **VGE** during each 30 minute period of the 240 minute exposure for a) profiles that subjects were breathing a nitrogen/oxygen gas mixture b) profiles that subjects were exposed to 25,000 ft and c) profiles where one hour of prior denitrogenation with 100% oxygen was employed.*

*Figure 5. Showing the cumulative number of subjects developing **grade 4 VGE** during each 30 minute period of the 240 minute exposure for a) profiles that subjects were breathing a nitrogen/oxygen gas mixture b) profiles that subjects were exposed to 25,000 ft and c) profiles where one hour of prior denitrogenation with 100% oxygen was employed.*

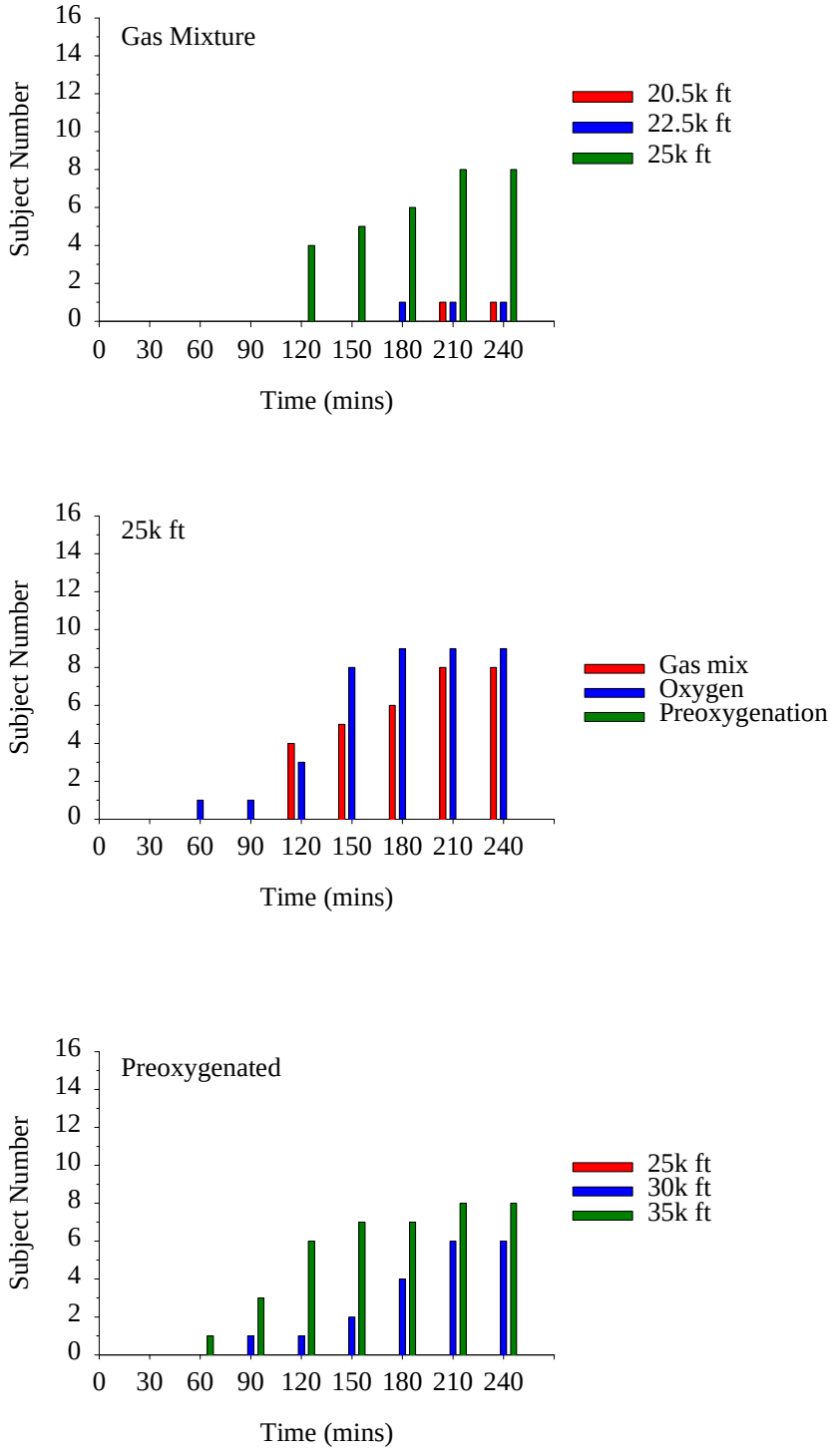


*Figure 6. Showing the cumulative number of subjects developing **symptoms** during each 30 minute period of the 240 minute exposure for a) profiles that subjects were breathing a nitrogen/oxygen gas mixture b) profiles that subjects were exposed to 25,000 ft and c) profiles where one hour of prior denitrogenation with 100% oxygen was employed.*

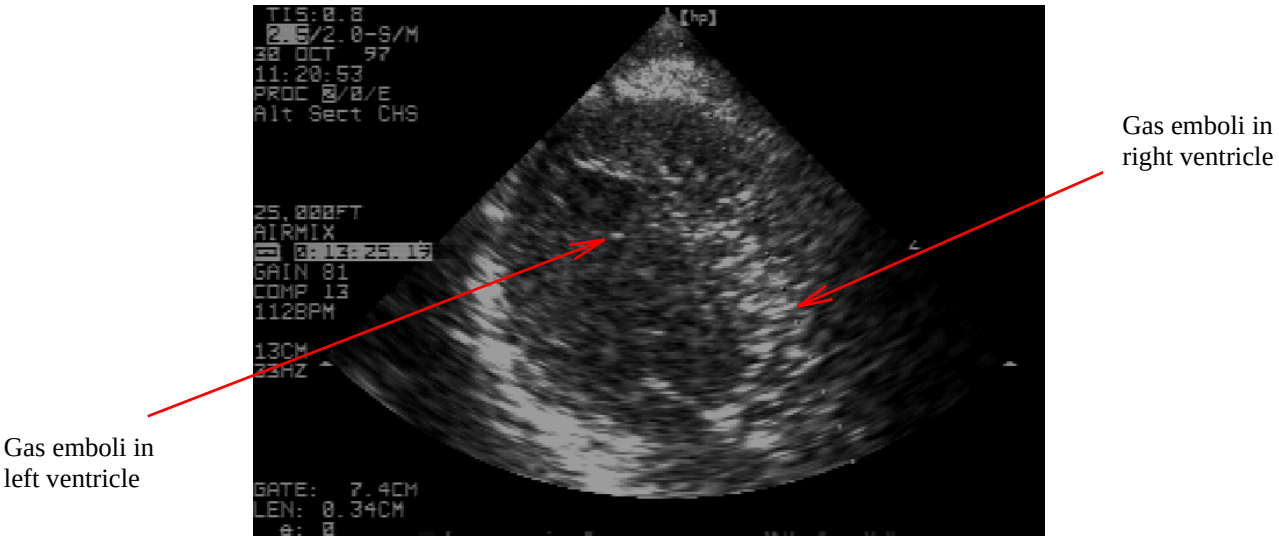


Figure 7. Echocardiograph from a subject at 25,000 ft breathing a nitrogen/oxygen gas mixture showing many gas emboli in the right ventricle and 2 gas emboli in the left ventricle.

Altitude (ft)	Preox	Breathing gas (% O_2)	N with AGE	VGE grade	Mean time to onset (mins)
20,500	N	56	1	4	212
22,500	N	56	1	3	77
25,000	N	63	2	4/4	63 ± 24
25,000	N	100	1	4	195
25,000	Y	100	0	-	-
30,000	Y	100	0	-	-
35,000	Y	100	1	4	150

Table 3. Number of subjects undergoing each profile exhibiting any AGE together with times (mins) to onset of AGE (mean ± SD) and grade of VGE.

Discussion

This study assessed the incidence of symptoms of DCI and VGE in subjects exposed to altitudes ranging from 20,500 ft to 35,000 ft. Breathing gas mixtures representative of those used operationally were used during exposures that simulated cabin altitudes. The effect of gas mixture vs 100% oxygen breathing gas was assessed at 25,000 ft together with the implications of prior denitrogenation. Finally, exposures were carried out between 25,000 ft and 35,000 ft using prior denitrogenation.

DCI at 20,500 ft and 22,500 ft and the Consequences of VGE Development

Exposure to 22,500 ft is representative of the maximum cabin altitude achievable in future aircraft such as EF. The studies conducted at CHS suggest that, assuming the aircrew are at rest, the incidence of DCI will below. These results are in contrast to those reported by Webb *et al* (1998) who found that more than 50% of subjects developed DCI within four hours at 22,500 ft while breathing 100% oxygen. It is likely, however,

that this discrepancy in the incidence of DCI is due to the additional use, by Webb *et al* (1998), of three sets of mild arm exercises each hour, to simulate extravehicular activity. The effect of exercise on the incidence of DCI is discussed later.

The results also indicated that between 80% and 67% developed VGE at 20,500 ft and 22,500 ft respectively, with a corresponding mean onset time of 77 and 54 minutes. The presence of such non-symptomatic bubbles in the venous side of the circulation has been demonstrated in many other studies (eg Dixon *et al* 1986, Kumar *et al* 1992). Most commonly venous gas emboli are thought to circulate through the right cardiac chambers and be filtered out in the pulmonary circulation (Spencer 1971). Gas emboli can, however, enter the arterial circulation via intracardiac septal defects, pulmonary arteriovenous shunts, or through the pulmonary microcirculation. Indeed, in this study gas emboli in the left ventricle were detected during six out of one hundred and fifteen exposures (5.2%). The presence of arterial gas emboli present a considerable hazard as they have potential to result in impairment of neurological function and cerebral damage.

Intracardiac septal defects, in the form of a patent foramen ovale (PFO), appear to exist in around 20-30% of the human population and have been implicated in neurological DCI in divers (Moon *et al* 1989). In one study a five fold increase in risk of decompression illness was associated with individuals with a PFO evident under resting conditions (Moon *et al* 1991). In contrast, no correlation was found, in individuals undergoing USAF hypobaric training exposures, between those with a PFO and those that reported neurological DCI (Clark & Hayes 1991). Furthermore, in a single subject with a PFO evident under resting conditions, and exhibiting grade 4 VGE at 21,000 ft, no symptoms were reported and no evidence for gas emboli in the left side of the heart was seen (Powell *et al* 1995). Present evidence indicates that the incidence of serious DCI in divers, and in particular in aviators, does not approach the percentage of the population with a PFO. Individuals with a PFO may not experience symptoms of DCI as a reversal of the normal left to right heart pressure gradient is usually necessary for gas emboli to traverse a septal defect into the left side of the heart. Such reversals in pressure can however be established upon release of a Valsalva and cessation of either positive pressure breathing or the anti-G straining manoeuvre (Garrett 1992). It is apparent, therefore, that there is greater potential for such reversals of pressure in aircrew of future high performance aircraft which might allow for venous gas emboli, provoked by the altitude exposure, to cross into the arterial circulation.

In addition to intracardiac septal defects, high grades of VGE have also been shown to result in gas emboli in the arterial circulation even when a PFO is not evident (Butler & Hills 1985, Vik *et al* 1993). Indeed, Pilmanis (1995) reported, that an atrial septal defect could only be established by transoesophageal contrast echocardiography in two of three subjects who exhibited arterial gas emboli at altitude. Pilmanis (1995) also reported that all the subjects with AGE were exhibiting the highest VGE score (grade 4) prior to the presence of arterial gas emboli, this is in common with all but one of the subjects in this study with arterial gas emboli. Thus, more than one mechanism may be responsible for the cross over of bubbles from the venous to arterial circulation. This study shows that bubble onset can occur within twenty two and nineteen minutes of exposure to 20,500 ft and 22,500 ft respectively, and that grade 4 VGE onset can occur within sixty one and thirty six minutes respectively. Therefore, although the risk of developing symptoms at altitudes up to 22,500 ft while at rest appears to be small, the exposure of aircrew to these altitudes can result in significant bubble formation. These conditions, particularly for those with PFOs, increase the risk of transfer of gas emboli to the arterial circulation which in turn could result in development of serious neurological symptoms.

VGE & Decompression

The development of VGE at cabin altitudes that are likely to be encountered routinely in future aircraft provides the potential for the development of arterial gas emboli, with the consequences discussed above. The presence of non-symptomatic bubbles is also likely to have considerable consequences in the event of cabin depressurisation. It is likely that an individual who has developed VGE under pressurised conditions, and who undergoes rapid decompression, will be exposed to an increased risk of DCI as bubbles in the tissues and circulation will rapidly increase in size on decompression in accordance with Boyle's Law. This may lead to rapid onset of symptoms directly or may facilitate transfer of gas to the arterial circulation.

Effect of Breathing Gas

A greater number of subjects breathing a nitrogen/oxygen gas mixture than breathing 100% oxygen exhibited VGE at 25,000 ft. Although the mean onset times to VGE in these subjects were similar, statistical analysis did show that the gas mixture significantly reduced the time to grade 4 VGE formation of the whole group exposed to 25,000 ft. These results are similar to those reported by Webb & Pilmanis (1993) who found that 100% oxygen significantly reduced the number of subjects exhibiting VGE at 16,500 ft, and below, compared with those breathing a 50:50 oxygen/nitrogen gas mixture. In contrast, however, there was no significant difference in the development of symptoms between the groups exposed to 25,000 ft breathing 100% oxygen or nitrogen/oxygen gas mixture.

Effect of Preoxygenation

Denitrogenation, by breathing 100% oxygen, results in a downward gradient of the partial pressure of nitrogen between the bloodstream and the alveoli as the nitrogen content in the lung falls. Nitrogen diffuses out of the bloodstream into the lungs across the downward gradient. In turn, as nitrogen poor blood passes through the tissue with high nitrogen content nitrogen passes from the tissues into the bloodstream. Thus, as the nitrogen content of the tissues falls the risk of formation of nitrogen bubbles in the tissues at altitude is reduced, and in turn, this is considered to reduce the risk of DCI symptoms .

The use of oxygen breathing prior to decompression to reduce the incidence of decompression illness was first demonstrated in the 1940s (Boothby *et al* 1940 and Gray *et al* 1946). More recently, it has been demonstrated that the formation of bubbles in the circulation and the manifestation of symptoms of DCI can be substantially reduced by breathing 100% oxygen at ground level and at altitudes up to 16,000 ft (Pilmanis & Olson 1991). This study showed that denitrogenation for one hour prior to ascent to 25,000 ft significantly reduced the onset of symptoms – with 60% demonstrating symptoms without denitrogenation compared with 0% with denitrogenation. These results contrast with those of Webb & Pilmanis (1995) who predict that one hour of prior denitrogenation would reduce the incidence of DCI at 25,000 ft by just 15% (from 90% to 75%). This discrepancy, however, may be due to the slight differences in the protocol with regard to activity during the altitude exposure. The one hour of denitrogenation prior to exposure to 25,000 ft also reduced the number of subjects exhibiting VGE from 87% to 33% and increased the latency to the onset of VGE from a mean time of 52 to 123 minutes.

Effect of Altitude

Increasing altitude from 25,000 ft to 35,000 ft had a significant effect on the time to VGE and symptom onset (although not on grade 4 VGE onset). Figure 8 shows mean times to onset of symptoms at 25,000 ft, 30,000 ft and 35,000 ft with denitrogenation, and 25,000 ft without prior denitrogenation. As for all statistical analysis applied to these data, it has been assumed that for subjects who did not develop symptoms during altitude exposure, symptom onset could have occurred at 240 minutes. This of course represents the worst possible case. The linear functions have been fitted to the mean time to symptom onset with denitrogenation. It has then been assumed that this equation holds under conditions of no denitrogenation, and the linear function has been applied to the data from subjects exposed to 25,000 ft without denitrogenation. This provides an estimate of the mean times to the onset of symptoms at altitudes above 25,000 ft if no denitrogenation was employed. With all these assumptions it can be estimated that mean time to symptom onset at 30,000 ft and 35,000 ft, with no prior denitrogenation, would be 135 and 99 minutes respectively.

Pilmanis & Stegmann (1991) collated DCI data from the Armstrong Laboratory DCI database together with published results from between 1944 and 1951, all studies included employed no greater than mild exercise. They concluded that, with no denitrogenation, the mean onset time for decompression illness at 35,000 ft would be about 35 minutes. Pilmanis & Stegmann (1991) concluded further that with 1 hr of denitrogenation the mean onset time to DCI symptoms at 35,000 ft would be about 82 minutes. This compares with this study where a mean onset time with denitrogenation of 102 minutes was seen, and a mean onset time of 99 minutes without denitrogenation was predicted.

Extrapolation of the data presented by Pilmanis & Stegmann (1991) suggests that, with no denitrogenation, the onset of DCI symptoms would be instantaneous at 40,000 ft. While with denitrogenation extrapolation suggests that mean onset time at 40,000 ft would fall to about 45 mins while onset would be instantaneous at about 48,000 ft. This however, is not confirmed by Fraser *et al* (1994) who saw no cases of DCI in 8 subjects who were rapidly decompressed to an altitude of 60,000 ft which was maintained for 3 minutes. Similarly, Gradwell (1993) conducted 135 human rapid decompressions to between 45,000 ft and 60,000 ft with up to 45 minutes of denitrogenation and up to two minutes exposure to the final altitude with no reported cases of DCI. Despite these data from rapid decompressions there is no evidence to confirm the suggestion that there is a critical period of time, at any altitude, before which symptoms of decompression illness will not occur (Pilmanis & Stegmann, 1991).

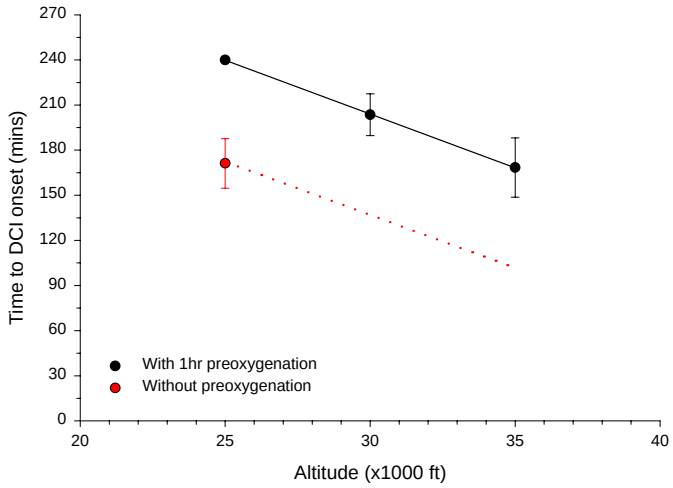


Figure 8. Linear regression applied to mean times to onset of DCI at 25,000 ft and above with 1 hour preoxygenation. An estimation has been made of times to onset of DCI using the mean time to DCI at 25,000 ft without preoxygenation.

Effect of Exercise

It has been demonstrated that even relatively modest increases in muscular activity increase the incidence of VGE and DCI symptoms. Krutz & Dixon (1987) demonstrated that five knee bends and five upward extensions of the arms with a 5lb weight every 15 minutes increased the number of subjects with symptoms at 30,000 ft, from 57% at rest (with limb flexion only) to 86%. Similarly, Ferris & Engel (1951) showed that while 55% of resting subjects reported symptoms at 35,000 ft, with a mean onset time of 61 minutes, 100% of subjects performing five knee bends every three minutes reported symptoms with a mean onset time of only 16 minutes. These authors also noted that the site of pain was often the site subjected to the maximum stress of exercise. Fryer (1969) concluded that exercise appears to have the equivalent effect, on DCI risk, of increasing the altitude by 3,000 ft - 5,000 ft.

In this study none of the subjects exposed to 25,000 ft at rest, with prior denitrogenation, exhibited symptoms of DCI. This is in contrast to Webb & Pilmanis (1995) who reported that 75% of subjects exposed to 25,000 ft, with limited arm exercises, reported DCI. Similarly, in comparison with the present study, Webb & Pilmanis (1995) predicted that 90% of subjects would report DCI within four hours at 25,000 ft with no preoxygenation, which is substantially greater than the 60% incidence of DCI reported in this study at 25,000 ft, with no preoxygenation. Such a difference in the incidence of DCI between these studies may be a result of the differing level of activity of the subjects. Indeed, the present data compare well with the incidence of DCI reported by Krutz & Dixon (1987) at 35,000 ft who found that 57% of resting subjects reported symptoms.

Conclusions

VGE formation occurs at cabin altitudes that will be encountered by aircrew of future agile aircraft. The presence of such VGE is likely to increase the risk of DCI in the event of cabin depressurisation and the presence of VGE *per se* has potential to result in arterial gas emboli and development of neurological symptoms.

Denitrogenation for one hour prior to decompression provides effective protection against development of symptoms of DCI at 25,000 ft for subjects under resting conditions.

Exposure to 25,000 ft for four hours breathing either gas mix or 100% oxygen, without prior denitrogenation, incurs a substantial risk of developing symptoms of DCI.

These data suggest that personnel exposed to 30,000 and 35,000 ft, at rest, are at risk of developing DCS even with one hour prior denitrogention.

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Expression of Neuronal and Inducible Nitric Oxide Synthase Isoforms and Generation of Protein Nitrotyrosine in Rat Brain Following Hypobaric Hypoxia

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Summary

The expression of neuronal and inducible nitric oxide synthase (nNOS and iNOS) and nitrotyrosine immunoreactivities in the cerebral cortex, caudate putamen, islands of Calleja, hippocampus, superior colliculus and cerebellum of rats submitted to hypobaric hypoxia equivalent to an altitude of 30,000 feet (9144 m; barometric pressure 230.4 Torr) were analyzed and semiquantitatively assessed by means of light microscopic immunocytochemistry and Western blotting using specific polyclonal antibodies. Changes in the expression of these components were directly related to the reduction of barometric pressure, time of exposure to hypobaric hypoxia and the post-hypoxic recovery period. After exposure to hypobaric hypoxia for 8 h and a recovery period of 24 h, an intense vasodilatation was also demonstrated in blood vessels throughout the brain and especially in blood vessels of the hypothalamic magnocellular accessory group. Animals treated with N^{ω}-nitro-L-arginine methyl ester (L-NAME) did not show changes in nNOS and iNOS expression but displayed decreased nitrotyrosine immunoreactivity. The anatomical and biochemical modifications following 4 or 8 h of hypobaric hypoxia demonstrated by this study may be related to some of the psychological changes described after human exposure to high altitude.

Introduction

Few experimental studies on animals have been carried out on the biological mechanisms underlying the debilitating neuropsychiatric disorders that may affect unacclimatized individuals when exposed to the hypobaric hypoxic conditions of high altitude for periods ranging from several hours to days (Carson et al., 1969; Hackett and Rennie, 1976; Hultgren, 1979). These disorders, characterized by symptoms such as headache, insomnia, irritability, depression and impaired sensory, memory and cognitive functions (Carson et al., 1969), are clearly related to functional changes in the central nervous system (CNS) and Forster et al. (1975) demonstrated increased cerebral electrical activity by electroencephalography (EEG) and a reduced visual evoked response signal.

The severity and duration of these symptoms vary with the exposed individual's condition, the altitude and rate of ascent (Hansen et al., 1967), and symptoms sometimes persist after returning to lower altitudes (Ryn, 1971; Sharma et al., 1975; Sharma and Malhotra, 1976; Townes et al., 1984; West and Lahiri, 1984; West, 1986; Cavaletti et al., 1987, 1990; Oelz and Regard, 1988; Regard et al., 1989; Cavaletti and Tredici, 1992; Shukitt-Hale et al., 1994). Cavaletti et al. (1987) reported a decrease in memory performance tested at sea level 75 days after a climb without supplementary oxygen to 7075 m (23,212 ft.). This was confirmed by Kassirer and Such (1989), who reported that certain neurologic symptoms (headache and taste dysfunction) persisted 15 days after an accidental exposure to hypoxia in a pressure chamber, simulating an altitude of 7620 m (25,000 ft.). The hippocampus, one of the cerebral regions most vulnerable to hypoxia (Arregui et al., 1991; Xun et al., 1991; Shukitt-Hale et al., 1996), also appears to show changes related to a definite impairment of mental ability (Haldane and Priestley, 1935).

It is generally accepted that psychomotor performance is not impaired at altitudes below about 3048 m (10,000 ft.) (Figarola and Billings, 1966; Pearson and Neal, 1970; Ernsting, 1978), but many neuropsychologic functions deteriorate as altitude increases above 4000 m (13,123 ft.) (Fine and Kobrick, 1978). However, there is evidence that learning of complex mental tasks is slower at pressures equivalent to an altitude of 2438 m (8000 ft.) (Denison et al., 1966), or even at altitudes as low as 1829 to 2438 m (6000 to 8000 ft.) (McFarland, 1971), than at sea level. Thus it appears that even at the cabin altitudes of today's commercial aircraft (2500 m or 8200 ft.) sensitive psychometric texts can detect minor degrees of impairment. After a prolonged stay at high altitude (3500 m or 11,483 ft.) changes in autonomic nervous activity were also reported by Malhotra and Mathew (1974), in the form of sympathetic and parasympathetic hyperactivity. Systolic and diastolic blood pressures and the mean pulse rate also increased at 4200 m (13,780 ft) (Forster, 1985).

The changes in the central and peripheral nervous systems consequent on exposure to hypobaric hypoxia may be mediated by the endogenous generation of nitric oxide (NO), which as an intercellular messenger and potent vasodilator is directly involved in various pathophysiologic mechanisms. NO is synthesized from L-arginine in the mammalian

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brain (Knowles et al., 1989; Bredt et al., 1990, 1991) as well as in invertebrate neural structures (Elphick et al., 1993; Martinez et al., 1994) by the enzyme nitric oxide synthase (NOS), which has been the subject of extensive study (for reviews, see Moncada and Higgs, 1993; Moncada et al., 1991; Rodrigo et al., 1994, 1997, 2000).

There is now evidence that at least three forms of NOS can be distinguished, two constitutive isoforms (cNOS) and an inducible isoform (iNOS) (Forstermann et al., 1991; Moncada et al., 1991). The cNOS isoform present in vascular endothelial cells is known as endothelial NOS (eNOS), and that present in the central and peripheral nervous system is known as neuronal NOS (nNOS) (Bredt et al., 1990, Moncada et al., 1991). The latter has been purified from rat brain and cerebellum (Bredt and Snyder, 1990; Knowles et al., 1990) and cloned from rat (Bredt et al., 1991) and human brains (Nakane et al., 1993). This isoform has been described as a soluble homodimer of 155 kDa (Bredt and Snyder, 1990; Schmidt and Murad, 1991), with a sequence similarity to cytochrome P-450 reductase at the carboxy-terminal end (Bredt et al., 1991). The molecule has recognition sites for nicotinamide adenine dinucleotide phosphate (NADPH), flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN) and calmodulin (Bredt et al., 1991). This form of the enzyme is cytosolic and totally dependent on activation by Ca^{2+}/calmodulin, using L-arginine as substrate and NADPH as cofactor (Knowles et al., 1989; Bredt and Snyder, 1990, 1992; Garthwaite, 1991; Moncada et al., 1991). Biochemical measurements in different regions of the brain have shown that the highest concentration of NOS is found in the cerebellum, followed by the hypothalamus, midbrain, striatum and hippocampus, with the lowest activity in the medulla oblongata (Forstermann et al., 1990).

The inducible isoform of NOS has been purified from the cytosol of activated murine macrophages (Hevel et al., 1991) and shown to have a molecular mass of 135 kDa. It has been identified in mast cells, lymphocytes, neutrophils, hepatocytes, vascular smooth muscle cells, mesangial cells, endothelial cells, neurons and in various tumors (Busse and Mulsch, 1990; Marsden and Ballermann, 1990; Salvemini et al., 1990; Gross et al., 1991; Moncada et al., 1991; Moro et al., 1998). In rodent macrophage cell lines (RAW 264,7 and J774) the synthesis of iNOS is dependent on induction by lipopolysaccharide (LPS) and cytokines (Marletta et al., 1988). The enzyme also requires NADPH, FAD and FMN and to varying degrees, tetrahydrobiopterin BH_4 and glutathione for full activity (Stuehr et al., 1990; Hevel et al., 1991). The induction of iNOS can be inhibited by glucocorticoids (Moncada et al., 1991). Murine iNOS was cloned (Lyons et al., 1992; Xie, 1992; Lowenstein et al., 1993) and found to be distinct from the two known constitutive isoenzymes. Human iNOS has also been cloned, both from chondrocytes (Charles et al., 1993) and hepatocytes (Geller et al., 1993).

The neurotoxic effects of NO is mediated by formation of peroxynitrite and other highly reactive nitrogen species (Beckman, 1996). Peroxynitrite is capable of nitrating tyrosine residues in tissue proteins, and the nitrotyrosine formed over a period of time can be used as a marker of peroxynitrite production (Beckman, 1996; Beckman et al., 1992). Immunohistochemical studies have revealed that nitration of tyrosine residues takes place in various organs after ischemia and in other pathological conditions (Ischiropoulos et al., 1992; Wang and Zweier, 1996)., e.g. in the brains of patients with Alzheimer's disease (Smith et al., 1998) or in the cerebral cortex of the aging rats (Uttenthal et al., 1998).

Pharmacological agents can reduce NO production or prevent its biological effects in a variety of ways, e.g. by inhibiting cellular L-arginine uptake, by reducing the cellular availability of necessary cofactors, by inhibiting the NOS enzymes, by scavenging NO once formed, or by inhibiting the cellular mechanisms leading to the induction of a particular NOS isoform (Moncada et al., 1997). One of the most frequently used agents, N^{ω}-nitro-L-arginine methyl ester (L-NAME), is an unselective inhibitor of NOS isoforms that has also been reported to reduce glutamate efflux, a phenomenon that was considered to contribute to the reduction of infarct size after focal ischemia (Buisson et al., 1992, 1993). However, the importance the latter effect is in doubt, as animals treated with L-NAME have been reported to show increased, decreased or unchanged glutamate efflux in comparison with controls (Zhao et al., 1999).

The aim of the present study was to investigate the effects of exposing rats to acute hypobaric hypoxia at 230.4 Torr (simulating an altitude of 30,000 ft. or 9144 m) for periods of 15 min to 8 h on the expression and localization of nNOS and iNOS in the CNS and to use nitrotyrosine in proteins as a marker for the production of reactive nitrogen species. Different brain cortical areas, the caudate putamen, the islands of Calleja, the hippocampus, superior colliculus and cerebellum were analyzed by immunocytochemistry and Western blotting using specific rabbit polyclonal antibodies against nNOS, iNOS and nitrotyrosine. We also investigated whether such changes could be suppressed by concurrent L-NAME administration, which might exert a protective effect on the brain under these conditions.

Material and methods

The study was performed on 60 young male albino Wistar rats (220-350 g body weight), which were subjected to periods of simulated high altitude in a hypobaric chamber (Environmental Tectonics Corporation International (EETC) type 10M. This chamber can simulate a variety of atmospheric conditions by reducing the ambient barometric pressure in combination with a precise control of temperature and relative humidity. The chamber is continuously purged with fresh air, replacing oxygen consumed by the rats and removing carbon dioxide. Altitude simulation is achieved by means of a vacuum pump to reduce pressure in the chambers.

Experimental procedures

Groups of 10 rats were exposed to a simulated altitude of 30,000 ft. (9144 m; 230.4 Torr) for 15 min, 45 min, 4 h or 8 hours, a control group being kept under normobaric, normoxic and standard conditions of light and temperature with free access to water and commercial rat chow. A further group of 10 rats were pretreated with 1.5 mM L-NAME (0.4 mg/ml) added to the drinking water (Cellek et al., 1999) for five days; six of these were submitted to the same simulated altitude for 8 h, the remaining four serving as L-NAME controls. This dose of L-NAME is higher than the 5 mg/kg dose considered to inhibit NO synthase activity (Navarro et al., 1994).

After exposure to simulated altitude, half the animals in each group were immediately perfused for either immunocytochemistry or Western blotting and the other half were perfused after a 24-h post-hypoxic recovery period under normobaric, normoxic conditions. L-NAME administration was continued throughout the recovery period in the L-NAME pretreated rats. Animals were then deeply anesthetized with pentobarbital (25 mg/kg i.p.) and perfused with 0.9% saline through the left ventricle via a blunt cannula (Minoject, St. Louis, MO, USA) connected to a peristaltic pump (Microtube pump MP3, Eyela, Tokyo, Japan). For Western blotting, perfusion was stopped after blood had been rinsed from the vasculature with 50-100 ml saline; the brain was then removed for extraction of proteins. For immunocytochemistry, perfusion was continued with 500 ml fixative solution containing 4% paraformaldehyde in 0.1 M phosphate buffer (PB), pH 7.4. The brains were removed, cut into blocks and postfixed for a further 4 h in the same fixative solution at room temperature. The blocks were then rinsed and cryoprotected by immersion overnight at 4°C in 0.1 M PB containing 30% sucrose, with continuous stirring.

Immunocytochemistry

Serial frontal frozen sections, 40 µm thick, were cut with a Leitz sledge microtome. Free-floating sections were processed by the avidin-biotin peroxidase complex (Rodrigo et al., 1994) to visualize nNOS, iNOS and nitrotyrosine immunoreactive sites. All sections were incubated for 30 minutes in PBS containing 3% normal goat serum (ICN Biochemicals, Barcelona, Spain) and 0.2 % Triton X-100, and then separately with nNOS, iNOS and nitrotyrosine antisera, diluted 1:3000, 1:5000 and 1:1000, respectively, in PBS/Triton X-100, overnight at 4EC. After several washes in PBS, the sections were incubated with biotinylated goat anti-rabbit immunoglobulin for 1 h. After washing, the sections were incubated with peroxidase-linked ABC (Vector Laboratories. Burlingame, CA, USA) for 90 minutes. The peroxidase activity was demonstrated by the nickel-enhanced diaminobenzidine procedure (Rodrigo et al., 1994).

Immunocytochemical controls. Control procedures were carried out on sections from two animals. No immunolabeling was observed when the primary antibodies were omitted or replaced with an equivalent concentration of preimmune and normal rabbit serum. The specificity of the nNOS antiserum was demonstrated by incubating the tissue sections with the primary antiserum dilution preabsorbed (overnight at 4°C) with 2 µg/ml recombinant nNOS; specificity of the iNOS antiserum was demonstrated by preabsorption with the respective immunizing peptide at 10 nmol/ml. The specificity of the nitrotyrosine antiserum was demonstrated by preabsorption with free 3-nitrotyrosine at 100 nmol/ml. This procedure abolished immunostaining in all three cases.

Western blotting

Unfixed brains were homogenized (1:5 w/v) in 50mM HEPES buffer, pH 7.4, containing 100 mM KCl, 10mM $MgCl_2$, 10 mM NaH_2PO_4, and 0.33 mg/ml soybean trypsin inhibitor. All procedures were carried out at 4ºC. Homogenates were centrifuged at 105,000g for 1 h and the supernatant collected. Protein concentrations were determined by the method of Bradford (1976), using BSA as standard. Samples of supernatants containing 30 µg protein were heated to 95ºC for 3 min in 62 mM Tris-HCl buffer, pH 6.8, containing 2% w/v SDS, 10% v/v glycerol and 10mM 1,4-dithiothreitol. Proteins were separated by SDS-PAGE in 7.5% gels for nNOS and 12.5% gels for protein nitrotyrosine, in a Bio-Rad Mini-Protein II apparatus (Bio-Rad, Madrid, Spain), and were then electroblotted onto 0.2 mm polyvinylidene difluoride (PVDF) membranes (Immobilon-P, Millipore, Bedford, MA, USA) by means of a semidry transfer apparatus (Hoeffer, Pharmacia, Barcelona, Spain) at 1.5 mA per cm^2 of membrane for 2 h in 10 mM CAPS buffer (Sigma, Madrid, Spain), pH 9.4, to which 10% v/v methanol had been added. The membranes were blocked with 5% w/v dried defatted milk and 0.05% v/v Tween-20 in 10 mM Tris-HCl buffer, pH 7.5, containing 100 mM NaCl. The membranes were then incubated with dilutions of the polyclonal nNOS, iNOS or nitrotyrosine antisera in blocking solution overnight at 4ºC. Bound antibody was revealed by means of an enhanced chemiluminescence kit (Amersham, Madrid, Spain), according to the manufacturer's instructions, and the membranes were scanned with a computer-assisted densitometer.

Antisera

Neuronal NOS. A rabbit polyclonal antiserum raised against full length recombinant rat brain nNOS (Riveros-Moreno et al., 1995) was a gift from Dr. V. Riveros-Moreno (Wellcome Research Laboratories, Beckenham, UK). This was characterized by immunocytochemistry and shown to react with neurons of different mammalian species, but only at low dilution with rat endothelium, its properties being closely similar to a polyclonal antiserum raised against purified rat brain NOS (Springall et al., 1992). It was further characterized in Western blots of rat liver and brain homogenates (Uttenthal et al., 1998). Rat endothelium was not stained by the antiserum at the dilution used in the present study.

Inducible NOS. Peptide PT387 (Ac-Cys-[residues 1131-1144]) from the C-terminus of the deduced sequence of murine iNOS (Moss et al., 1995) was custom synthesized by an automated 9-fluorenyl methoxycarbonyl (FMOC) solid-phase method (Peptide Therapeutics, Cambridge, UK), purified by reverse-phase high-pressure liquid chromatography (HPLC) and characterized by mass spectrometry. The peptide (1 mg) was conjugated via the Cys residue to 1 mg keyhole limpet hemocyanin (KLH) by the method of O'Sullivan et al. (1979) using maleimidobenzoic acid N-hydroxysuccinimide ester. One third of the conjugate was emulsified in an equal volume of Freund's complete adjuvant and used to immunize 4 New Zealand white rabbits by subcutaneous injection at multiple sites on the back. Four boosts of 1/6 of the conjugate emulsified in Freund's incomplete adjuvant were given by subcutaneous injection at monthly intervals thereafter, and the animals were bled from the marginal ear vein 14 days after each boost. Antibody titers were checked by enzyme-linked immunoassay in microwells coated with 5 µg/ml of a BSA conjugate of the same peptide (molar ratio peptide:protein 4:1) and characterized by Western blotting (Uttenthal et al., 1998).

Nitrotyrosine. Peroxynitrite was generated in aqueous solution as described by Blough and Zafiriou (1985) and stored in aliquots at -80°C. KLH (20 mg) was dissolved in 2 ml 25 mM sodium bicarbonate containing 1 nM EDTA and 1 mM ferric chloride. Peroxynitrite solution was thawed, its concentration determined by optical density at 302 nm, and added as a single aliquot to a calculated final concentration of 9 mM under continuous agitation at room temperature. The resulting solution (nitrated KLH) was dialyzed at 4EC for 24 hours against three changes of 1 l of phosphate-buffered saline, pH 7.4 (PBS). BSA (20 mg) was treated with peroxynitrite in parallel, following the same protocol. Two New Zealand white rabbits were each immunized at multiple subcutaneous sites with 2 mg nitrated KLH emulsified in a equal volume of Freund's complete adjuvant and boosted at monthly intervals with the same dose emulsified in Freund's incomplete adjuvant. Animals were bled as above and antibody titers were determined by EIA in microwells coated with nitrated BSA at 1µg/ml. The chosen antiserum showed 50% and 90% inhibition of antibody binding by 1.25 µM and 64 µM free 3-nitrotyrosine, respectively (Uttenthal et al., 1998).

Results

Immunocytochemistry

Control rats

nNOS immunoreactivity. Immunoreactive neurons were found at all levels of the cerebral cortex from rostral to caudal poles of the brain. These immunoreactive neurons, of fusiform, triangular and multipolar morphology, were distributed in layers II, III, IV and VI (Fig. 1A). They possessed a few long primary processes, which occasionally gave off long varicose collaterals (Fig. 1B). In general, all cortical areas showed discrete immunoreactive nerve fibers, which were especially densely distributed in layer I, where punctate immunoreactive fibers were also found.

The caudate putamen contained a large number of nNOS neurons which contributed processes to a varicose interstitial plexus between the unreactive fascicles crossing this region (Fig. 1C). The neurons were of medium size (15-20 µm) and showed a variable morphology, from fusiform to multipolar, with long, varicose and aspiny processes and few collaterals. The highest concentration of these immunoreactive neurons was found near the wall of the lateral ventricle.

The islands of Calleja contained numerous nNOS-immunoreactive granular cells. The insula magna at the mediodorsal border of the accumbens nucleus was limited medially by large immunoreactive neurons making up the vertical limb of the diagonal band of Broca. The other islands of Calleja are situated in the deep portion of the polymorph layer of the olfactory tubercle, limiting the ventral border of the accumbens nucleus (Fig. 1D). The granular cells of the islands of Calleja surrounded a dense network of small blood vessels. The clusters of granular cells in the area of the olfactory tubercle were included in a dense plexus of nNOS-immunoreactive varicose nerve fibers and large multipolar neurons of the polymorph layer of the olfactory tubercle.

The hippocampus showed scattered nNOS-immunoreactive neurons in all the areas studied (Fig. 2A). The dentate gyrus contained numerous nNOS neurons in the basal layer of the ectal and endal limbs of the granular cell layer. These neurons were multipolar with a large apical process and a few collaterals, which were mainly located between unreactive granular cells (Fig. 2B). Occasional nNOS neurons were found in the molecular layer of the dentate gyrus, mostly showing a fusiform morphology. The rostral sections of the hippocampus showed some nNOS neurons distributed in the pyramidal cell layer of the subiculum, and the CA1, CA2 and CA3 fields of Ammon's horn. These nNOS neurons (Fig. 2C) showed basal varicose processes in the stratum oriens and an apical dendrite composed of a single process with a few branches running through the stratum radiatum and forming a discrete tuft in the stratum lacunosum moleculare.

In the caudal sections of the hippocampus nNOS neurons were more numerous in the CA1 field and the parasubiculum, showing a pyramidal morphology with dense tufts distributed in the stratum radiatum and stratum lacunosum moleculare.

The superior colliculus contained immunoreactive neurons in all layers. A modest number of nNOS neurons was found in the intermediate gray and white layers and a small number of nNOS neurons was scattered in the deep white layer (Fig. 2D). These immunoreactive neurons were of medium size and multipolar morphology (Fig. 2E).

The cerebellum showed nNOS-immunoreactive stellate and basket cells in the upper and deep portions of the cerebellar molecular layer. The basket terminals around the initial portion of the axons of the mostly non-

immunoreactive Purkinje cells were also immunoreactive (Fig. 2F and G). The granular cell layer contained occasional weakly immunoreactive granular cells. The deep portion of the cerebellum showed immunoreactive varicose fibers and a few nNOS-immunoreactive neurons in the lateral and anterior interposed cerebellar nuclei. Occasional Purkinje cells were stained in the midline of the vermis and in the paraflocculus.

iNOS immunoreactivity. A very small number of scattered iNOS-immunoreactive neurons was found in the cortical areas studied, but iNOS-immunoreactive neurons were a constant feature of the ectal and endal portions of the hippocampal dentate gyrus, where they were distributed in the basal part of the granular cell layer (Fig. 3A). Some cerebellar Purkinje cells were also found to contain iNOS immunoreactivity. All neurons showed the reaction product as small granular deposits in the cytoplasm and the initial portion of main processes.

Nitrotyrosine immunoreactivity. Immunoreactive neurons were found in the cerebral cortex, caudate putamen, islands of Calleja, olfactory tubercle, hippocampus, superior colliculus and cerebellum. The reaction product appeared as granular deposits preferentially distributed in or around the nucleus, but the product was also occasionally found in the cytoplasm of the cell body and/or in the initial portion of the processes (Figs. 3B-H). In the cerebellum, nitrotyrosine immunoreactivity was present in the stellate, basket and Purkinje cells (Figs. 3HI). The glial cells (Fig. 3 J) found in all the cerebral areas studied were also reactive to nitrotyrosine.

15 and 45 min hypobaric hypoxia/24 h reoxygenation

nNOS immunoreactivity. This remained similar to that in control animals after both periods of hypobaric hypoxia (Figs. 4 A-C). The superior colliculus showed a decrease in the number of immunoreactive neurons, which were mainly distributed in the zonal and superficial gray layers. Blood vessels, which retained a normal diameter, were generally surrounded by numerous nNOS-immunoreactive fibers, but no immunoreactivity was found in their endothelial cells (Fig. 5 A-D).

iNOS immunoreactivity. A few iNOS neurons showing the structure and morphology previously described were distributed in the cortical areas (Fig. 5 E), hippocampus (Fig. 5 F and G) and cerebellum (Fig. 5 H and I), the reaction product showing its characteristic granular form in the cytoplasm. Weak immunoreactivity was found in the cerebellar Purkinje cells.

Nitrotyrosine immunoreactivity. This was found in neurons of all areas studied, the reaction product being mainly related to the nuclear area (Fig. 6 A-C).

4 h hypobaric hypoxia/24 h reoxygenation

nNOS immunoreactivity. The number of nNOS-immunoreactive neurons showed an increase in all cortical areas and layers, retaining a morphology similar to those in control animals. Numerous immunoreactive varicose nerve fibers were found in all cortical layers (Fig. 6 D and E), forming a dense network which surrounded the immunoreactive neurons. Blood vessels were slightly dilated in all areas. Small immunoreactive neurons were also seen in all cortical regions, mainly distributed in the upper layer.

The caudate putamen also showed an increase in the number of immunoreactive neurons, these being most numerous just below the ependymal cells of the lateral wall of the lateral ventricle. In addition, nNOS-positive varicose nerve fibers were more prominent in all areas of the caudate putamen (Fig. 7 A and B).

The islands of Calleja in the olfactory tubercle showed intense immunoreactivity in the granular cells that surrounded dilated blood vessels. The nitrergic plexus of the molecular, pyramidal and polymorph layers of olfactory tubercle showed immunoreactive fibers and neurons (Fig. 7 C and D).

The hippocampus also showed increased nNOS immunoreactivity in all regions of Ammon's horn, in the ectal and endal areas of the dentate gyrus and in the hilar region. In general, the processes of the immunoreactive neurons were well developed and showed a varicose structure (Fig. 7 E and F). Dilated blood vessels were also found.

The superior colliculus showed immunoreactive neurons distributed in all layers, which contained numerous dilated blood vessels, giving a spongy appearance to the structure (Fig. 8 A). The dilated blood vessels appeared to stretch the surrounding neural parenchyma, changing the morphology of the many nNOS-immunoreactive neurons from a multipolar to a fusiform shape.

The cerebellum showed a more prominent nitrergic plexus in the molecular layer, where occasional immunoreactive apical processes of Purkinje cells were also seen. The stellate cells, basket cells and basket terminals surrounding the Purkinje cell bodies were also immunoreactive. The granular cells also showed increased immunoreactivity (Fig. 8 B - D).

iNOS immunoreactivity. This was more prominent in all cerebral areas studied. Numerous iNOS neurons were found in the cerebral cortex, specifically as large pyramidal neurons in layers IV-V or small neurons in layer VI of the parietal and temporal regions (Fig. 8 E and D). In the hippocampus immunoreactive pyramidal neurons were also found in the pyramidal layer of the subiculum, and the CA1, CA2 and CA3 fields of Ammon's horn (Fig. 8 F). Immunoreactive multipolar neurons were also distributed in the basal layer of the dentate gyrus, just below the numerous immunopositive granular cells that were also seen in that region. The superior colliculus contained iNOS-immunoreactive neurons in all layers (Fig. 8 G) and some iNOS-immunoreactive Purkinje cells were found in the cerebellum (Figs. 8 H).

Nitrotyrosine immunoreactivity. Numerous nitrotyrosine-immunoreactive neurons were found in the cerebral cortex, olfactory tubercle, superior colliculus and cerebellum (Figs 8 A-F). These showed the reaction product around the nucleus, but reaction product was now also more prominent in the cytoplasm. In the cerebellum, the stellate, basket and Purkinje cells were immunoreactive.

8 h hypobaric hypoxia/24 h reoxygenation

nNOS immunoreactivity. The cerebral cortex showed a general decrease in nNOS immunoreactivity, all areas now acquiring a spongy appearance due to the intensely dilated blood vessels. These blood vessels separated the neural parenchyma into narrow elongated portions which showed an immunopositive network formed by a small number of fusiform or elongated immunoreactive neurons with their sparse processes and collaterals (Fig. 10 A and B). The nitrergic plexus was less prominent in all cortical regions and layers.

The caudate putamen also showed a small number of immunoreactive neurons and nerve fibers forming a nitrergic plexus (Fig. 10 C). The islands of Calleja contained numerous, intensely immunoreactive granular cells surrounding dilated blood vessels (Fig. 10 D).

A few immunoreactive neurons with short processes and collaterals were found in all hippocampal areas (Fig. 10 E). Some pyramidal cells with well-stained cell bodies and processes were occasionally found in CA1 (Fig. 10 F). The blood vessels were also dilated, forming a dense vascular network pervading the hippocampal parenchyma, the ectal and endal regions of the dentate gyrus showing a particularly spongy structure.

Immunoreactivity to nNOS had decreased in all layers of the superior colliculus, where immunoreactive neurons and processes were seen in the compressed bands of parenchyma resulting from the intense dilatation of the blood vessels that gave rise to the characteristic spongy appearance (Fig. 11 A-B).

A similar appearance was found in the cerebellum, where dilated blood vessels crossed the molecular and granular cell layers. Some Purkinje cells showed immunoreactive apical processes and perikarya, which were surrounded by immunoreactive basket terminals (Fig. 11 C-F).

iNOS immunoreactivity. Some iNOS-immunoreactive neurons were scattered throughout the cortical areas, but in layers IV-V of the parietal and temporal cortex these neurons were pyramidal (Fig. 11 G). The hippocampus (Fig. 11 H and I) showed immunoreactive neurons with well-developed immunoreactive processes distributed in different areas of Ammon's horn and among the granular cells of the dentate gyrus. The Purkinje cells in the cerebellum were also stained (Fig. 11 J).

Nitrotyrosine immunoreactivity. All the regions examined contained nitrotyrosine-immunoreactive neurons. Cerebellar Purkinje cells and neurons of the cerebellar nuclei were especially prominent (Fig. 12 A-E).

Blood vessels

In general, the blood vessels of the cerebral cortex showed an intense vasodilatation after exposure to hypobaric hypoxia for 4 or 8 h, followed by 24 h of reoxygenation. This gave rise to the separation of the neuronal parenchyma in narrow, elongated portions in which the stretched nNOS-immunoreactive neurons and their processes appeared to surround the blood vessels as a dense nitrergic plexus (Fig. 13 A).

In particular, the nucleus circularis of the magnocellular accessory group in the anteromedial preoptic area of the hypothalamus, which forms part of the chiasmatic perivascular neurosecretory system, showed nNOS-immunoreactive neurons and processes surrounding the dilated blood vessels after 4 h of hypoxia and 24 h of reoxygenation (Fig. 13 B). After 8 h of hypoxia and 24 h of reoxygenation the dilatation of the blood vessels was the main characteristic, the number of nNOS-immunoreactive neurons surrounding these blood vessels having decreased (Fig. 13 C). At this stages the numerous dilated blood vessels showed nitrotyrosine immunoreactivity in the endothelial cells (Fig. 13 D-E).

L-NAME administration

L-NAME administration did not produce any general changes in neuronal structures, which retained showed a normal appearance in the L-NAME control group.

nNOS immunoreactivity. As in control animals, the cerebral cortex contained nNOS immunoreactive neurons distributed in all layers within a nitrergic plexus (Fig 14 A). The caudate putamen and the islands of Calleja also showed a similar distribution and intensity of immunoreactivity to that seen in controls (Fig. 14 B).

The morphology, intensity of immunoreaction and distribution of nNOS neurons and fibers of the hippocampus (Fig. 14 C and D), cerebellum (Fig. 14 A) and cerebellar nuclei (Fig. 14 B) were also similar to those found in control animals not subjected to hypobaric hypoxia.

iNOS immunoreactivity. The cortex, hippocampus and cerebellum contained iNOS-immunoreactive neurons. The frontal, parietal and temporal cortex showed a small number of immunostained pyramidal cells (Figs. 15 C and D). Some iNOS neurons were also found in the basal portion of the unreactive granular cell layer of the hippocampal dentate gyrus (Fig 15 E).

Nitrotyrosine immunoreactivity. Neurons that were immunoreactive to nitrotyrosine were found in all areas studied, but these were fewer than in animals exposed to the same periods of hypobaric hypoxia and reoxygenation without L-NAME treatment (Fig. 15 F - H).

Western blotting

Cerebral cortical and cerebellar supernatants from control brains and those submitted to 4 and 8 h of hypobaric hypoxia followed by 0 or 24 h of reoxygenation were analyzed by Western blotting using the antisera against whole rat recombinant nNOS, C-terminal peptide of murine iNOS and nitrotyrosine. The nNOS antibody reacted strongly with nNOS, giving a band at 153 kDa. The iNOS antibody give a band at 135 kDa and nitrotyrosine immunoreactivity was shown in two or three bands running between 53 and 23 kDa.

nNOS. The nNOS protein band in the cortex decreased with respect to control animals after 4 and 8 h of hypobaric hypoxia followed by 0 or 24 h of reoxygenation (Fig. 16 A and B). The nNOS protein band in the cerebellum increased after 4 h of hypobaric hypoxia without reoxygenation (Fig. 16 A) but was similar to that of controls after 24 h of reoxygenation (Fig. 16 B). After 8 h of hypobaric hypoxia with 0 or 24 h of reoxygenation the cerebellar nNOS band was similar to or slightly decreased with respect to controls (Fig. 16 C and D).

iNOS. The iNOS protein band in the cortex showed some increase after 4 and 8 h of hypobaric hypoxia followed by 0 or 24 h of reoxygenation, the increase being more marked after reoxygenation (Fig. 17 A and B). The cerebellar iNOS band was maintained after 4 h of hypobaric hypoxia without reoxygenation, decreasing after 8 h of hypobaric hypoxia. A slight decrease in the cerebellar iNOS band was seen after 4 h of hypobaric hypoxia and 24 h of reoxygenation (Fig. 17 C and D).

Nitrotyrosine. Nitrotyrosine immunoreactivity was found in two or three principal protein bands among a considerable number of faint bands. Two main bands of 53 kDa and 23 kDa were found in the cortex and cerebellum. These were little changed in the cortex after 4 and 8 h of hypobaric hypoxia without reoxygenation (Fig. 18 A), but decreased after 24 h of reoxygenation (Fig 18 B). In the cerebellum, both main bands after 4 and 8 h of hypobaric hypoxia with or without reoxygenation (Fig. 18 C and D).

Discussion

These results represent the first extensive immunocytochemical study of the expression of nNOS and iNOS isoforms and the formation of protein nitrotyrosine in the CNS of rats exposed for short periods (15 min to 8 h) to hypobaric hypoxia simulating an altitude of 30,000 ft. (9144 m, 230.4 Torr). They form the basis for a preliminary attempt to assess the role of nNOS, iNOS and protein nitration in the physiological or pathophysiological neural responses to hypobaric hypoxia.

The cerebral cortex, caudate putamen, hippocampus, superior colliculus and cerebellum were studied by immunocytochemistry. The nucleus circularis of the hypothalamus and the islands of Calleja were also studied as two specific types of vascular nuclei, respectively related to the hypothalamic chiasmatic perivascular neurosecretory system and the control of vascular flow to the basal forebrain. The cerebral cortex and cerebellum were analyzed by Western blotting, which reflects overall changes in the concentrations of the studied components in the many different cell types present in these areas and is thus incapable of demonstrating changes confined to minority cell populations.

In general, there is a decreased immunocytochemical expression of nNOS in most cerebral areas by 8 h of hypobaric hypoxia, counterbalanced by an increased expression of iNOS. Protein nitrotyrosine reflecting nitration due principally to peroxynitrite formation did not show significant global modifications immediately after 4 or 8 h of hypoxia, but the distribution of the reaction product ran in parallel with the nNOS and iNOS immunoreactivities in the areas studied.

Some parallels with these results have been observed by us in previous immunocytochemical studies. Thus iNOS appeared in cortical neurons of rat forebrain slices subjected to 3 h of oxygen and glucose deprivation *in vitro*, at which time nNOS expression had decreased (Moro et al., 1998). In a perfusion model of global cerebral ischemia, nNOS immunostaining increased in cerebellar stellate and basket cells and iNOS appeared in Purkinje cells after 2-4 h of reperfusion following 30 min of oxygen and glucose deprivation, accompanied by an increase and morphological changes in the intracellular distribution of protein nitrotyrosine (Rodrigo et al., 2000). The cerebral cortex of aging rats shows iNOS expression by pyramidal neurons of layers IV-V (Uttenthal et al., 1998) and this is also observed in the cerebral cortex from brains subjected to global ischemia (Alonso et al., 2001, in preparation).

Western blotting shows that the overall expression of nNOS in the cerebral cortex tends to decrease after 4 or 8 h of hypobaric hypoxia, while iNOS expression shows an increase that is particularly apparent after 24 h of reoxygenation. While iNOS immunoreactivity increases in cerebellar Purkinje cells after 4-8 h of hypobaric hypoxia, overall iNOS expression showed little change or tended to decrease. Nitrotyrosine immunoreactivity was present in two main protein bands of 53 and 23 kDa respectively, which decreased in the cortex and increased in the cerebellum after 4-8 h of hypobaric hypoxia.

Prabhakar et al. (1996) have reported immunocytochemical changes in nNOS in the cerebellum of adult rats exposed to hypobaric hypoxia (304 mm Hg/0.4 atm.) for up to 24 h, showing that the increase in nNOS immunoreactivity depended on the time of exposure. Our results suggest that not only exposure time but also the reoxygenation period may influence the magnitude of changes in the expression of the NOS isoforms studied.

Histological changes consequent on hypoxia have previously been described in the hippocampus, which is the cerebral area most sensitive to hypoxia and the seat of various cognitive and memory functions (Ando et al., 1987) These changes involved damage to the pyramidal cells of the CA1 field of Ammon’s horn and the dentate gyrus (Brierly, 1976; Jensen et al., 1991; Katoh et al., 1992; Kirino, 1982; Shukitt-Hale et al., 1994, 1996). Other cerebral

regions such as the cerebral cortex, striatum, thalamus, cerebellum and amygdala were also described as being affected by neuronal damage following hypoxia (Brierly, 1976; Katoh et al., 1992; Shukitt-Hale et al., 1994, 1996).

In the present study we have not only found that the immunocytochemical expression of nNOS, iNOS and nitrotyrosine underwent changes in the cortex, striatum, islands of Calleja, hippocampus, superior colliculus and cerebellum, but also that these cerebral areas show numerous dilated blood vessels after hypobaric hypoxia. These dilated vessels displace the neural parenchyma, giving rise to a markedly spongy appearance of the nervous tissue. This dramatic vasodilatation must directly affect the cerebral blood flow and influence the aerobic mechanisms that sustain the Krebs cycle and the cellular respiratory chain (Bolaños et al., 1994), as well as synaptic neurotransmission (Cavaletti and Tredici 1991).

It is possible that this extreme vasodilatation, by displacing and stretching the neural parenchyma with its many neural elements, may produce transient or even permanent changes in neuronal connections and relations, and thus contribute to some of the various clinical symptoms described by Bahrke and Shukitt-Hale (1993).

While the expression of iNOS in cerebellar neurons can be induced by LPS and interferon-γ (Minc-Golomb et al., 1994, 1995), the iNOS gene promoter can also be activated by a hypoxia-responsive element (Melillo et al., 1995). We have recently demonstrated that oxygen and glucose deprivation induced iNOS expression in rat forebrain slices, as assessed by the detection of iNOS mRNA and protein. A six-fold increase in iNOS mRNA was observed at 180 minutes and the time course of iNOS mRNA expression was in agreement with the temporal profile of iNOS (calcium independent) enzymatic activity. Immunocytochemistry revealed that iNOS was expressed in neurons, astrocytes and microglial cells (Moro et al., 1998).

The rise in intracellular calcium levels, which activates the constitutive isoform nNOS, appears to play an integral role in the production of ischemic and hypoxic cell damage. *In vivo* calcium accumulates in the cells that are selectively vulnerable to ischemia (Deshpande and Wierloch, 1985; Deshpande et al., 1987; Gibson et al., 1988; Jensen et al., 1991) and mediates cellular damage (Griffiths et al., 1982, 1983; Simon et al., 1984a,b; Van Reempts et al., 1984). Calcium antagonists or glutamate-receptor blocking agents ameliorate ischemic damage (Newberg et al., 1984; Deshpande et al., 1987, Vibulsresth et al., 1987; Buisson et al., 1993) and the omission of calcium from the medium diminishes the biochemical (Gibson and Mykytyn, 1987; Harvey et al., 1983) and electrophysiological (Kass and Lipton, 1982) effects of an anoxic preincubation. The elevated intracellular free calcium levels could also disrupt cellular metabolic activity and eventually cause neuronal death (Mitani et al., 1990).

The activation of nNOS by elevated intracellular calcium and the induction of iNOS expression by hypoxia leads to an increase in the biosynthesis of NO. NO decays in solution with a half-life of 5-10 seconds, whereas the citrulline that is formed in equimolar amounts remains in the cells and can be reconverted into L-arginine to provide further substrate for NO synthesis (Bredt and Snyder, 1990; Knowles et al., 1989; Moncada et al., 1991). The increased generation of NO that takes place during hypoxia, at first due to nNOS activation by calcium and subsequently sustained by induction of the highly active iNOS, produces a strong vasodilatation that would appear to permit a compensatory increase in cerebral blood flow. However, the dramatic extent of the vasodilatation observed may also result in the potentially damaging structural neural changes described above.

NO reacts with superoxide radicals to form peroxynitrite, a potent oxidant that is capable of nitrating tyrosyl residues in tissue proteins (Beckman et al., 1994; Beckman, 1996; Szabó, 1996). The nitrotyrosine formed thus acts as a direct marker of peroxynitrite generation over a period that is determined by the turnover of the protein in question. The existence of possible denitration mechanisms (Kamisaki et al., 1998) will also influence the amount of nitrotyrosine immunoreactivity observed. As peroxynitrite is formed by the combination of NO with superoxide, nitrotyrosine also acts as an indirect marker of NO production and its possible neurotoxic effect (Lipton et al., 1993; Zhang and Snyder, 1995). Our immunocytochemical results suggest a certain parallelism of nitrotyrosine formation with the expression of nNOS and iNOS during hypobaric hypoxia. In normal conditions the reaction product is usually found in the cell nucleus and perinuclear areas, but not in the cell processes (Uttenthal et al., 1998; Bolan et al., 2000; Rodrigo et al., 2000). However, after acute ischemia or hypoxia the reaction product appears in the cytoplasm and processes (Rodrigo et al., 2000). This anatomical translocation is more remarkable than any quantitative changes in overall protein nitration as determined by Western blotting.

A moderate amount of protein nitrotyrosine is present in some cells throughout life and is considered to be a feature of normal physiology (Uttenthal et al., 1998). However, large amounts of nitrotyrosine have been demonstrated in some inflammatory disorders, atherosclerotic lesions and neurodegenerative diseases (Beckman et al., 1994; Bagasra et al., 1995; Beckman, 1996; Eiserich et al., 1998), in the brains of aging rats (Uttenthal et al., 1998) and brains submitted to global ischemia (Rodrigo et al., 2000; Alonso et al., 2001). Different nitrated protein bands may be detected under different circumstances. A nitrated 53-54 kDa band is commonly seen in rat brain extracts together with nitrated bands of lower molecular mass, and in the present experiments the major nitrated bands were found at 53 and 23 kDa. How protein nitration and other types of oxidative damage caused by peroxynitrite and other reactive nitrogen species cause neuronal death is not understood in detail, but it has been postulated that a neurotoxic effect might be produced by the nitration of mitochondrial respiratory chain enzymes (Bolaños et al., 1994), or in general, that nitration of tyrosine residues alters the conformation and functional activity of proteins, as well as their susceptibility to digestion (Castro et al 1994; Berlett et al., 1996; Crow et al., 1994). The nitration of tyrosine residues may also decrease the effectiveness of

certain proteins as substrates for tyrosine kinases (Martin et al., 1990, Crow et al., 1994; Wink et al., 1993a,b). These neurotoxic effects of the NO-peroxynitrite-nitrotyrosine pathway may directly participate, in an irreversible or only slowly reversible manner, in the interruption of cellular signaling processes.

The administration of L-NAME for five days prior to submitting the rats to hypobaric hypoxia blocked the appearance of the marked cerebral vasodilatation, indicating that this effect is directly related to the activity of NOS isoforms synthesizing NO, which acts as a potent physiological vasodilator. L-NAME administration also attenuated many of the other immunocytochemical changes observed in the rats submitted to 8 h of hypobaric hypoxia, so that sections from these brains were generally similar in appearance to those from control rats. Exceptions to this generalization were that iNOS still appeared in some cortical neurons and that nitrotyrosine immunoreactivity was attenuated to below control levels.

Finally, it is possible that the anatomical changes observed after 4-8 h of hypobaric hypoxia are reversible after a longer recovery period and may be related to some of changes in neuropsychological functions observed after human exposure to high altitude.

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Intérêt du caisson d'altitude pour l'évaluation de manifestations indirectes de dysperméabilité tubaire

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RESUME

Pour assurer leur mission en toute sécurité, les équipages d'aéronefs subissent régulièrement un examen médical qui vise à s'assurer de l'intégrité de leurs grandes fonctions. L'examen de l'oreille est centré sur les fonctions de l'audition, de l'équilibration et de la perméabilité tubaire.

Lors de la visite médicale d'admission, la perméabilité tubaire est quantifiée par un tympanogramme. Une anomalie du tympanogramme entraîne à prioriune inaptitude. C'est pourquoi, le candidat ayant un tympanogramme anormal est mis en situation réelle de variation de pression dans un caisson d'altitude pour s'assurer qu'une décision erronnée d'inaptitude ne sera pas prise.

Sur 19 candidats testés, deux seulement ont présenté des troubles, l'une a présenté une douleur nécessitant l'arrêt de la descente d'altitude, l'autre a présenté un barotraumatisme sans manifestation algique. 1es 17 autres personnes ont eu une perméabilité tubaire telle que le test s'est effectué dans de bonnes conditions. Leur aptitude médicale a donc été prononcée.

Ce travail discute des conditions dans lesquelles ce test s'est effectué et les précautions méthodologiques prises pour assurer la sécurité.

1. INTRODUCTION

Le personnel navigant militaire ou civil est soumis à des tests d'aptitude médicale car il accompli sa mission dans un environnement spécifique pour lequel il est nécessaire de s'assurer de l'intégrité de ses grandes fonctions physiologiques. Il accomplit des tâches qui nécessitent des prises d'informations visuelle et auditive dans un environnement pressionnel variable. Le médecin chargé du personnel navigant doit donc veiller à l'intégrité de ces fonctions.

L'otorhinolaryngologiste (ORL) est de la sphère nasale, buccopharyngée et de l'ensemble de l'oreille, chargé de contrôler l'absence de trouble ou d'affection

L'examen de l'oreille est centré sur les fonctions de l'audition, de l'équilibration ainsi que sur la perméabilité tubaire. Cette perméabilité est quantifiée par un examen spécifique le tympanogramme. Si cet examen est anormal et en l'absence de pathologie clairement identifiée, lors des visites médicales d'admission, la personne est considérée en France comme inapte. Elle ne pourra donc jamais être pilote commandant de bord ou membre d'équipage. Or, ces personnes peuvent, au cours de cette visite médicale se trouver à un niveau de cursus professionnel tel que leur inaptitude fait perdre un acquis incontestable et utile à leur employeur.

Pour des raisons économiques, il peut être intéressant de reconsiderer l'inaptitude prononcée et de remettre en question la validité du tympanogramme. En effet, un tympanogramme anormal est considéré souvent comme étant le témoin d'une dysperméabilité tubaire. Le travail, présenté ci-après, consiste à soumettre à un test au

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caisson d'altitude des personnes, volontaires, a priori considérées comme inaptes car ayant un tympanogramme anormal.

Ce travail est basé sur l'anatomie et la physiologie de l'oreille. L'investigation de la perméabilité tubaire par impédancemétrie est confrontée aux tests en caisson d'altitude pour permettre à l'expert de mieux prononcer l'avis d'aptitude.

2. ANATOMIE-PHYSIOLOGIE ET PHYSIOPATHOLOGIE DE L'OREILLE MOYENNE

L'oreille comprend classiquement trois parties : l'oreille externe, l'oreille moyenne et l'oreille interne.

L'oreille moyenne est l'ensemble des cavités aériennes qui résultent du développement embryologique d'un bourgeon né dans la partie postérieure des fosses nasales et qui se dirige en haut, en dehors et en arrière pour former successivement la trompe d'Eustache, la caisse du tympan, les cellules de la mastoïde. Cet axe aérien est tapissé par une muqueuse respiratoire, invagination de la muqueuse nasale. Ceci souligne l'unité anatomique et fonctionnelle des cavités del'oreille moyenne ainsi que leur rapport avec les fosses nasales

La caisse du tympan située à l'intersection de l'axe aérien et de l'axe sensoriel, joue un rôle fondamental dans la transmission sonore. Cette cavité abrite la chaîne ossiculaire (marteau-enclume-étrier) fixée d'une part à la membrane du tympan dont elle transmet et amplifie les vibrations (x2.5) et d'autre part à la paroi externe de l'oreille interne qui reçoit ces vibrations.

La trompe d'Eustache est un canal de 40 mm de long dont seule la moitié antérieure est mobile. En effet, cette zone fibro-cartilagineuse est contrôlée par les muscles péristaphylins. Ces muscles jouent un rôle physiologique fondamental car ils permettent l'ouverture de la trompe d'Eustache de façon active et par la même assurent l'équipression de l'oreille moyenne. On dit que la trompe d'Eustache s'ouvre en bec de canard. Cette ouverture en bec de canard permet à la trompe d'Eustache, lorsqu'elle est saine, de s'ouvrir de façon passive lorsque la pression de l'oreille moyenne est supérieure de 70 hPa à la pression extérieure et donc de la pression régnant au sein des cavités nasales. Par contre, du fait de sa constitution, lorsque le rapport de pression est inversé, cette ouverture n'est possible que par une action des muscles péristaphylins. L'équipression de part et d'autre du tympan est indispensable au bon fonctionnement de la chaîne tympano-ossiculaire et à une bonne audition. En effet, elle permet au tympan de vibrer avec le maximum d'amplitude.

Le tympan constitue la partie principale de la paroi externe de la caisse du tympan. Cette membrane souple de couleur nacrée fait 10 mm de diamètre. Elle est le reflet de ce qui se passe dans l'oreille moyenne et donc de la bonne perméabilité de la Trompe d'Eustache.

L'altération de la perméabilité de la Trompe d'Eustache entraîne la perte des échanges (équipression) entre l'oreille moyenne et l'extérieur. La dépression ou la surpression occasionnée par les conditions de vol va dans un premier temps tendre le tympan. Dans ce cas, le tympan et la chaîne des osselets n'amplifient plus les vibrations sonores et une surdité de transmission temporelle survient. Dans un second temps, lorsque la différentielle de pression de part et d'autre du tympan est trop importante, il apparaît une souffrance de celui-ci. Cette souffrance se manifeste par une douleur induite par la tension des terminaisons nerveuses qui aboutit à une gène telle que les activités de l'opérateur et la sécurité des vols sont altérées. De façon concommittante, des manifestations objectives de lésions apparaissent et le barotraumatisme est alors constitué. A l'extrême limite, le tympan est déchiré constituant un barotraumatisme majeur.

Enfin, la trompe d'Eustache assure aussi le drainage de l'oreille moyenne.

Les fonctions aératrice et drainage de la trompe d'Eustache sont indispensables au bon fonctionnement de l'oreille moyenne en permettant l'impédance la plus basse possible du système tympano-ossiculaire

3. TYMPANOMETRIE

La tympanométrie consiste à soumettre le tympan à des variations rapides de pression qui modifient la compliance de celui-ci.

Pour assurer à la fois la stimulation et la mesure, on introduit à l'intérieur du conduit auditif externe un manchon muni de petits canaux ayant plusieurs rôles :

- la stimulation du tympan par variation de pression,

- la transmission de la pression au niveau du conduit auditif externe proche du tympan au niveau d'un capteur,

- L'échappement par une fuite calibrée du volume d'air en excés induit par l'examen.

Ces variations de pressions sont établies de façon rapide : + 200 à - 400. La compliance du tympan est d'autant plus élevée que la pression se répartie de façon égale de part et d'autre du tympan. En effet, dans cette situation, la membrane souple du tympan se déforme de façon harmonieuse sous la variation rapide de pression.

Le tympanogramme se présente, a priori, en forme de chapeau chinois et s'interprète en fonction de :

- sa hauteur, qui dépend de la valeur statique de l'impédance,

- la position du sommet par rapport à l'axe zéro, correspondant à l'équipression entre le conduit et la caisse,

- sa forme : un tympanogramme normal comporte un sommet aigu. Toute entrave à l'élasticité du tympan le modifie, l'abaisse, l'arrondit ou le fait disparaître.

Les tympanogrammes peuvent avoir plusieurs formes :

- Tympanogrammes à pics centrés sur le zéro. Ce sont des tympanogrammes normaux. Mais lorsque le pic est supérieur à la normale, cela traduit une souplesse excessive du tympan (flacide, disjonction). A l'inverse, lorsque le pic est de faible amplitude, cela traduit une diminution de la souplesse.

- Tympanogrammes à pic centré vers les la zone de dépression. Ceci traduit une pression négative au sein de l'oreille moyenne et donc une dysperméabilité tubaire.

- Tympanogrammes arrondis ou plats. Le graphique prend alors un aspect en dôme plat ou arrondi, le plus souvent en raison d'un épanchement dans la caisse de l'oreille moyenne. Plus rarement, la rigidité est liée à une modification cicatricielle de la texture tympanique ou à un processus adhésif.

- Tympanogrammes atypiques. Presque toutes les formes peuvent être observées dans les séquelles d'otites. D'autres pathologies (tumeurs,…) peuvent être à l'origine de tympanogrammes anormaux et atypiques.

Devant l'ensemble de ces tympanogrammes anormaux, le clinicien pense à une pathologie dont la dysperméabilité tubaire est une expression fréquente. C'est pourquoi l'expert ORL doit logiquement mettre inapte la personne qui présente un tympanogramme anormal à la viste médicale d'admission.

En revanche, le même expert est perplexe devant la discordance entre une mobilité tympanique normale observée à l'otoscope lors d'une manœuvre de Valsalva et un tympanogramme anormal. C'est la raison même du test au caisson d'altitude.

4. EPREUVE AU CAISSON D'ALTITUDE

4.1. Méthodologie

L'épreuve au caisson d'altitude s'effectue au laboratoire de médecine aérospatiale dans le respect de la norme ISO 9001.

Avant que le test ne s'effectue, le médecin expose les problèmes de barotraumatisme à l'intéressé et examine ses tympans. De plus, lors de cet examen, le médecin demande que la personne effectue une manœuvre de Valsalva pour vérifier la mobilité du tympan. La personne expertisée est installée à l'intérieur du caisson. Elle est alors équipée d'un masque à mise en place rapide et d'écouteurs. Le test en caisson s'effectue avec la présence d'un médecin qui dispose d'un corticoïde, d'un otoscope. Depuis l'extérieur, via un hublot et une liaison phonique, un autre médecin surveille le déroulement du test et dirige les opérations.

Le profil de montée et de descente consiste en une montée jusqu'à 16 500 pieds à raison de 20 m/s. A l'issue de cette montée, un plateau pressionnel de quelques secondes est respecté. Il permet à l'intéressé d'effectuer une manœuvre de Valsalva. La descente s'effectue à un taux de 20m/s jusqu'à 12 000 pieds et à 10 m/s jusqu'au sol.

Une examen otoscopique est pratiqué à l'issue.

La personne doit pouvoir effecteur ce test sans qu'aucun trouble ne survienne.

4.2. Résultats

Depuis deux ans, 19 personnes ayant un tympanogramme anormal ont effectué ce test. Trois d'entre elles étaient de sexe féminin.

Toutes ont effectué cette montée sans anomalie. En revanche, au cours de la descente, une des personne a signalé une douleur nécessitant une interruption de la descente. Le plus souvent, l'opérateur a alors effectué une remontée en altitude en dépressurisant le caisson. Le médecin a instillé des corticoïdes par voie nasale, laissé agir et la descente s'est effectuée à un taux plus faible. Par ailleurs, une autre personne expertisée n'a pas présenté de douleur lors du test mais a présenté des manifestations objectives de barotraumatisme à l'examen.

5. DISCUSSION

A la vue de ces résultats, il semblerait que les tympanogrammes anormaux soient loin de traduire une dysperméabilité tubaire. En effet, dans 90 % des cas, les personnes ont pu effectuer des manœuvres de Valsalva efficaces.

La technique de l'examen tympanographique n'est pas à remettre en question car, dans de nombreux cas, ces personnes avaient eu plusieurs examens effectués par des personnes différentes et l'allure du tracés était toujours le même.

Par ailleurs, si très souvent ces personnes avaient un passé d'otites infectieuses dans la prime enfance, elles n'avaient pas d'épanchement séreux au moment du test au caisson.

S'il reste avant tout nécessaire de confirmer ces observations, la seule hypothèse acceptable serait un tympan ayant une souplesse altérée sans avoir pour autant une dysperméabilité tubaire.

Enfin, à l'issue du test au caisson d'altitude, alors que l'une des personnes expertisée n'avait pas présenté d'algie, son tympan était hématié. Cette manifestation doit être rapprochée de travaux menés au laboratoire et présentés il y a trois au congrés de l'association américaine de médecine aérospatiale. En effet, une vingtaine de personnes avaient participé à une expérimentation qui avait pour but de déterminer le seuil douloureux lors de variations positives ou négatives de la pression au niveau du conduit auditif externe. Cette étude avait montré que plusieurs personnes avaient présenté des discrètes manifestations objectives de barotraumatisme sans avoir ressenti une

quelconque douleur. Dans ce cas, il est logique que la personne ne puisse être retenue en tant que personnel navigant car elle serait soumise à des barotraumatismes répétitifs et non douloureux et donc à des otites barotraumatiques chroniques.

6. CONCLUSION

Les candidats au personnel navigant sont soumis à des examens très stricts lors de la visite médicale d'admission. En France, un candidat n'ayant pas un tympanogramme normal lors de cette visite est considéré comme inapte. Il s'agit, dans certains cas, d'une perte pour l'employeur car ces personnes ont déjà une qualification professionnelle intéressante.

Une étude a été menée qui a consisté à soumettre à un test au caisson d'altitude les personnes ayant un tympanogramme anormal et ne présentant pas par ailleurs une pathologie clairement identifiée. Ce test semble montrer que les causes de l'anormalité du tympanogramme ne doit pas être mis en relation avec une dysperméabilité tubaire.

Ce travail doit être complété pour que l'expert ORL puisse avoir une attitude moins restrictive lorsqu'il a des personnes ayant un tympanogramme anormal.

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Altitude DCS Research in Support of Special Operations Forces (SOF)

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The potential impact of altitude decompression sickness on special operations missions may manifest primarily in high altitude airdrop operations and operations using unpressurized aircraft such as AC-130 and the CV-22 Osprey. Research at AFRL, Brooks AFB on altitude DCS has for many years produced findings directly applicable to SOF mission scenarios. This paper summarizes 3 areas of research with current applicability. Complete publications are in preparation and the results presented here should be considered preliminary.

1. THE EFFECT OF REPEATED ALTITUDE EXPOSURES ON THE INCIDENCE OF DECOMPRESSION SICKNESS (DCS)

Repeated exposures to reduced pressure are inherent to airdrop training operations, chamber training, and flying operations in unpressurized aircraft. Timely conduct of these activities requires that the personnel not be exposed to significant risk of decompression sickness (DCS) because symptoms may result in interference with or termination of operations. Treatment which could delay further training is also an impediment to effective scheduling and represents significant cost.

During any altitude exposure, the decompression is accomplished from full nitrogen saturation at ground level pressure to a lowered pressure, where gas emboli may be created. The preoxygenation prior to decompression reduces the supersaturation in "fast" tissues, i.e. tissues that take up or eliminated nitrogen rapidly. However, the slower tissues such as bone, ligaments, and tendons do not denitrogenate as quickly during preoxygenation Thus, each repeated altitude decompression eliminates successively more nitrogen, particularly if the breathing gas remains 100% oxygen during any recompression-decompression sequence.

There exists a potential for uptake of nitrogen during an air-breathing, ground-level break between altitude exposures. If the uptake allowed addition of nitrogen to gas emboli formed during the previous decompression, the effect could be one of increased DCS risk due to increased gas emboli size during the next decompression. The elimination of inert gas starts during the decompression and the fast tissues will be eliminated first followed by the slow tissues. The slow tissues may take a very long time to eliminate inert gas. The altitude exposure is, however, followed by recompression to ground level pressure, which may decrease or eliminate the already existing bubbles. If bubbles still exist at ground level, they may expand during a succeeding hypobaric exposure and cause symptoms of DCS.

Knowledge of the threshold for repeated altitude exposure effect on DCS incidence or severity could be helpful in:

- planning for high altitude reconnaissance operations
- manning and scheduling of inside observers for USAF training chamber operations
- scheduling of airdrop pilot training which involves moderate to high altitudes
- scheduling of training and operational multi-sortie gunship missions

Such knowledge may also benefit technology transfer to civilian pilot education and procedural guidelines.

Inconclusive data are available concerning the question of repeated decompression effect on DCS (1, 3, 4, 5, 6, 7, 8, 9). Specific to SOF, Butler in 1991 (2) described a case of DCS presented as optic neuropathy, which he believed could be attributed to repeated parachuting decompressions. Operationally, it is assumed that there is a detrimental effect of repeated altitude decompressions on DCS risk and, therefore, various ground interval requirements between flights have been imposed. The origin of this

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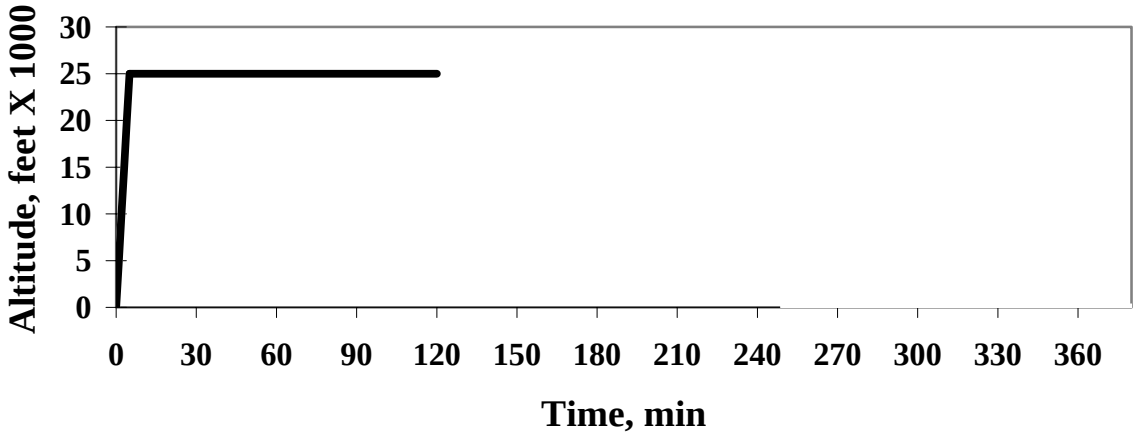
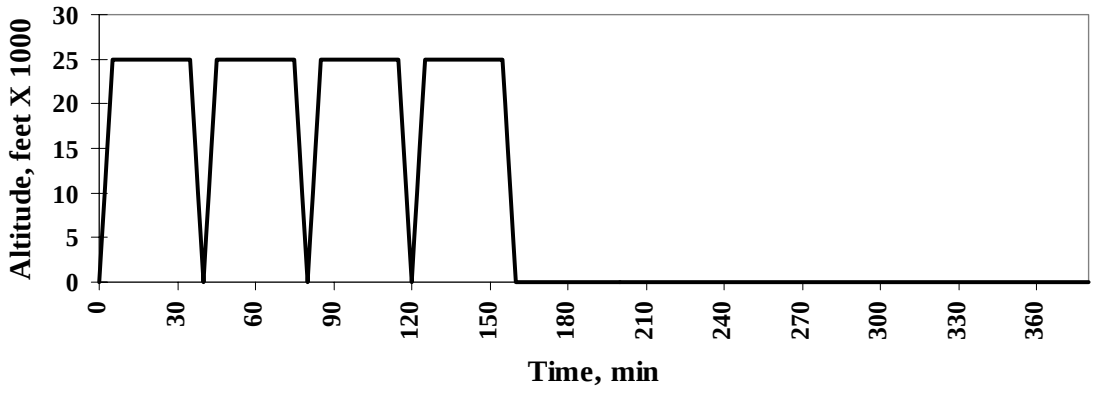
assumption has been the observation that many of the DCS cases occur late in the day. A typical day might include 5+ parachute jumps.

Thirty-two research subjects were exposed to the 3 profiles pictured in Figure 1. Condition A consisted of one, 2-hr exposure to pressure corresponding to an altitude of 25,000 ft, with no preoxygenation. Condition B consisted of four, 30-min exposures to the same simulated altitude, and with zero time at ground level in between and no preoxygenation. Condition C consisted of four, 30-min exposures to the same simulated altitude, but with 1-hr ground level interval breathing air. At altitude, the subjects performed four sets of mild exercises each hour. They consisted of turning a crank by hand for 4 min, operating a wrench each 5-10 s for 4 min, and pulling a rope with alternating hands with a resistance of 7.7 kg (17 lbs.) for 4 min. Precordial echo-imaging/Doppler monitoring was accomplished with an HP SONOS 1000 Echo-Imaging System after each exercise sequence to provide information on development of venous gas emboli (VGE).

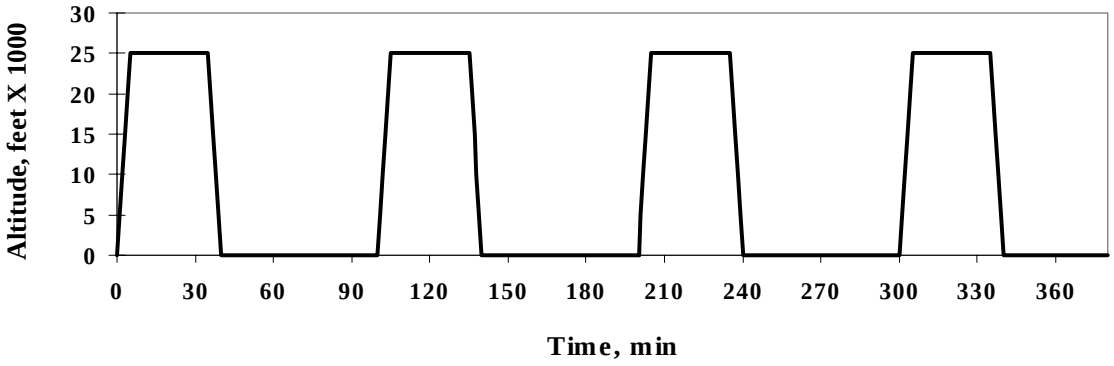
Figure 1. Exposure profiles



A. One, 2-hour exposure, zero-preoxygenation



B. Four, 30-min exposures, zero time at ground level, zero-preoxygenation



C. Four, 30-min exposures, 1-hour ground level interval on air, zero preoxygenation

The results are presented in Table I and Figures 2 and 3. In condition A, with 2 hr continuous hypobaric exposure at 25, 000 ft, 59% DCS occurred. In conditions B (four, 30-min altitude exposures with no ground time in between) and C (four, 30-min altitude exposures, but with a 1-hr ground level interval breathing air) 22% and 6% DCS occurred respectively. Both conditions were significantly different from condition A ($p<0.05$). The mean onset time for DCS was longer for condition A than for both conditions B and C.

Exposure	DCS Incidence %	DCS Onset) (min)	VGE Incidence %	VGE Onset (min)
A (control)	**19 cases (59%)**	**70 ± 7**	**28 cases (88%)**	**32 ± 5**
B	**7 cases (22%)***	**54 ± 10**	**21 cases (66%)**	**40 ± 8**
C	**2 cases (6%)***	**40 ± 13**	**21 cases (66%)**	**43 ± 8**

TABLE I. Incidence of DCS and VGE and onset time of DCS and VGE are given for the three conditions A, B and C.

VGE occurred in 88% in condition A, but only in 66% for both of the conditions B and C (B and C were significantly different from A, $p<0.05$) The mean onset time of VGE was not significantly different the three conditions. Condition A resulted in 4 cases of serious respiratory/ neurological symptoms, while condition B only had one and condition C had none. All other cases involved pain, paresthesia, and/or skin symptoms. All symptoms resolved during recompression to ground level.

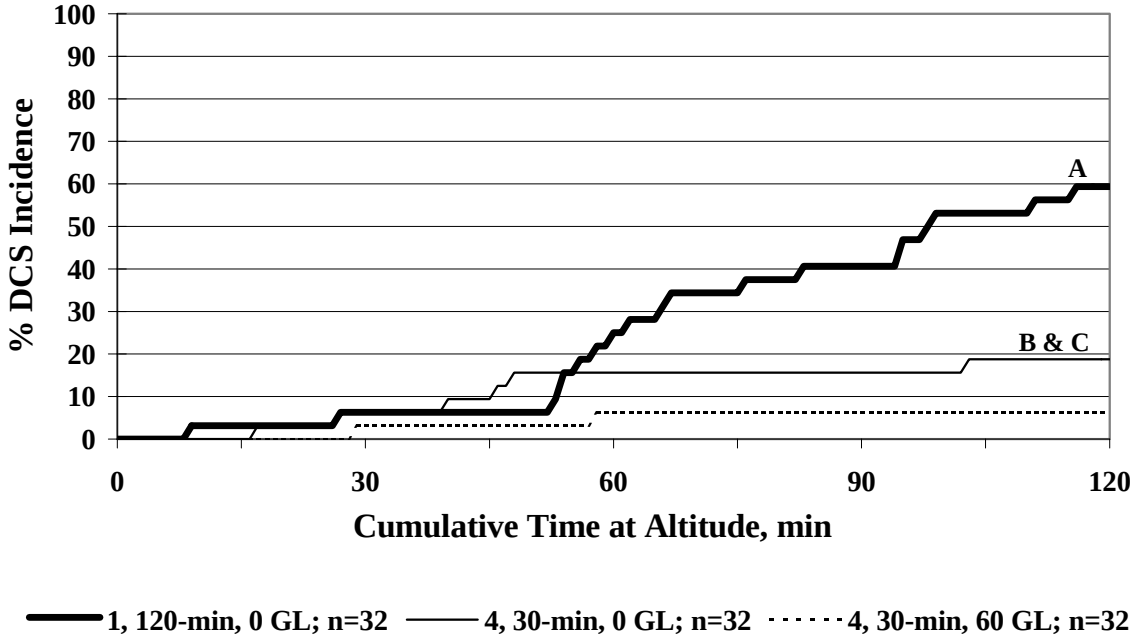


Figure 2. The percentage of cumulative DCS incidence plotted versus cumulative time at altitude for the three conditions A, B and C .

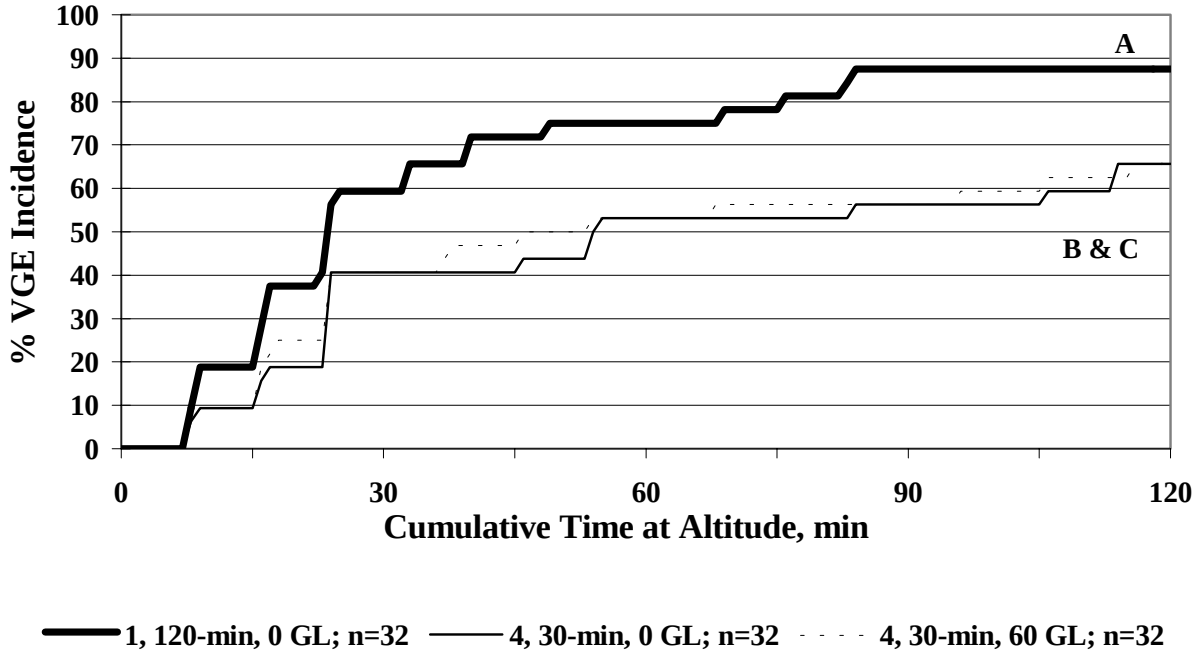


Figure 3. The percentage of cumulative VGE incidence plotted versus cumulative time at altitude in the conditions A, B and C.

This study indicates a decreased risk of DCS with multiple short flights both without ground level intervals and with 1 hour air-breathing intervals, than with a single continuous flight of equal time duration.

2. POST-LANDING EXERCISE AND RISK OF DCS IN HIGH ALTITUDE PARACHUTE

Special Operations Forces employment of high altitude airdrop in the execution of the insertion phase of their missions involves altitude exposures that pose a risk of developing decompression sickness (DCS) symptoms. Moderate to heavy exercise performed immediately after landing may further increase the incidence and severity of DCS and could become a serious factor in mission success or failure. The mission impact of DCS symptoms developed after landing is unknown. SOF teams should not be faced with a situation where a **preventable** decrement in performance affects the accomplishment of the mission or survival of the team. The mental and physical fitness required for these missions is very high and any decrement in performance due to pain or other DCS symptoms needs to be quantified and recommendations offered for protection from DCS symptom development. Since reviews of DCS research are silent about post-exposure exercise effects on DCS incidence and severity (10,12), no scientific basis exists for determining the effect of such activity. However, AFI 11-403 (7.2.1; 1 Dec 96) and AFP 160-5 (16-3; 23 Jan 76) contain post-flight restrictions for personnel who take part in chamber flights: "No physical exercise, strenuous or extended duty for a period of 12 hours." Such a restriction is not compatible with SOF missions involving high altitude exposures.

In this on-going study, 120 subjects are scheduled to complete one exposure each. The target population (SOF) is highly fit (top 5% of general population's aerobic capacity) and matching that subset with an identically-fit subset of subjects is impractical due to availability of such subjects. However, subjects were able to pass the USAF fitness test, which placed them in the top 50% of the general population's aerobic capacity. The subjects completed a maximal exercise test to establish the level of post-exposure exercise to be accomplished.

The exposure/testing scheme (Figure 4) involves exposures predicted to result in approximately 50% decompression sickness (DCS) followed by post-exposure rest or exercise (Test). The reason for using an altitude exposure which is predicted to yield 50% DCS was to yield a wide range of reactions which provided a diverse set or reactors subjected to the next stressor, post-exposure exercise. As the subjects reached ground-level pressure, they were randomly selected to perform rest or exercise. The control, resting post-exposure activity consisted of 2 hours of seated rest. Half of the subjects served as controls, resting post-exposure activity, and half performed strenuous dual-cycle ergometry simulating post-landing activity during the same period of time. One resting control and one exercising test accomplished after identical altitude exposure conditions and DCS results become a matched test for statistical purposes. The post-exposure exercise was accomplished in three sets of approximately 15 minutes each at approximately 50% of $\mathbf{V}O_{2peak}$ over a period of 2 hours after the altitude exposure.

Figure 4. Exposure/Testing Scheme

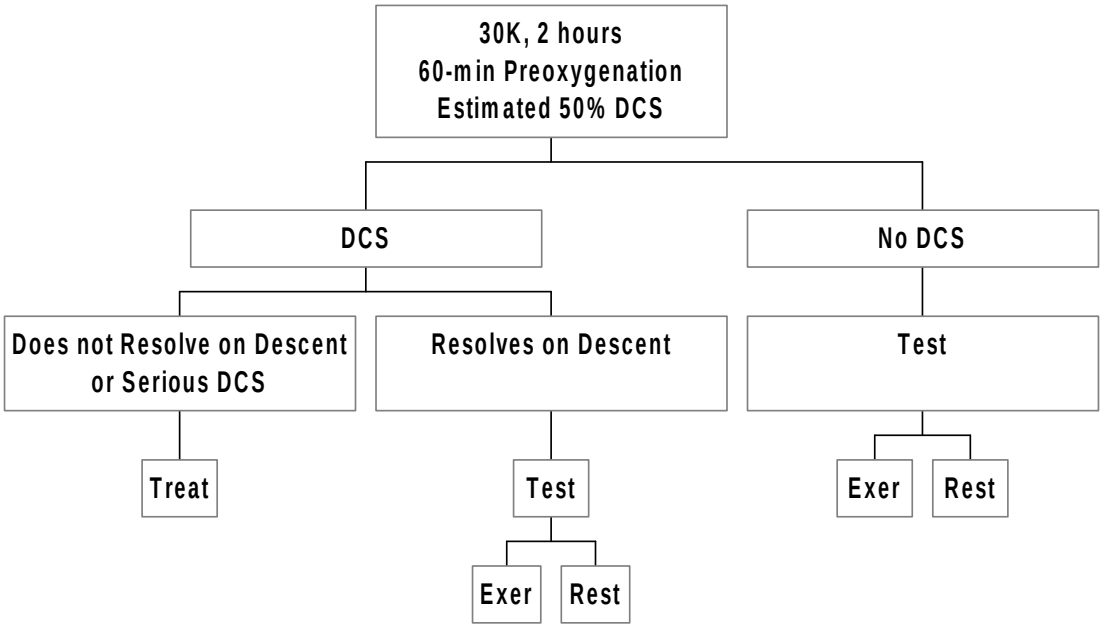
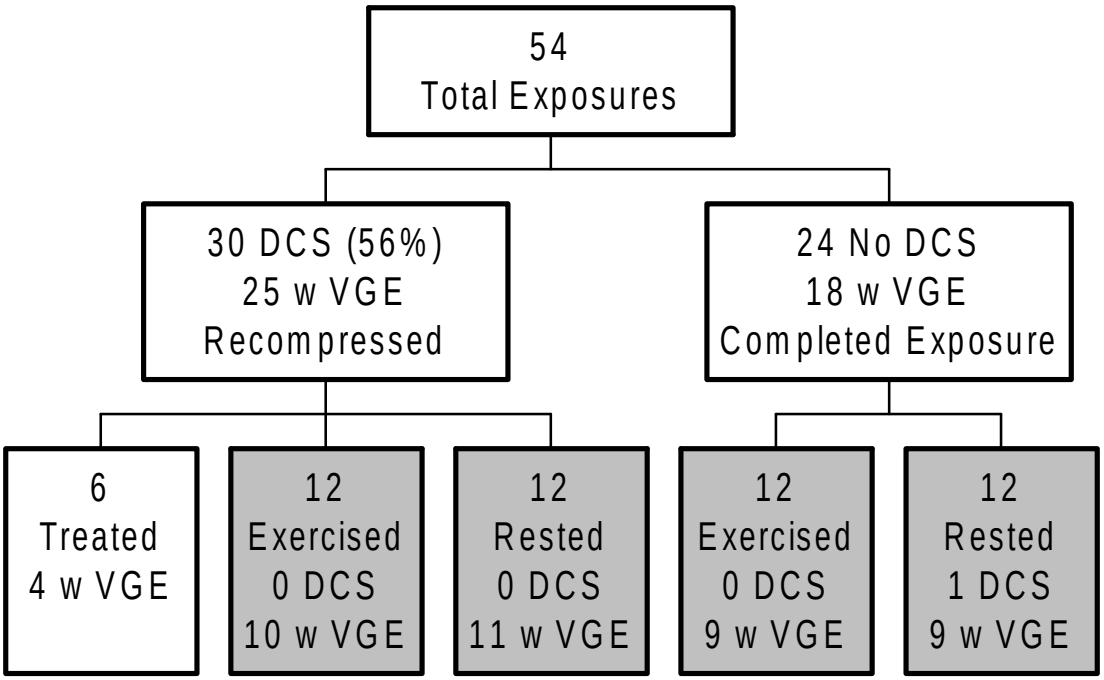


Figure 5. Preliminary results



It is too early in the study to draw conclusions since less than half of the exposures have been completed. However, the preliminary results in Figure 5 are of great interest to SOF. Post-flight exercise has resulted in NO DCS symptoms. The control (resting) has resulted in one case of post-flight DCS.

3. THE EFFECT OF EXPOSURE TO 35,000 AND 40,000 FT ON THE INCIDENCE OF ALTITUDE DECOMPRESSION SICKNESS

The potential for development of altitude DCS during high altitude airdrop missions conducted by the USAF has been largely avoided by restricting time of exposure and requiring preoxygenation. For example, airdrop from 35,000 ft requires 75 min of preoxygenation and exposure time limited to 30 min. An airdrop is dependent on many factors; e.g. weather, aircraft and personal equipment, and mission timing. Variation in these and other factors could delay the airdrop following decompression of the aircraft and extend the duration of exposure. It would benefit the airdrop community to know the change in DCS risk caused by extending the exposure time beyond 30 min.

One of the variables in determining DCS risk is the activity level of individuals involved in the mission; e.g. aircrew in the cockpit, loadmasters coordinating the airdrop, and the jumpers. Level of exercise is of considerable importance in determining DCS risk (14,15). Ferris et al. (11) found that seated rest at 35,000 ft without preoxygenation was as effective at preventing DCS as 2 h of preoxygenation prior to an exercising exposure to 35,000 ft. A 4-h preoxygenation provided protection for 10 of 12 subjects exposed to 35,000 ft while exercising. In another test with 7 exercising subjects at 35,000 ft, eight h of preoxygenation provided complete protection from DCS (11). Fulton (12) reviewed the effects of rest versus exercise (five deep knee bends every 3 min) during zero-prebreathe exposures to 35,000 ft and showed 55% DCS incidence in 90 resting subjects and 100% DCS in 158 exercising subjects. The mean time to DCS in that study was 61 min while at rest and 16 min while exercising. With four h of prebreathe, the incidence of DCS was reduced to 55% in the exercising group.

The current study provided information on risk and effect of exercise using the current criteria for declaration of DCS symptom existence. Data on venous gas emboli (VGE) were unavailable during the WWII studies because the equipment for non-invasive measurement of VGE was not developed until the 1970s. During the current study, the data on VGE were collected to determine relative exposure severity in

addition to observed or reported DCS symptoms. The information provided by this study could be used to verify or recommend changes to existing Air Force policy.

Prior to each 3-h altitude exposure, a physician conducted a short physical examination of subjects to identify any signs of illness or other problem that would endanger the subject or bias the experimental results. Chamber ascent and descent were at a rate not exceeding 5,000 fpm from ground level pressure to 20,000 ft and at a rate not exceeding 10,000 fpm from 20,000 ft to 35,000 ft.

At 10-15 min intervals, the subjects were monitored for VGE using a Hewlett Packard Sonos 1000 Doppler/Echo-Imaging System. This system permits both audio and visual monitoring and recording of gas emboli in all four chambers of the heart.

Subjects were either seated at rest for the entire exposure or performed strenuous or mild exercise at intervals throughout the exposure. The strenuous exercise consisted of cycle ergometery at 60 rpm for 3 of every 10 min with a resistance of 2kp. Walking to the Monarch 818E ergometer and echo-imaging station between periods of seated rest involved less than ten steps in any direction. Mild exercise consisted of three upper-body exercises. Thirty male and thirty female subjects performed strenuous exercise during one exposure and remained seated at rest for a second exposure, allowing matched controls for the effect of strenuous exercise. Thirty-two different subjects were used for the exposures involving mild exercise.

The DCS incidence with strenuous exercise was not significantly different (Chi Square = 0.54; P = 0.47) than that with mild exercise (Fig. 6). DCS symptoms occur more rapidly with mild or strenuous exercise compared with symptom onset during rest ($P < 0.0001$; Fig. 6). The same statistical result was found with comparisons of incidence and onset time of VGE.

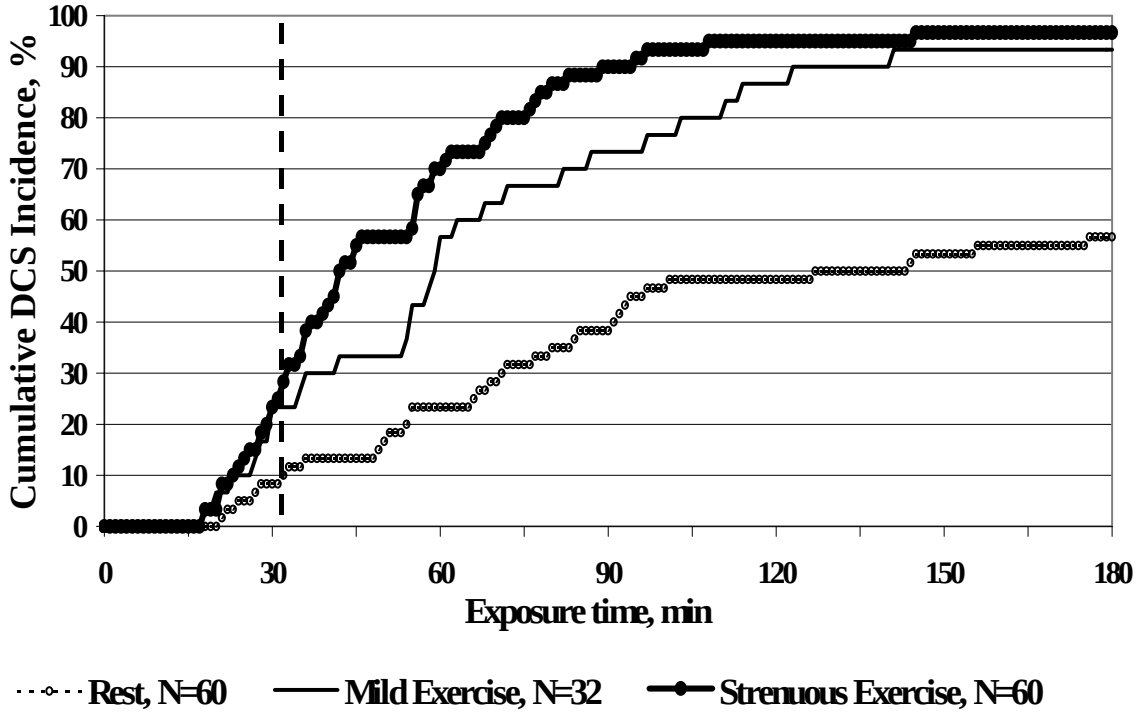


Figure 6. Cumulative DCS vs. exposure time to 35,000 ft

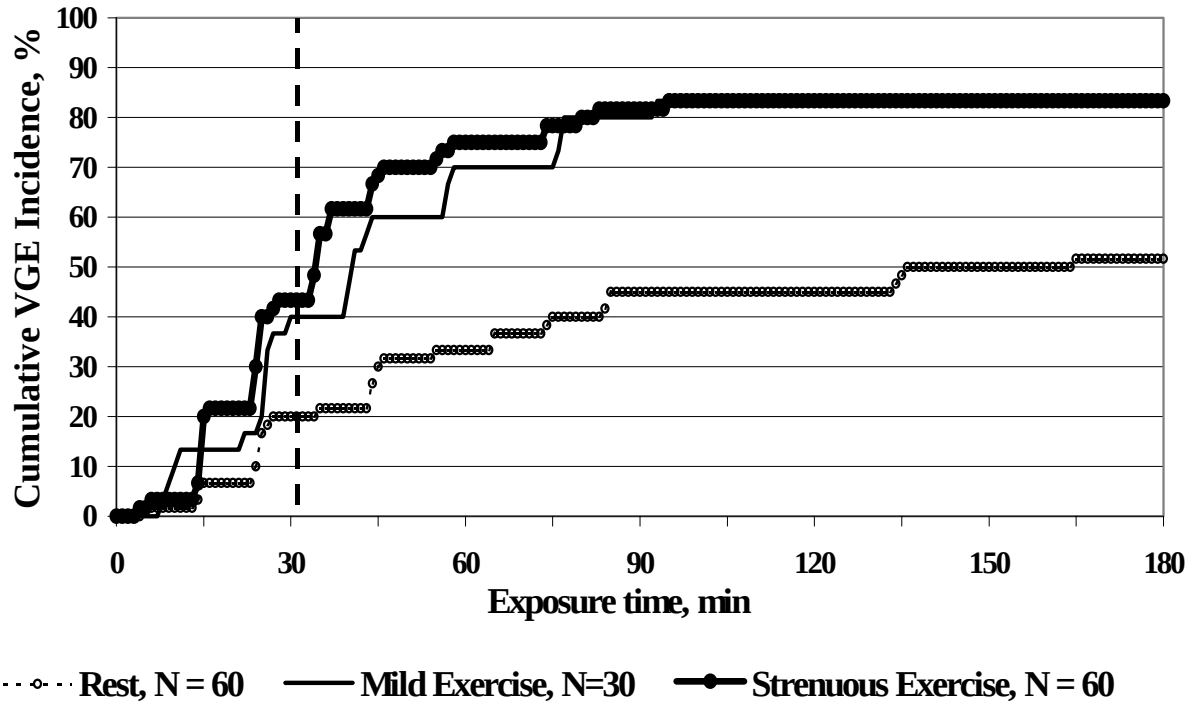


Figure 7. Cumulative VGE vs. exposure time to 35,000 ft

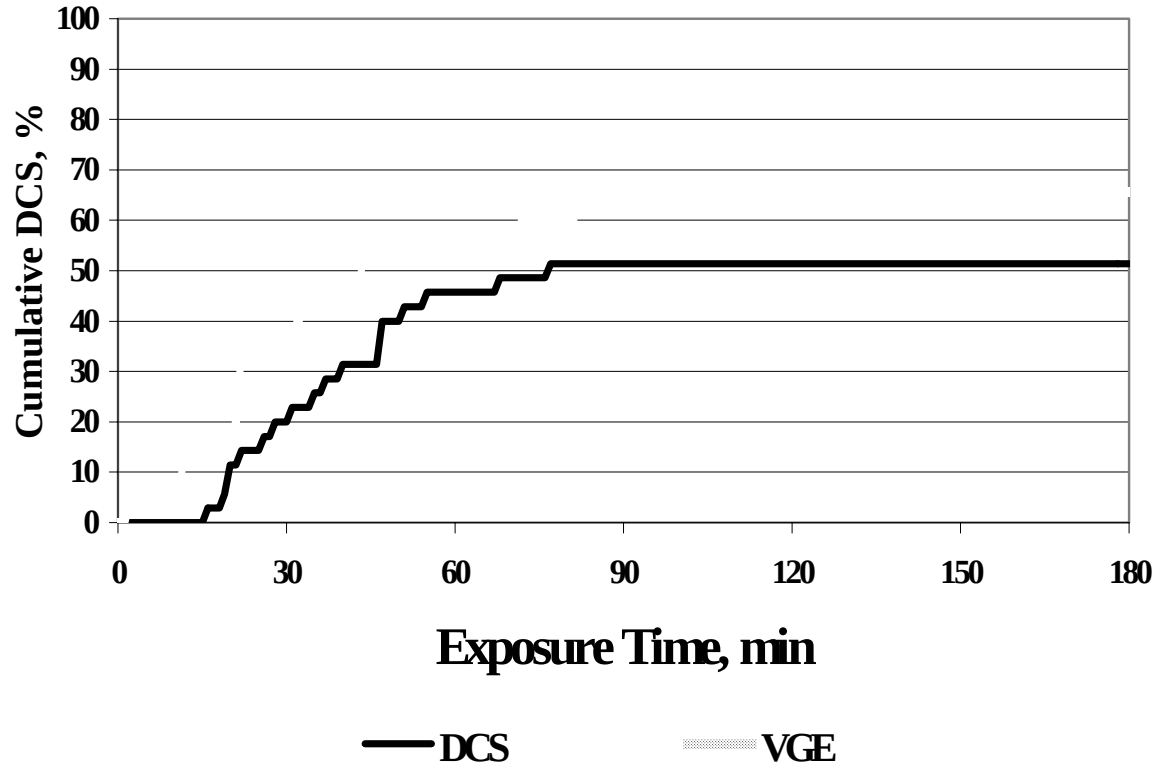


Figure 8. Cumulative DCS vs. exposure time to 40,000 ft

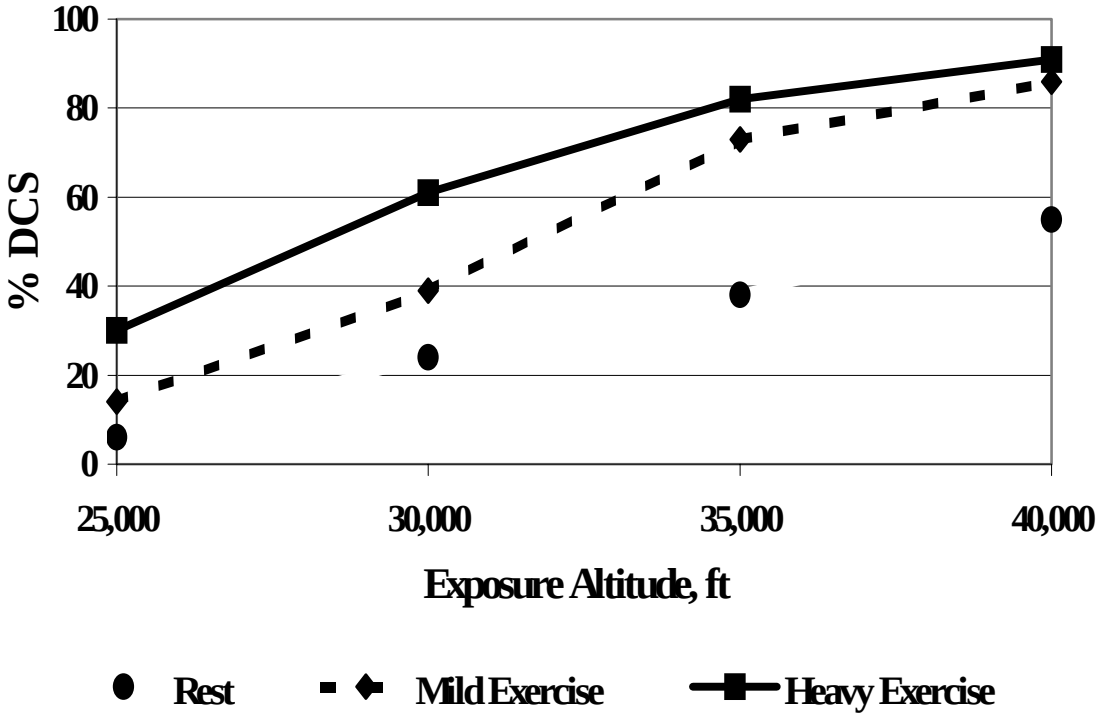


Figure 9. DCS vs. exposure altitude for rest, mild and strenuous exercise at altitude.

With 75 min of preoxygenation, a 3-h resting exposure to 35,000 ft produces a relatively high incidence of DCS (57%). Performance of mild exercise results in 94% DCS (Fig. 6) and strenuous exercise results in 97% DCS. No difference was observed in the shape of the incidence versus exposure time curves between mild and
strenuous exercise.

Although the onset of DCS is more rapid at 35,000 ft than at lower altitudes with similar preoxygenation, the incidence of severe DCS symptoms was very low during these studies. The results of exposures to 35,000 ft during WWII, during which severe symptoms were commonplace, were probably influenced by both shorter (or nonexistent) preoxygenation and termination criteria which allowed more severe symptom development prior to recompression (11, 17, 19). Severity of symptoms during the current studies was kept low due to rapid recompression at symptom onset which probably reduced progressive symptom development.

These findings reinforce the current Air Force policy regarding exposure to 35,000 ft. The current 30-min limit on exposures to 35,000 ft following 75 min of preoxygenation has been shown to keep symptoms relatively low, especially if no exercise is performed (10%). This information emphasizes the need to avoid exercise while decompressed. The consequence of exceeding 30 min of exposure, especially if exercising, is a rapid increase in DCS incidence.

Figure 8 shows preliminary data for 3 hour resting exposures to 40,000 ft with 90 min of preoxygenation. The DCS onset curve is slightly steeper than at 35,000 ft., otherwise, the results appear to be similar to those at 35,000 ft. Finally, in Figure 9 the relationship between DCS incidence and increasing altitude appears to be almost linear. At the higher altitudes there is no difference between mild and strenuous exercise, while at lower altitudes the difference is apparent. The numbers for this figure were generated by the ADRAC model which is based on validated human trials (ADRAC was described in an earlier paper at this meeting).

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Modeling Approach for Oxygen Exchange in the Human Lung under Hypobaric Conditions

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1. Introduction.

Physical effort at high altitude can result in serious complications in the human respiratory system even for healthy and well-trained persons. For people with a pulmonary disorder, already a stay at moderate altitude, or transportation by air (e.g. in case of medical evacuation) can lead to significant problems caused by hypoxemia.

In both circumstances the oxygen tension of the inspired air (PI,O_2) and therefore of the arterial blood (Pa,O_2) drops substantially. For healthy people - if at rest - this causes no considerable problems because their arterial oxygen saturation at such altitudes still will be at the horizontal part of the oxyhaemoglobin dissociation curve.

Problem area

Patients with COPD and interstitial lung diseases have mild to severe obstructive and/or restrictive impairment of the lung function. So they may deal with unequal ventilation, ventilation-perfusion mismatch, diffusion disorders, ventilatory restriction, and changes in arterial blood gas tensions. In this kind of lung diseases there is a diminished reserve of gas exchanging surface because of degeneration of alveoli and/or fibrosis of the lungs.

For the individual patient with COPD or interstitial lung diseases the Pa,O_2 at altitude can not be predicted from the sea level value (Ref. 1). Even with normal blood gas tensions at sea level severe drop in oxygen saturation may occur at altitude. Predicting factors seem to be a FEV1 (forced expiratory volume 1st second) < 30 % VC (vital capacity) and/or a significant decrease of the Pa,O_2 with comparatively low exercise. Other empirical formulas to predict Pa,O_2 at altitude from sea level conditions have been derived by Gong (Ref. 2) and Dillard (Ref. 3). These statistical formulas indicate more or less average responses but are not suitable for the predictions for the individual patient.

HAST (high altitude simulation test) may provide more clearness in the individual for the extent of the gas exchanging surface. An important difference of this test with regard to reality is the constant barometric pressure and the comparatively limited duration (30 min). Besides, this test is not without any risk for the patient (hypoxemia induced arrhythmias).

Approach

In this paper we explore the modeling of the human lung gas-exchange under hypobaric conditions. At first the concept of the ventilation-perfusion mismatch is applied to model the pulmonary performance of a healthy person at rest at increasing altitudes. Model results are compared with experimental data from literature at varying altitude. The model is also used for a patient with COPD at moderate altitude. The results illustrate the limited applicability of the mismatch model. Inclusion of diffusion effects improves the results. Only a preliminary validation of the model has been attempted yet. The focus is predominantly on understanding and modeling of possible underlying physics.

2. The ventilation-perfusion mismatch model.

Compartments

The algorithm for the exchange of O_2 and CO_2 is based on the subdivision of the human lung into a number of compartments. Several units, consisting of alveoli and the network of capillaries, are lumped together in each compartment. One assumes that the conditions for all units in one compartment are the same. The ventilation-perfusion ratio v’/q’ for a compartment dictates the transfer of O_2 and CO_2 as a function of their mixed venous values PV,O_2, PV,CO_2 and the oxygen inspired presure PI,O_2. Two examples for a range of values of v’/q’ are shown in figure 1. Curve A shows the variation of end-capillary values of partial oxygen pressure Pec,O_2 versus Pec,CO_2 for sea level atmospheric conditions, curve B for hypobaric conditions. Each point on a curve represents a compartment with a certain ventilation-perfusion ratio.

The basis for the construction of these curves is that complete equilibration of O_2 and CO_2 has taken place between the capillary blood flow and the alveoli. For CO_2 this is not an issue because its transfer through the alveolar membrane takes place very rapidly. However for O_2 this is only true if: a) the blood barrier resistance of the membrane

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is not too high, b) the contact time of the capillary flow with the alveolar tissue, is not too small, and c) the initial PO_2 difference over the membrane is not small as might occur in hypobaric conditions. We will discuss items b) and c) later on.

The method of Rahn and Riley & Cournand described by Farhi (Ref. 4) is used to find the points of figure 1. The equations are given for completeness:

$$v'_n O_2 = v'_n * (PI, O_2 - PA, O_2) * \frac{1}{k} \equiv q'_n O_2 = q'_n * (cec, O_2 - cV, O_2) \qquad \text{n =1 ….N} \qquad (1)$$

It states that for each compartment n the amount of loss of O_2 in the gaseous state, v'_nO_2, equals the transfer of O_2 to the capillaries, q'_nO_2. The concentration in the blood at the end of the capillary is indicated by cec,O_2, at the venous point cV,O_2 ; k is a conversion factor, v'_n and q'_n are the ventilation and perfusion of compartment n.
The uptake of CO_2 into the alveolar gas from the blood is expressed as:

$$v'_n CO_2 = v'_n * PA, CO_2 * \frac{1}{k} \equiv q'_n CO_2 = q'_n * (cec, CO_2 - cV, CO_2) \qquad (2)$$

The equations for the concentrations cO_2 and cCO_2 are taken from West and Wagner (Ref. 5). They are both non-linear functions of Hb, hematocrit, PO_2, PCO_2 and body temperature. By the assumption of fully equilibration the end-capillary values for PO_2 and PCO_2 are equal to their corresponding alveolar values:

$$\begin{aligned} P_n A, O_2 &= P_n ec, O_2 \\ P_n A, CO_2 &= P_n ec, CO_2 \end{aligned} \qquad (3)$$

Ventilation-perfusion distributions

In analogy to the model of West and Wagner we assume a discrete lognormal distribution of ventilation and perfusion over the compartments:

$$v'_n = \frac{V'A \cdot \Delta\xi}{\sigma\sqrt{2\pi}} * \exp\left[-\tfrac{1}{2} \cdot \left(\frac{\xi_n - \mu_v}{\sigma} \right)^2 \right] \qquad (4)$$

$$q'_n = \frac{Q' \cdot \Delta\xi}{\sigma\sqrt{2\pi}} * \exp\left[-\tfrac{1}{2} \cdot \left(\frac{\xi_n - \mu_q}{\sigma} \right)^2 \right] \qquad (5)$$

.

V'A and Q' are the total alveolar ventilation and pulmonary perfusion. In figure 2 an example is shown. The v'_n and the q'_n are plotted versus their logarithmic ratio $\xi_n = \log (v'_n / q'_n)$. The discrete compartments are centered at ξ_n. All compartments are equidistant in ξ and have equal widths $\Delta\xi$. The parameter σ functions in these formulae in two ways. In both the single distributions for v'_n and q'_n it is a measure of the deviation from the means μ_v and μ_q. Its square σ^2 also separates both peaks. From (4) and (5) it follows:

$$\begin{aligned} \mu_v &= \log\left(\tfrac{V'A}{Q'}\right) + \tfrac{1}{2} \cdot \sigma^2 \\ \mu_q &= \log\left(\tfrac{V'A}{Q'}\right) - \tfrac{1}{2} \cdot \sigma^2 \end{aligned} \qquad (6)$$

We will use σ as the parameter representing the ventilation-perfusion mismatch. For a healthy young person the mismatch σ is small Then both peaks for ventilation and perfusion lie close together and the width σ of their bell shaped distributions is also small. We assume in case of COPD that the lung degradation can be expressed in an increase of σ. An example of a pure variation in mismatch is shown in figure 3. The growth of σ will lead to a steady decrease of Pa,O_2 and, to a lesser degree, to a steady increase of Pa,CO_2. The responses of the pulmonary ventilation to an increase of Pa,CO_2 or a decrease of Pa,O_2 are not taken into account yet. The metabolic indices $V'O_2$ and $V'CO_2$ are kept constant. Therefore the values of alveolar partial pressures of O_2 and CO_2, averaged over all compartments, are constant as well. By the assumption of fully equilibration one can refrain from the inclusion of alveolar membrane properties and from the effect of reaction speed of the O_2 molecules with Hb.

Circulation

We use two extra equations due to Fick's principle. They describe the consumption of O_2 and the production of CO_2 at the systemic side of the circulation:

$$\begin{aligned} V'O_2 &= CO \cdot (ca, O_2 - cV, O_2) \\ V'CO_2 &= CO \cdot (cV, CO_2 - ca, CO_2) \end{aligned} \qquad (7)$$

The first equation states that the total O_2 consumption equals the arterial and mixed venous concentration difference times the cardiac output CO. The second equation expresses the equivalent for CO_2 production. By the summation of equations (1) and (2) over all compartments including the right-to-left shunt, the same quantities have to found for the O_2 and CO_2 transfer in the total lung.

Baseline conditions

To estimate the mismatch parameter σ for a person, our point of departure is the knowledge of (measured) arterial partial gas pressures Pa,O_2 and Pa,CO_2. The cardiac output CO under resting conditions is estimated from the body surface area BSA. Also the pulmonary shunt fraction psh has to be measured or estimated. The metabolic rates $V'O_2$ and $V'CO_2$ are usually measured as a part of exercise testing. For the perfusion distribution to be fully known only σ has to be determined. The ventilation distribution requires also σ but in addition the total alveolar ventilation V'A. V'A will be determined simultaneously with σ. The non-linear system of equations (1) to (7) is solved by Broydn's procedure (Ref. 6) for chosen values of the interval Δξ and the total number of compartments N. The Broydn procedure is a fast and robust method that finds the roots in analogy with the secant method working in two dimensions. Hence it does not require the elaborate evaluation of a Jacobian matrix. The matching procedure delivers the four quantities: mismatch parameter σ, alveolar ventilation V'A and the mixed venous partial pressures PV,O_2 and PV,CO_2.

To display the interactions of the solution process consider figure 4. It shows Pa,O_2 and Pa,CO_2 as functions of σ and alveolar ventilation V'A. The mixed venous partial pressures are not visualised. According to physical feeling Pa,CO_2 is a decreasing dominant function of V'A and it is a weakly increasing function of σ. Pa,O_2 depends equally on both variables. In general it increases with V'A and it decreases with σ. For a measured pair of arterial partial pressures of O_2 and CO_2 the corresponding values of V'A and σ can be found by the Broydn procedure. From a first guess of V'A and σ with probably incorrect corresponding values of Pa,O_2 and Pa,CO_2 a trajectory in the V'A-σ plane is traversed that tends to approach the measured values of Pa,O_2 and Pa,CO_2.

Hypobaric conditions

In our model no explicit reference is made to the atmospheric pressure, hence we study the consequences of hypobaric conditions by changing the O_2 fraction FI,O_2 of the inspiratory gas. As a starting point we assume that the mismatch parameter σ and cardiac output and the right-left shunt are kept the same and hence the perfusion distribution is kept the same. However the ventilation is allowed to increase as a response to hypoxia:

$$V'E = V'^{b}E - G_{Sa} * (S^{b}a,O_2 - Sa,O_2)^{p} \tag{8}$$

Where V'E is the pulmonary minute ventilation, superscript b indicates quantities measured or calculated under basic (i.e. sea level atmospheric and resting) conditions. G_{Sa} is the sensitivity (a negative number) of the minute ventilation to arterial oxygen saturation. For an exponent p = 1 G_{sa} is in the range of -1.55 ±0.98 (Ref. 7). A hypocapnic effect on G_{Sa} is not taken explicitly into account. The real response to hypoxic conditions depends also on the speed by which hypoxic conditions are imposed and on the additional control of alveolar PA,CO_2. (Ref. 8).
From the minute ventilation the alveolar ventilation can be found by:

$$V'A = V'E - f(V'E) * VD \tag{9}$$

The breathing frequency f is a weak function of V'E itself; VD is the physiological dead space. The system of equations (1) to (9) can be solved for the venous and arterial blood gasses using Broydn's procedure. The mismatch σ is kept fixed now, but the ventilation V'A is allowed to adapt itself to hypoxic conditions according to (8) and (9).

3. Application of the model.

Healthy person

At first the mismatch model is applied to a healthy subject starting at sea level and decreasing its FI,O_2 to an equivalent altitude of 9 km (Figure 5). From the barometric pressure for standard atmosphere the PI,O_2 is found and used as an input of the model. A low value of mismatch σ is assumed that is kept fixed. The pulmonary ventilation was allowed to respond to hypoxia according to (8) with an exponent ½. This weak response is a result of hypoxia, damped by the decreased PA,CO_2. The results for arterial pressures are quite comparable with actual measurements of a simulated ascent of the Everest (Ref. 9). In the measured realistic conditions the alveolar-arterial PO_2 difference increases with altitude. At 9 km this amounts to a $P(A\text{-}a),O_2$ = 6 mmHg. This might be attributed to the lack of complete equilibration. The results of the present model show a steady decrease of the alveolar-arterial difference, practically approaching zero for the higher altitudes. This is due to the pattern of the O_2 dissociation curve. At low O_2 saturation the same shunt gives a smaller effect on Pa,O_2 versus PA,O_2.

Patient with COPD

So far things seem to compare reasonably well. However application of the present method to the data of a COPD patient, put forward by the St. Antonius Hospital, showed results deviating from the measured data (Fig. 6). It seems that the ventilation-perfusion mismatch is not the only source attributing to the failure of this subject to cope with the lowered P_{I,O_2}. One of the possibilities is discussed below.

Diffusion limitations

Many patients suffering severe COPD have lost a great deal of their oxygen transfer capabilities. Under normal resting conditions this does not necessarily lead to hypoxemia. But in exercise and under hypobaric conditions this can be a cause of hypoxemia. The transfer properties of the lung are evaluated clinically by measuring a.o. $T_{L,CO}$ that is defined as:

$$TL,CO = \frac{V'CO}{PA,CO} \tag{10}$$

Which measures the uptake of carbon monoxide, CO. See e.g reference 10 for a careful analysis of $T_{L,CO}$ measurements. CO has such a large affinity for Hb that its capillary pressure can be assumed zero and $P_{A,CO}$ can be considered as the driving pressure. Therefore $T_{L,CO}$ characterizes the properties of the blood gas barrier. It is proportional to the membrane surface area and the solubility of CO and is inversely proportional to membrane thickness and the square root of the molecular weight of CO. A reduction of membrane area by COPD will lead to a proportional reduction in transit time of the blood in the capillary bed if the same cardiac output has to be maintained. All other membrane properties are assumed the same. A decrease of transit time *tc* is no problem if the oxygen equilibration time *te* remains sufficient small. However for lower values of $P_{A,O2}$ this is not possible. In figure 7 three examples are shown of alveolar capillary PO_2 differences during the passage of blood along alveolar tissue. The curves are obtained from approximations of the diffusing equation for oxygen:

$$\frac{dcO_2}{dt} = g * D_{O2} * (PA,O_2 - Pc,O_2) \tag{11}$$

In which t is the time coordinate for a blood parcel moving along a capillary. g is a geometrical shape parameter and DO_2 is the O_2 membrane permeability factor. The O_2 concentration cO_2 in the capillary vascular system depends on the local gas pressures P_{c,CO_2} and P_{c,O_2}. All parameters are taken for healthy non-degraded tissue. Normal value for the contact time is *tc* = 0.76 sec (Ref. 11). Equilibration time *te* is small for a large alveolar-venous oxygen pressure difference and a P_{A,O_2} on the horizontal part of the O_2 dissociation function (upper curve). *te* increases strongly with decreasing alveolar oxygen pressures (curves P_{A,O_2}=90, 60). For a fixed *tc* < *te*, the alveolar-end-capillary difference $P_{(A\text{-}ec),O_2}$ is small for high P_{A,O_2} because *te* is small. $P_{(A\text{-}ec),O_2}$ increases for intermediate values (e.g. P_{A,O_2} = 90) because *te* is increasing. However $P_{(A\text{-}ec),O_2}$ decreases again for smaller P_{A,O_2}, because the alveolar-venous difference is decreasing. But it will not vanish. For lower P_{A,O_2} there is always a condition where no equilibration can occur because *te* will be much larger than any *tc*.

In our system of equations the first of equation (3) is replaced by:

$$P_n ec,O_2(tc) = P_n A,O_2 - P_n(A-ec),O_2\left[g, D_{O2}; tc\right] \qquad \text{n =1 …. N} \tag{12}$$

Where the last term follows from an approximate solution of (11) for each compartment and for the yet unknown initial condition P_{V,O_2} and the compartment dependent P_{A,O_2}. Broydn's procedure again is applied but now with N additional non-linear equations (12).

Patient with COPD and diffusion limitations

Baseline results for F_{I,O_2} =0.21 of our COPD patient are shown in figure 8A. It displays alveolar and end-capillary values of PO_2 versus the ventilation-perfusion ratio. From $T_{L,CO}$ data it is inferred that the average contact time was reduced to about *tc*=0.38 sec. For alveolar P_{A,O_2} = 120 mmHg and higher the equilibration takes place before the end of the capillary is reached. For lower alveolar values this is not the case and alveolar-end-capillary differences are shown. This has however not a strong detrimental influence because the ventilation as well as the perfusion are smaller in that region. Figure 8B shows the distributions for F_{I,O_2} = 0.15. Over the whole range of ventilation-perfusion ratios a substantial alveolar-end-capillary difference occurs in PO_2. The smaller differences now appear at the lower side of the P_{A,O_2} because here the smaller alveolar-venous difference starts to reduce the alveolar-end-capillary differences. Figure 9 depicts the course of the blood gas values starting from normal F_{I,O_2} = 0.21 to gradual lower F_{I,O_2}. A reasonable match with HAST measurements is obtained.

4. Concluding remarks.

At hand of a healthy person and one with COPD the application of the ventilation-perfusion mismatch model of the human lung has been investigated. The model can not predict the pulmonary performance at moderate altitude for a COPD patient. It is likely from diffusion data that the reduced contact time of the blood flow in the alveolar bed

may cause the remaining discrepancies. To include such possible effects, the model has been extended with a capillary O_2 equation that accounts for alveolar-end-capillary PO_2 differences. A better match with the Pa,O_2 drop observed in HAST data appears to justify these model extensions. The validation of the improved model requires however the application to a greater number of subjects. This will be pursued in future work. A satisfactory prediction of oxygen saturation at altitude has to take into account more person specific characteristics. Hence the extension of the model might not be limited to ventilation-perfusion mismatch and diffusion effects alone.

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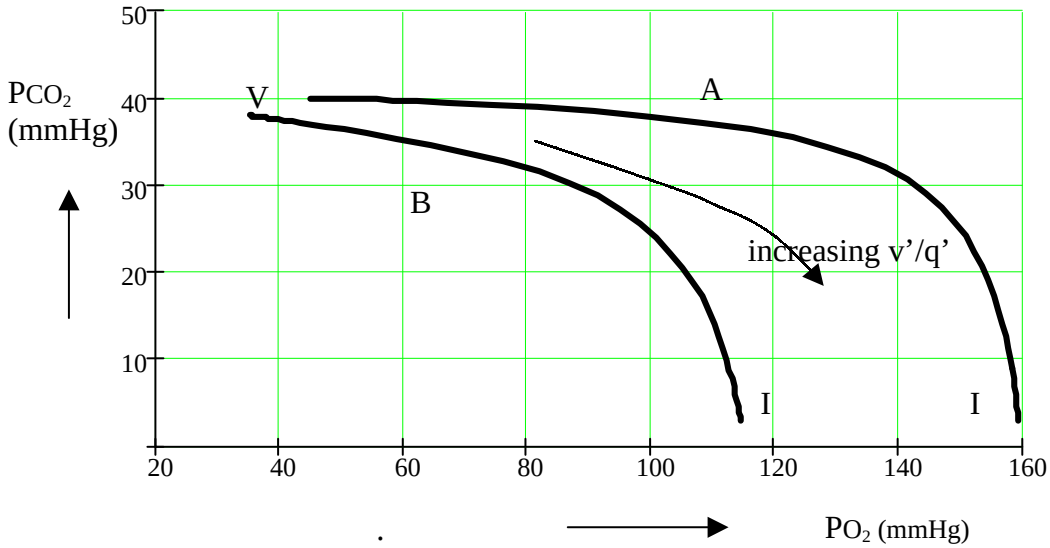

Figure 1. Alveolar PCO_2 versus PO_2 for a subject at sea level (curve A) and at h = 2500 m (curve B). Each point on a curve represents a compartment with a certain v'/q' combination. At the venous points (V) v'/q'=0 and at the inspired points (I) v'/q' approaches infinite.

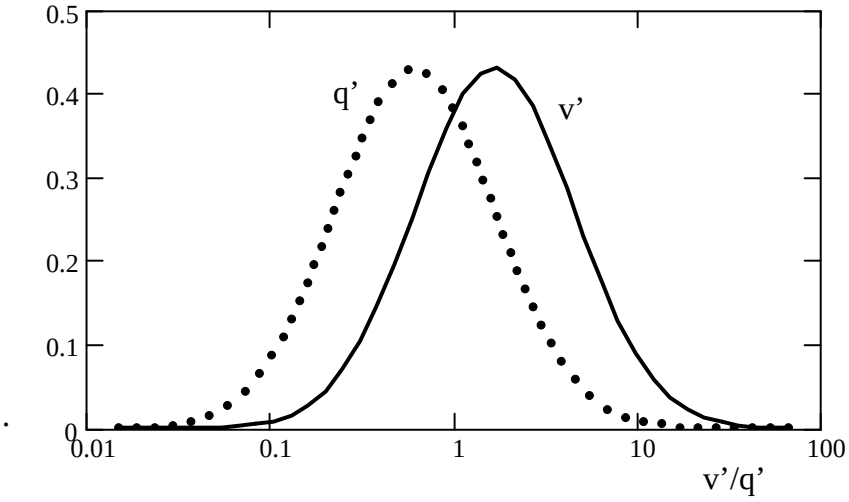

Figure 2. Ventilation v' (L/min) and perfusion q' (L/min) lognormal distributions as function of their ratio v'/q'.

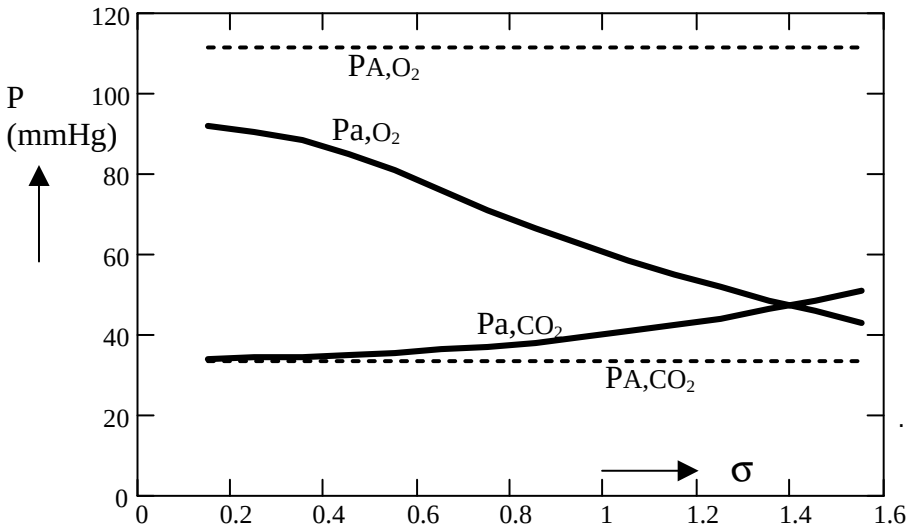

Figure 3. Effect of mismatch parameter σ on alveolar (P_{A,O_2}, P_{A,CO_2}) and arterial partial pressures (Pa,O_2, Pa,CO_2).

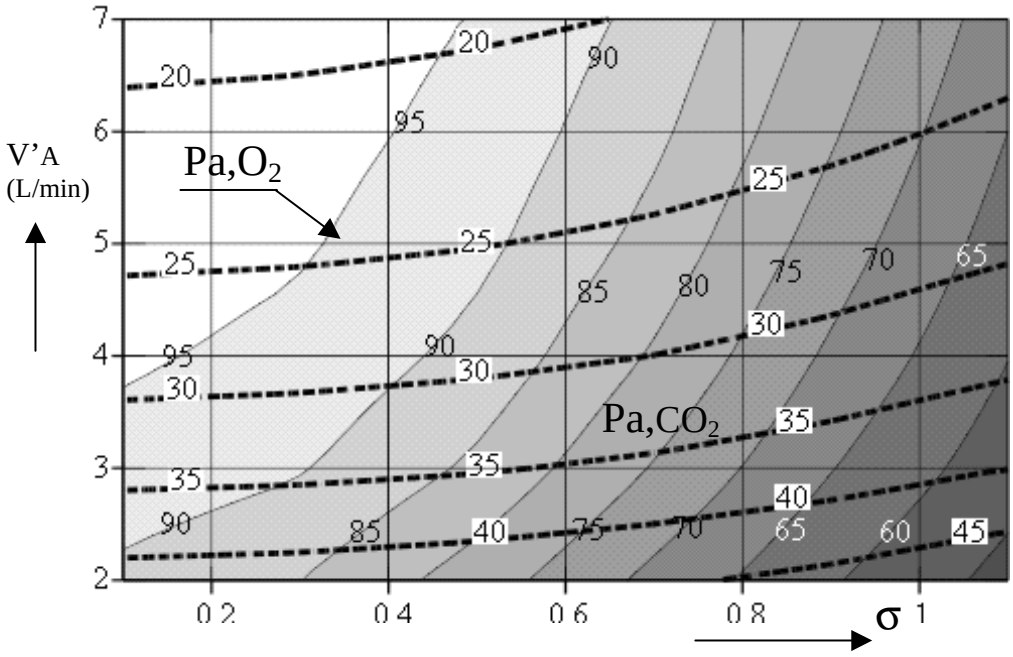

Figure 4. Lines of constant Pa,O_2 (thin lines with grey fill) and of constant Pa,CO_2 (dotted heavy lines) in mmHg as function of mismatch parameter σ and alveolar ventilation V'A. For a pair of measured values of Pa,O_2 and Pa,CO_2 the characteristics V'A and σ can be found.

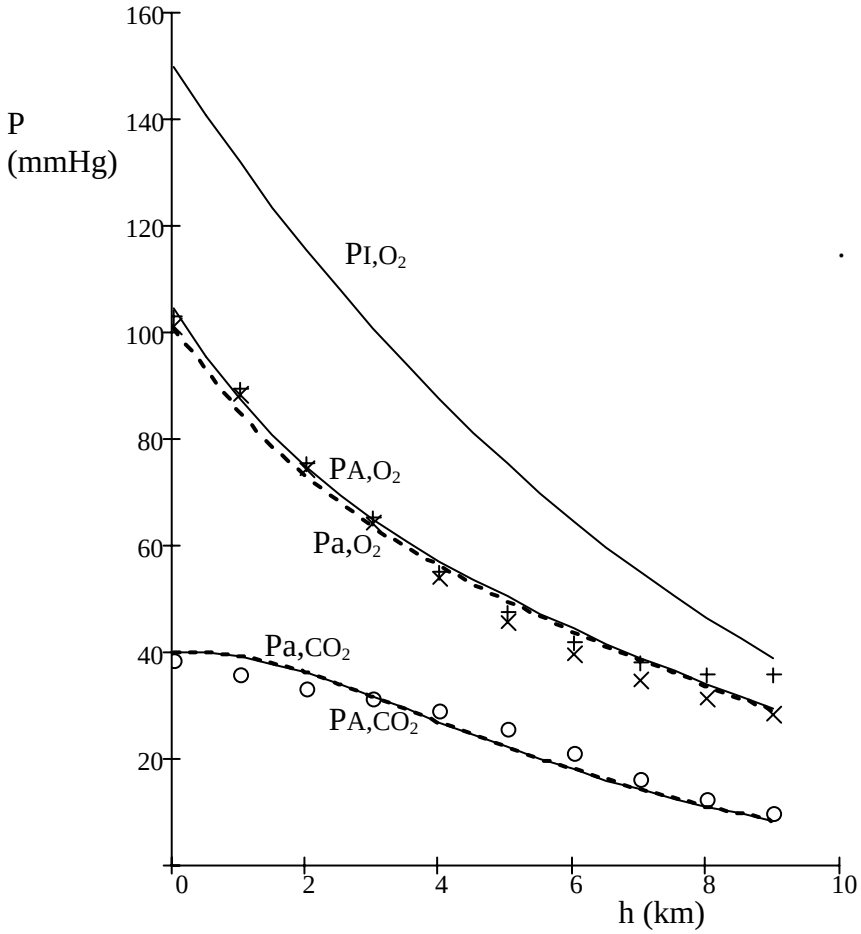

Figure 5. Calculated model and experimental results for a healthy subject.
Calculations: Alveolar (P_{A,O_2}, P_{A,CO_2}): solid lines. Arterial (P_{a,O_2}, P_{a,CO_2}): dashed lines.
Experimental data (Ref. 9): P_{a,CO_2}: o's; P_{a,O_2}: x's; P_{A,O_2}: +'s.
Standard atmosphere P_{I,O_2}: solid line.

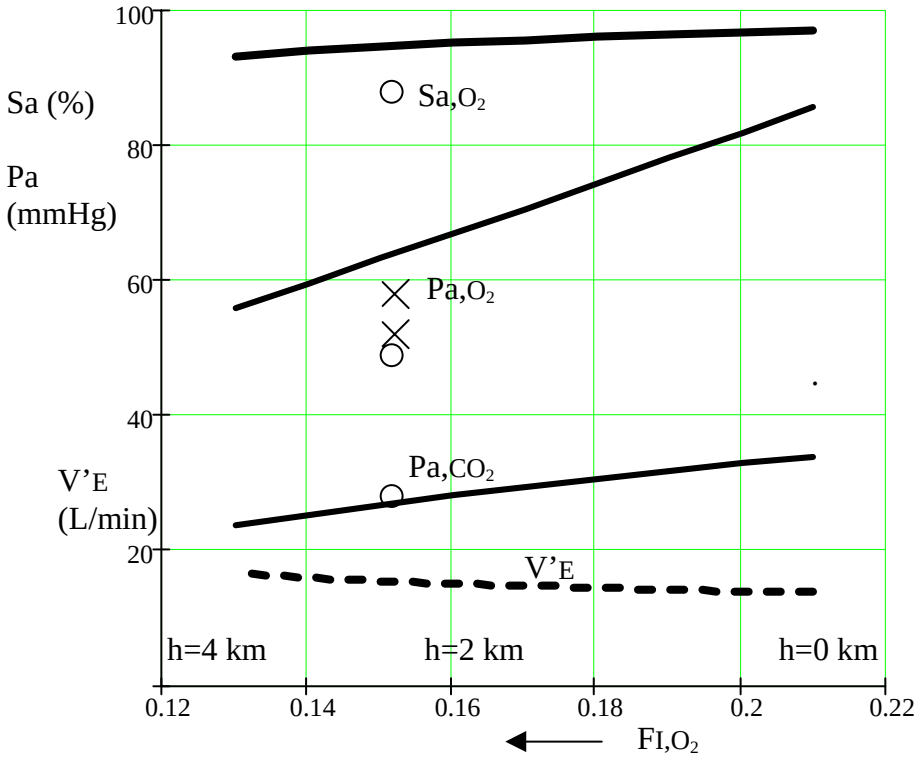

Figure 6. Effect of lowering FI,O_2 on Sa,O_2, Pa,O_2, Pa,CO_2 and V'_E of a COPD patient.
Equivalent altitude in km is indicated at the bottom of figure.
Crosses indicate Pa,O_2 from statistical formulae of Gong (upper) and Dillard (lower) (Ref. 2, 3).
Open symbols represent HAST measurements for Sa,O_2, Pa,O_2, Pa,CO_2.
Lines are computed by the present ventilation-perfusion mismatch method. Initial baseline conditions at $FI,O_2 = 0.21$ are derived from measurements.

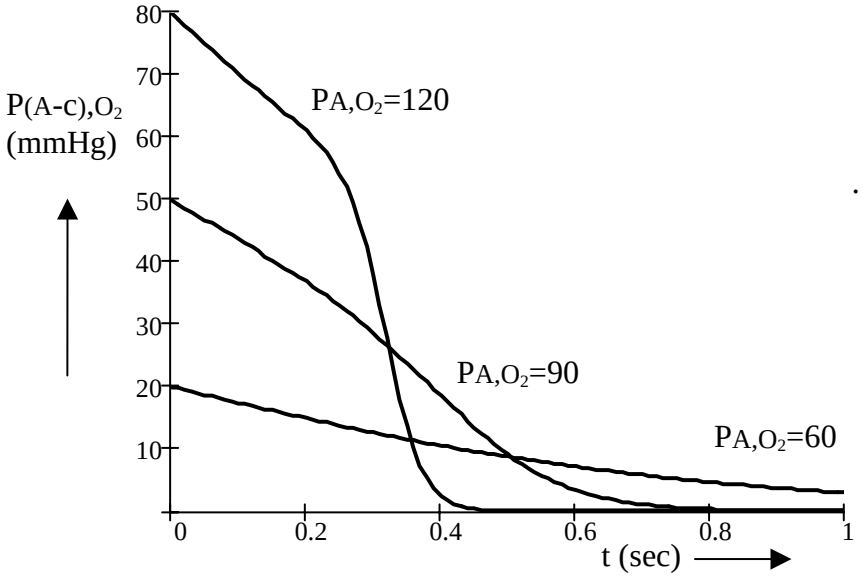

Figure 7. Alveolar-capillary difference of PO_2 in pulmonary capillary as function of time for three values of alveolar PA,O_2 for the same venous PV,O_2=40 mmHg at t=0 sec.

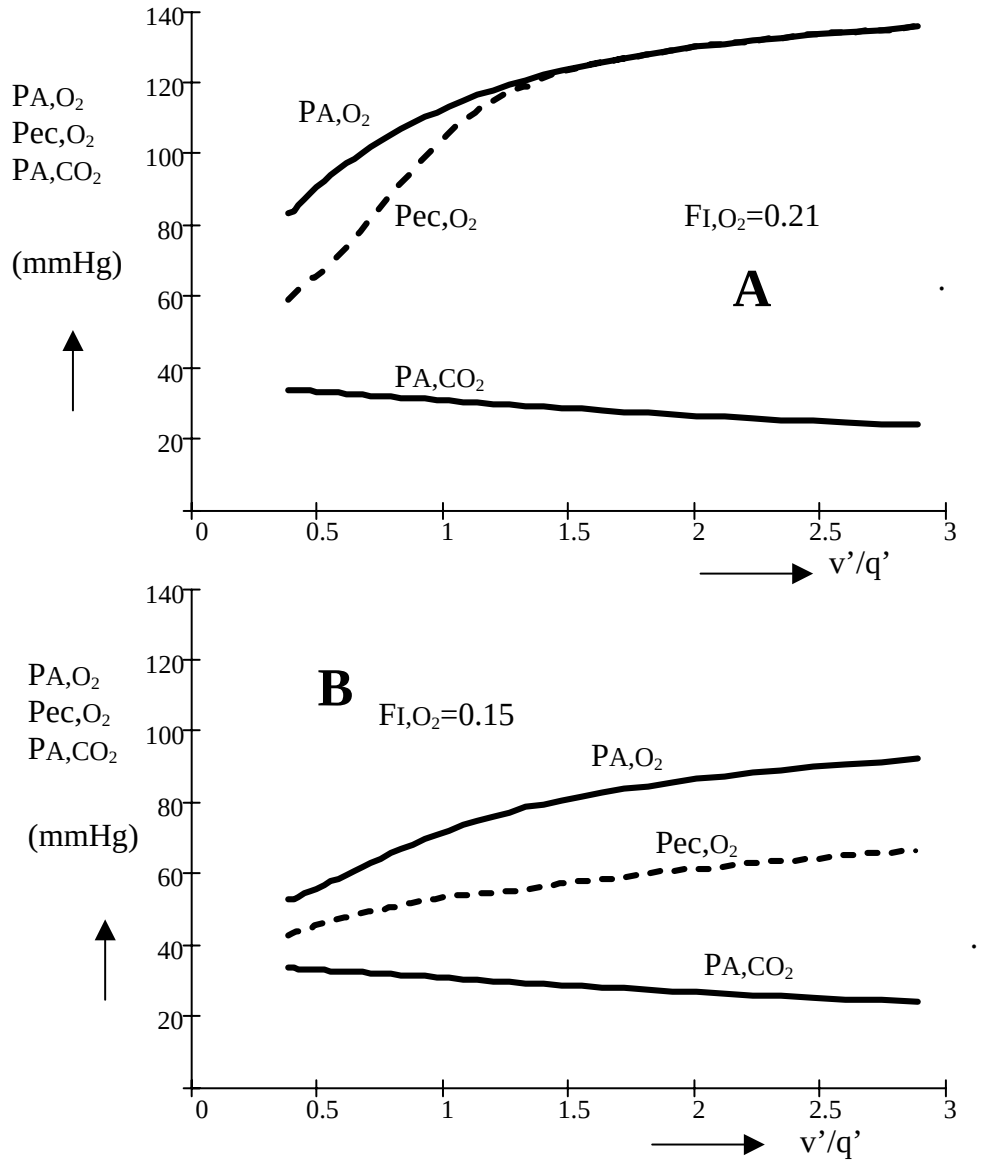

Figure 8. Partial pressures of O_2 and CO_2 versus ventilation-perfusion ratios including the effect of alveolar-end-capillary PO_2 difference.
Top figure A: normal FI,O_2=0.21, bottom figure B: FI,O_2=0.15.

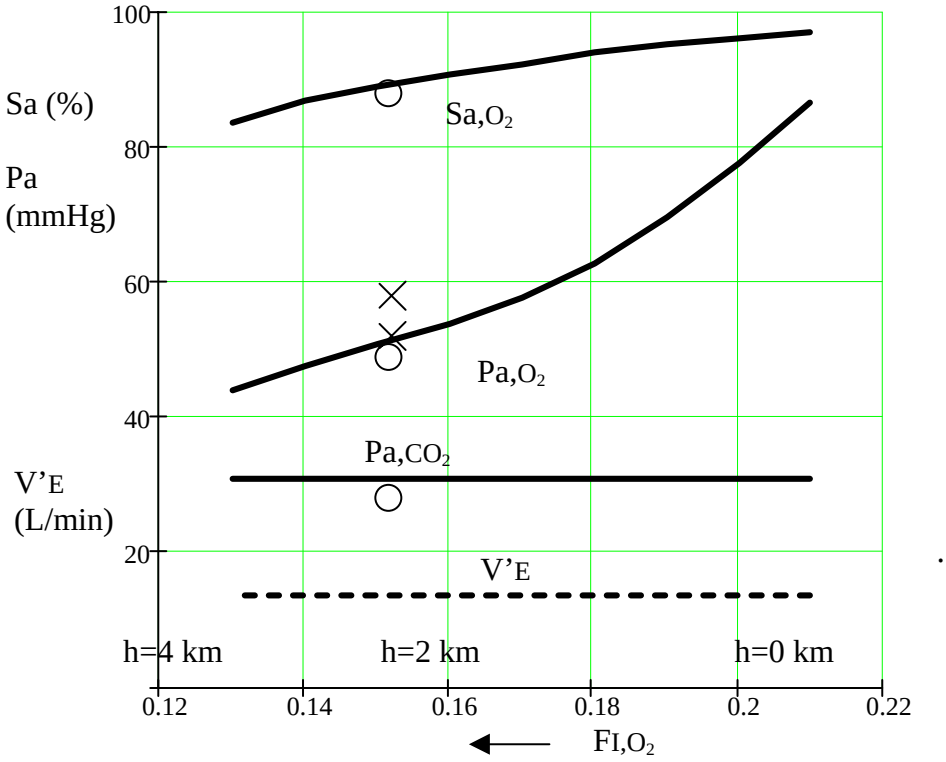

Figure 9. Effect of lowering F_{I,O_2} on Sa,O_2, Pa,O_2, Pa,CO_2 and V'_E. At the bottom altitude is given in km.
Open symbols represent HAST measurements of Sa,O_2, Pa,O_2, Pa,CO_2 of COPD patient.
Crosses are Pa,O_2 from statistical formulae of Gong and Dillard (Refs. 2,3).
Lines are computed by ventilation-perfusion mismatch method including non-equilibration of capillary PO_2.
Initial conditions at $F_{I,O_2}=0.21$ are derived from measurements.

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Changes of Ventilator Generated Volume and Pressure under Simulated Cabin Pressure Profiles of Military Aircraft C160 Transall

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Introduction :

Pulmonary traumata and special intensive care therapies often lead to a respirator treatment.
After stabilisation of the patient vital functions in the medical installations of the operation area the respirator-treatment has to be continued during the air-transport for repatriation.
Patient and ventilation equipment are exposed to certain influences caused by the air-transport. Originaly respirators are built for the use on the ground (air-pressure 1013 mbar) with only slight changes (+/- 20 mbar) in air-pressure.
In military Medevac-airplanes there are significant and quick changes (de- and increases) of the pressure cabin in cruising altitude and in tactical flight manouvers.
Aim of this study was to examine the influence of cabin pressure on important parameters of ventilation using different transport ventilators. Simulating cabin-pressure conditions, differences in the applied tidal volume and PEEP to a preset value were to be determined.
The results of this study may help to develop guidelines to reduce the risk of the treatment of ventilated patients during air-transport.

Method :

The experiment was based on the continuous recording of pressure changes in a lung-model with known compliance. After measuring and recording on-line, volumes applied by the respirator were calculated and PEEP-levels were read.
The experiment consisted of the respirators Oxylog 2000 and EVITA 4 (Dräger Co., GE), their tubing system and a lung-model (Isolung: glasballoon 54 l filled with 10 kg copperwool to guaranty isothermic condition changes)
The pressure differences between decompression-chamber and isolung, the pressure inside the decompression-chamber, the temperature in the lung-model and in the decompression chamber were measured by gauges.
To verify the influence of environmental pressure-conditions to the respirator functions in a plane (C160 Transall) the experiment was performed in the decompression-chamber of the German Air Force Institute of Aerospacemedicine in Fürstenfeldbruck.

After defining ventilation modes and parameters the apparatus were exposed to simulated cruising level (max. 10.000 ft), emergency decent (-6000 ft/min) and rapid decompression.
The arrangement of the test allowed pressure-changes which correspond to altitude differences of 14.000 ft in the EVITA 4 and of 8.ooo ft. in the Oxylog 2000. Immediately after the emergency descent of 6000 ft/min was simulated.
Inside the lung-model pressure changes up to 40 mbar could be measured.

Results :

Table 1 shows the applied tidal volume during minimal cabin pressure (10.000 ft). The Oxylog 2000 increases the tidal volume by 50 % to 1200 ml (preset value 800 ml) in IPPV mode.
The EVITA 4 in IPPV mode generates a plus of 22 % to a preset tidal volume of 800ml which results in a value of 980 ml. In the pressure-controlled BIPAP Mode, with preset values of p max=20 mbar and PEEP of 5 mbar a tidal volume of 1080 ml is generated (+38 %).

Paper presented at the RTO HFM Symposium on "Operational Medical Issues in Hypo- and Hyperbaric Conditions", held in Toronto, Canada, 16-19 October 2000, and published in RTO MP-062.

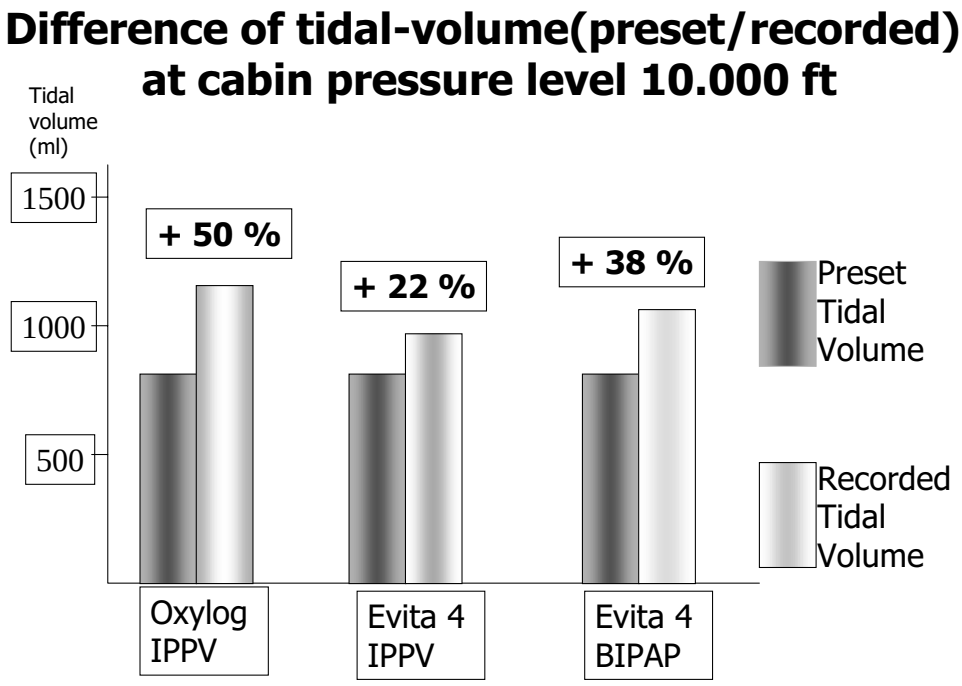
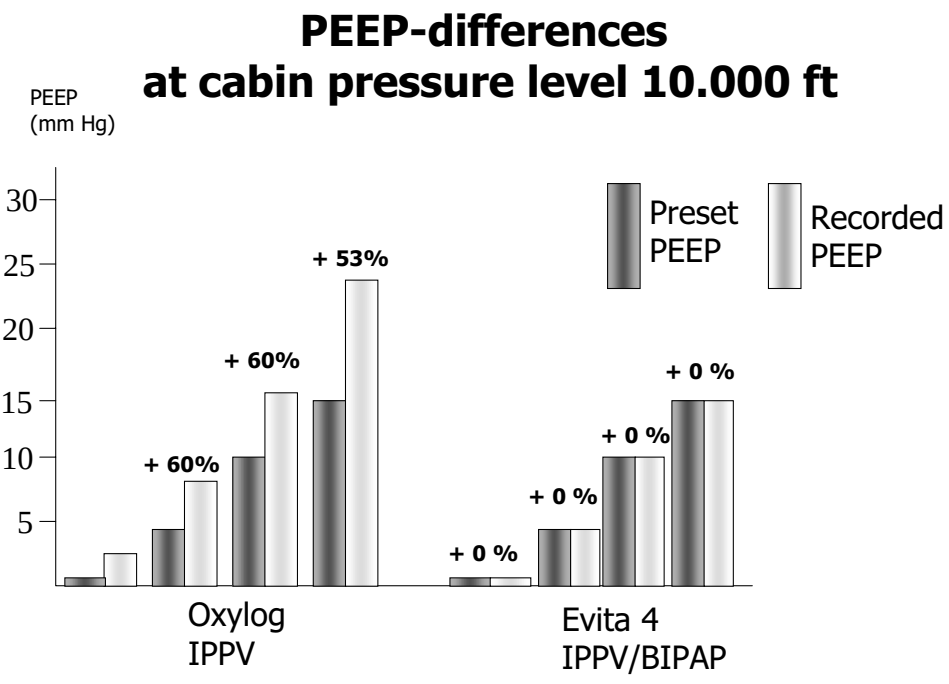


Table 1

To the beginning of climbing the Oxylog reacts with an alternation of the tidal volume by + 160 ml. Starting the descent the tidal volume is once elevated by +280 ml compared to the previous breathing cycle. Immediatley after reaching ground level-pressure the applied tidal volume falls by –80 ml in comparison to the earlier breathing cycle. Between the cycles there are variations up to 60 ml.
Using the EVITA 4 in IPPV mode the variations during climb amount to 20 ml. At the beginning and during the descent differences up to 150 ml occur.
In BIPAP ventilation the differences remain smaller than 10 ml, only initially of descent there is a tidal volume peak of +150 ml.
The measured PEEP-values show obvious differences (s. Table 2) .
The registred shift during the whole test using the Oxylog 2000 was +2,5 mbar (preset 0 mbar). Picture 2 shows the PEEP levels in cabin-pressure 10.000 ft, differences up to 50 % can be seen.
The EVITA 4 creates both in volume as in pressure-controlled ventilation-mode stable values on preset level.

Table 2



Emergency descent :

Oxylog 2000 :
Calculated 1200 ml tidal volume at 10.000 ft (preset 800 ml) are decreased by 50 % to 600 ml initially in descent. During the following 55 sec the tidal volume varies between 600-700-ml, than a continuously increase occurs. Approximately 20 sec. after reaching ground level-pressure constant tidal volume is produced. Starting the emergency descent PEEP of 8 mbar (preset 5mbar) immediately falls to 0 mbar, then 1 mbar is registered constantly. When reaching original tidal volume the Oxylog 2000 produces stable value of 7 mbar (Table 3).

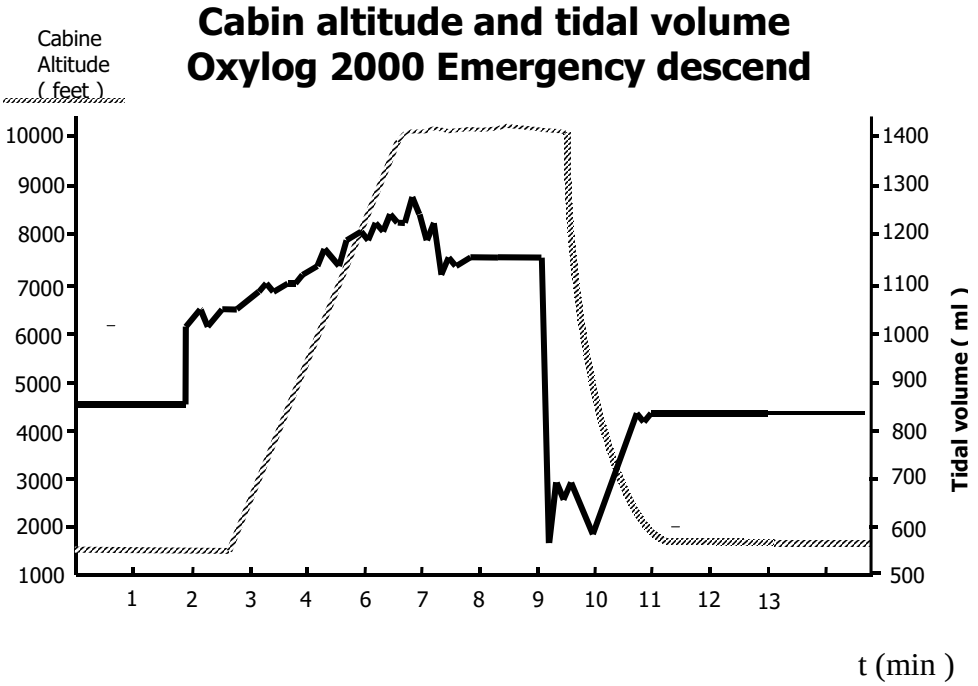


Table 3

Evita 4/IPPV: Calculated 920 ml tidal volume (preset 800 ml) was reduced by 250 ml at the beginning of emergency descent, then varies from 350 ml to 800 ml and reaches and maintains a constant tidal volume directly on ground. The chosen PEEP of 0 mbar decreases to –1 mbar but shows starting value towards the end of the test (Table 4).

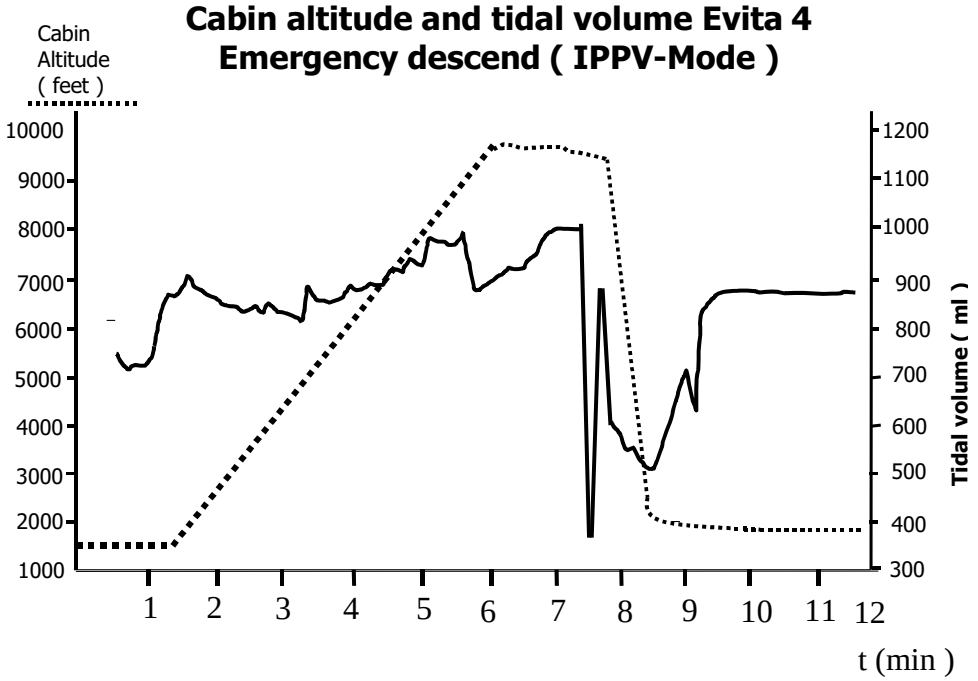


Table 4

Evita 4/BIPAP: When cabin pressure rises, the applied plateau pressure of 20 mbar falls to 8 mbar, the correspond tidal volume decreases from 1060 ml to 280 ml (-73,6%). 25 sec after the the beginning of the emergency descent the original tidal volume calculated increase and stay stable during the course. PEEP decreases from 5 mbar (preset 5mbar) to 4 mbar .

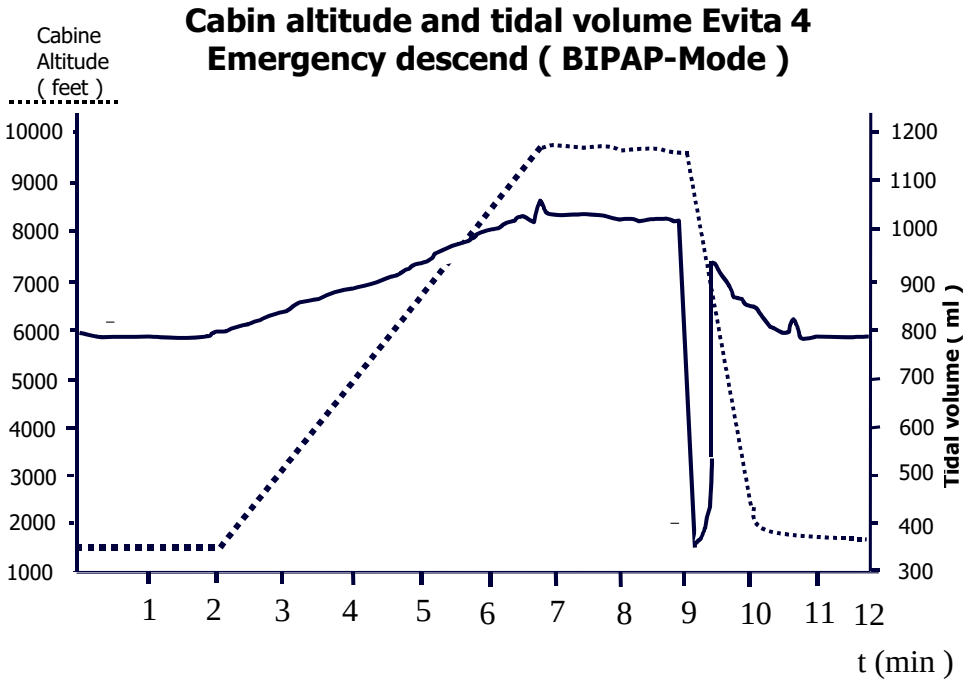


Table 5

Rapid decompression

The results of tidal-volume during rapid-decompression-tests are – due to unisothermic conditions of pressure-changes - of limited validity.
Oxylog 2000:
At the beginning of rapid decompression the system pressure increases rapidly up to 40 mbar registered.
In comparison to the results of emergency descend the tidal volume decreases from 1150 ml to 900 ml ;
varitions from 950 to 600 ml ocured; after reaching ground level pressure a contineous tidal volume of 800 ml is generated.(Table 6)

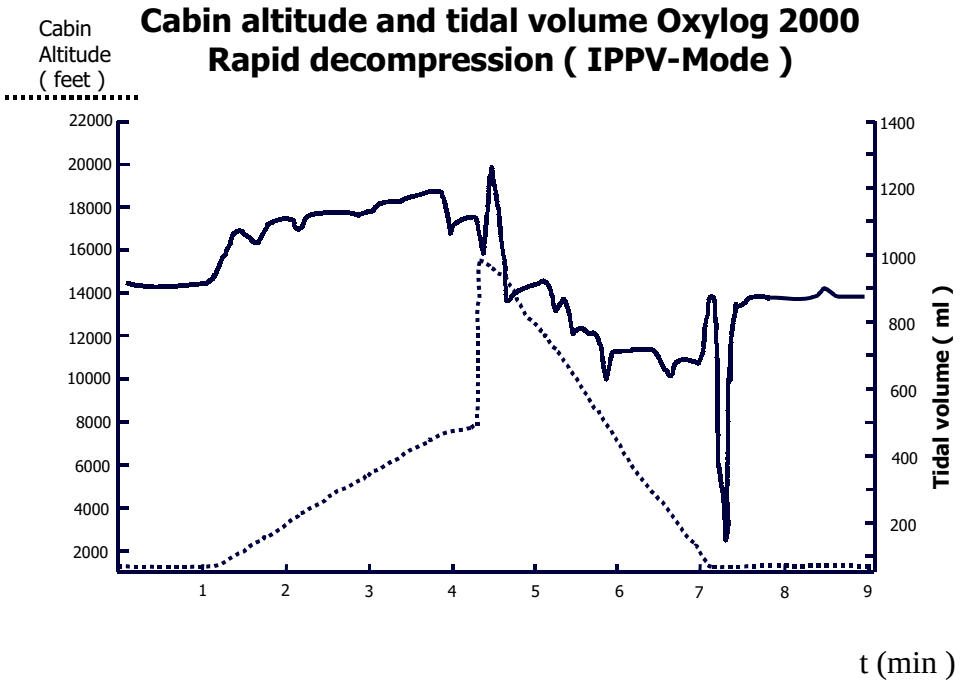


Table 6

Evita 4 (IPPV):
Like the Oxylog performance initialy the system pressure decreases up to measured 40 mbar. Then the tidal volume falls from 950 ml to 500 ml. In the next 30 sec the tidal volume increases to 800 ml; till the end of the cabin pressure chances the tidal volume decreases to 550 ml. After reaching ground level pressure a tidal volume of 840 ml is generated (Table 7).

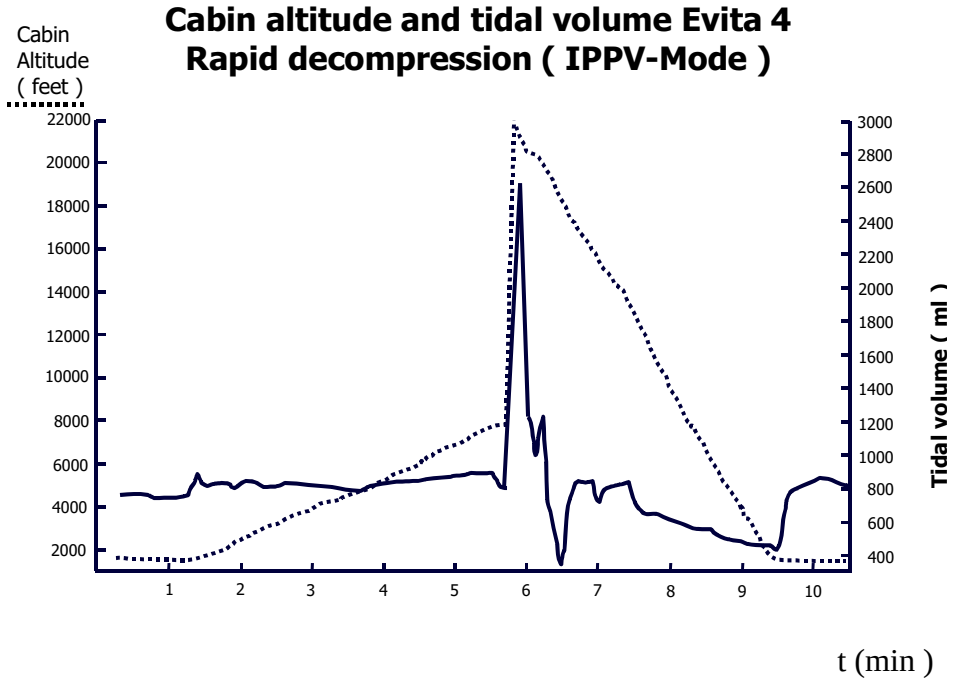


Table 7

Conclusions

The respirators tested under simulated cabin-pressure-conditions of the military airplane C160 Oxylog 2000 and Evita 4 basically proved that they work securely.
The surrounding pressure has a considerable impact on essential ventilation-parameters.

It was shown that both devices – to a different extent - delivered higher tidal volume to the lung-model when exposed to simulated cabin pressure. Possible clinically relevant consequences are hyperventilation, shifts in acid-base-balance and barotrauma.
The Oxylog 2000 in comparison shows high variations in PEEP. The variations are of clinical relevance that exceed a plus of 50 % of the preset value. Stress of the cardio-vasculary system caused by intrathoracic fluid shifts, of the downstream cerebrovascular system with consecutive increase in intracranial pressure, of the alveolar structure and the surfactant-layer are likely.

The pressure – controlled ventilation mode BIPAP of the Evita4 offers obvious advantages compared to the IPPV mode – even though higher change in the tidal volume occurs.
Reasons herefor are the constant increase of the tidal volume during climb and descent, the neglectable variations in applied volume between the breathing cycles and the faster generation of a sufficient tidal volume in case of emergency descent.

If the apnoic oxygenation of the patient with high oxygen-flow may be an easier alternative to the controlled ventilation in case of an emergency descent has to be examined.

The rapid loss of cabin-pressure represents a threatening situation for t the whole crew and especially for the ventilated patient.There was no damage to the tested equipment detected and the devices worked without interference after ending the pressure variations.
Because of the massive increase of pressure in the system patient-lung – ventilation tubes barotrauma of the pulmonary system are possible.
Devices like the Evita 4 surely offer a higher patient security in this case, as the expiratory flow and fast switching valves allow a quicker decrease of the pressure in the respiratory system.
Prophylactic precautions to prevent damage of the lungs by the rapid decompression can hardly be taken as of the peracute nature (and the unpredictable occurrence) of this situation.

The air-transport of ventilated patients - especially in military operation conditions - is always full of risks even when using modern respirators. To guaranty the highest patient security the following checklist should be looked at before the transport:

- controlling of breathing tube position, respirator function and patient – respirator interaction before engine noise sets in
- sufficient sedation and analgesia, generous indication for muscular relaxation (prophylaxis of coughing)
- insertion of a stomach tube
- application of nasal decongestants (pain when cabin pressure increases during descend)
- setting of pressure limitations
- general use of (minmal) PEEP to prevent negative airway pressures during descent
- reduction of PEEP during climb when using Oxylog 2000
- cuff pressure measurement
- decompression of pneumothoraces
- capnography / pulsoxymetry for monitoring
- BGA control to uncover hyperventilation

The Effect of Increased Full Coverage Anti-G Trouser Inflation Pressure on the Cardiovascular Responses to Positive Pressure Breathing

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Abstract

Positive pressure breathing (PPB) provides short term emergency protection against hypoxia in the event of cabin depressurisation in military aircraft operating at altitudes exceeding 40,000 feet. PPB, however, causes significant disturbance to the normal function of the respiratory and circulatory systems, thus limiting the level and duration of pressure breathing that can be tolerated.

The adverse effects of PPB can be lessened by the use of counter-pressure garments, which apply an external pressure to the surfaces of the trunk and the lower limbs. We investigated the potential benefits of increased lower limb counter-pressure as a measure to optimise cardiovascular function during PPB.

A trans-cranial Doppler sonograph was used to measure the cerebral blood velocity (CBV) during PPB whilst wearing full coverage anti-G trousers (FCAGT) inflated to various pressures. Six subjects were exposed to 45mmHg PPB for 10 minutes at ground level, and 70mmHg PPB for 4 minutes at ground level. At each PPB level, subjects were exposed to 4 levels of FCAGT inflation – 1 x PPB pressure, 1.5 x PPB pressure, 2 x PPB pressure, and 2.5 x PPB pressure. Subjects also completed a control during normal breathing at rest. CBV during PPB was lower than CBV during the control condition ($p<0.05$), irrespective of FCAGT inflation level. Heart rate during PPB at a FCAGT inflation pressure of 1 x PPB pressure was greater than heart rate during the control condition ($p<0.05$). In addition, alveolar CO_2 pressure ($PACO_2$) during PPB was lower than $PACO_2$ during the control condition ($p<0.05$), irrespective of FCAGT pressure. We cannot wholly attribute the observed reduction in CBV during PPB to cardiovascular dysfunction, as the reduction in $PACO_2$ during PPB is suggestive of a decreased arterial PCO_2, a factor known to induce cerebral vasoconstriction.

In a second study, a rebreathing based lung function test was used to assess effective pulmonary blood flow (QP_{eff}) and diffusing capacity of the lungs (Dl) during PPB whilst wearing full coverage anti-G trousers inflated to various pressures. Six subjects were exposed to 45mmHg PPB for 2.5 minutes at ground level, and 60mmHg PPB for 2.5 minutes at ground level. At each level of PPB, subjects were exposed to 4 levels of FCAGT inflation pressure – 1 x PPB pressure, 1.5 x PPB pressure, 2 x PPB pressure, and 2.5 x PPB pressure. The subjects also completed a control during normal breathing at rest. QP_{eff} and Dl during PPB was not significantly different to QP_{eff} and Dl during the control condition, irrespective of FCAGT inflation pressure. Heart rate during PPB at a FCAGT inflation pressure of 1 x PPB pressure was greater than heart rate during the control condition ($p<0.05$), and greater than heart-rate during PPB at the other levels of FCAGT inflation pressure ($p<0.05$).

We conclude that cardiovascular function is impaired during PPB whilst wearing FCAGTs inflated to a pressure equal to PPB pressure. In addition, our results demonstrate that near normal cardiovascular function can be maintained during PPB if FCAGTs are inflated to 1.5 x PPB pressure, 2 x PPB pressure, or 2.5 x PPB pressure.

Paper presented at the RTO HFM Symposium on "Operational Medical Issues in Hypo- and Hyperbaric Conditions", held in Toronto, Canada, 16-19 October 2000, and published in RTO MP-062.

Introduction

In the event of cockpit pressurisation failure or forced ejection at altitudes exceeding 40,000 feet, aircrew are exposed to the risk of significant hypoxia. At these altitudes, breathing 100% oxygen does not maintain physiologically adequate blood oxygen saturation, due to an insufficient oxygen pressure gradient between the inspired gas and the blood flowing through capillaries in ventilated regions of the lungs. Theoretically, under these conditions a physiologically acceptable inspired oxygen tension could be achieved simply by increasing the absolute pressure of the 100% oxygen breathing gas delivered to the pilot's oxygen mask. Unfortunately, breathing a gas delivered to the airway at a pressure exceeding ambient pressure ('positive pressure breathing') imposes significant physiological penalties, thus limiting the effectiveness of this procedure as a measure to prevent hypoxia following rapid decompression at altitudes exceeding 40,000 feet.

Positive pressure breathing (PPB) adversely affects the normal mechanical function of the respiratory apparatus, resulting in hyperinflation of the lungs and an increased work of breathing. The most significant consequence of PPB is, however, the effect on the circulation. PPB raises intrathoracic pressure, resulting in a displacement of blood from the thoracic cavity and a temporary abolition of the normal peripheral to central venous pressure gradient, and hence a reduction in venous return. Progressive accumulation of the blood displaced from the thorax in the peripheral veins results in an increase in peripheral venous pressure, which continues until a peripheral to central venous pressure gradient is re-established. Thus, during PPB the circulation of blood is maintained at the cost of a reduction in the volume of circulating blood, compromising the supply of oxygenated blood to the brain.

The development of counter pressure garment assemblies has reduced the severity of the adverse effects of PPB. Application of an equal counter pressure to the external surface of the trunk and abdomen almost wholly alleviates the respiratory dysfunction associated with PPB. The addition of lower limb counter pressure, via the use of anti-G trousers, provides some protection against PPB-induced circulatory dysfunction. Research data demonstrate that the degree of cardiovascular protection provided by anti-G trousers during PPB is dependent on the garment design, the extent of lower body surface area coverage, and the inflation pressure of the garment relative to the pressure of the breathing gas.

Earlier standard coverage anti-G trouser designs, which provide bladder coverage of approximately 30% of the lower body surface area below the umbilicus, have been shown to provide only limited protection against PPB induced cardiovascular dysfunction. Although studies have shown that inflating standard coverage anti-G trousers to a pressure up to four times PPB pressure improves cardiovascular function during PPB (Ackles et al, 1978; Gradwell, 1993), available data demonstrate that standard coverage anti-G trousers are incapable of facilitating maintenance of normal circulatory function during PPB (Goodman, Fraser, Eastman, and Ackles, 1992; Goodman, Fraser, Ackles, Mohn, and Pecaric, 1993; Goodman, Freeman, Yang, Hsia, and Chan, 1994).

The recent development of full coverage anti-G trousers (FCAGTs), which provide circumferential bladder coverage of up to 90% of the lower body surface area below the umbilicus, has improved the degree of circulatory protection available to aircrew during PPB (Goodman et al, 1992; Goodman et al, 1993; Goodman et al, 1994).

Theoretically, extended bladder coverage provided by FCAGTs affords the possibility of using garment inflation pressures that are substantially lower than those previously recommended for standard coverage anti-G trousers during PPB. Currently, however, there is no consensus amongst researchers as to the optimum FCAGT inflation pressure during PPB. Establishment of the lowest FCAGT inflation pressure sufficient to facilitate maintenance of normal cardiovascular function during PPB will reduce the discomfort and impaired mobility arising from excessive lower body pressurisation.

The present study aimed to determine the lowest FCAGT inflation pressure that facilitated maintenance of optimum physiological function during ground level PPB not exceeding 70mmHg. Two separate experiments assessed various physiological responses to PPB in subjects wearing a counter pressure

assembly incorporating FCAGTs inflated to various multiples of PPB pressure (1 x PPB pressure, 1.5 x PPB pressure, 2 x PPB pressure, or 2.5 x PPB pressure).

Methods

Phase 1

Six male subjects from the DERA staff gave informed consent to participate in this part of the study. All subjects were aged under 45 years, were medically screened and received positive pressure breathing (PPB) training prior to participation in the study.

Prior to each experimental exposure, an adjustable headband device, incorporating the probe of a transcranial Doppler (TCD) sonograph (Pioneer 4040, Nicolet Biomedical/EME, Madison, USA), was fitted to the subject's head. The TCD probe was placed on the portion of the scalp covering the right temporal region of the subject's skull. The TCD probe emits an ultrasound signal at a constant rate and frequency, which is backscattered and reflected by red blood cells moving through the selected blood vessel at the measurement site. The resultant frequency shift of the ultrasound signal is proportional to the velocity of the blood cells within the selected vessel. A point 2-5mm proximal to the bifurcation in the Middle Cerebral Artery (MCA) at the Circle of Willis was selected as the measurement site. The MCA is considered inextensible, and hence changes in blood velocity are directly proportional to changes in blood flow. Thus, the TCD device allowed non-invasive measurement of a direct correlate of cerebral blood flow. In addition to the TCD device, subjects were fitted with 3 electrodes to enable display of their electrocardiogram (ECG) using a standard 3-lead ECG configuration.

Following instrumentation fitting, subjects donned a representative aircrew equipment assembly (AEA) comprising aircrew underwear, Royal Air Force (RAF) Mk14b aircrew flying coverall, a RAF G-type flying helmet (modified to accommodate the TCD probe), RAF Type P/Q oronasal oxygen mask, representative FCAGTs, and a representative chest counter-pressure garment (CCPG). The FCAGTs provided circumferential bladder coverage of approximately 90% of the lower body surface area below the umbilicus. The CCPG provided bladder coverage of the shoulders, and the anterior and posterior external surfaces of the chest and upper abdomen.

Subjects underwent experimental exposures at two levels of PPB (45mmHg for 10 minutes, and 70mmHg for 4 minutes), at four FCAGT inflation pressures (1 x PPB, 1.5 x PPB, 2 x PPB, and 2.5 x PPB). Thus, subjects completed eight individual PPB experimental conditions. In addition, subjects underwent two control conditions to provide a baseline comparison with data obtained during 10-minute 45mmHg PPB exposures and 4-minute 70mmHg PPB exposures. The control conditions involved normal breathing at ambient pressure, and were identical in all aspects to the PPB experimental conditions, save for the absence of PPB and counter pressure garment inflation.

During all experimental exposures, subjects were seated on a chair positioned in a hypobaric chamber. On each visit to the laboratory, subjects underwent a maximum of three PPB experimental exposures per half day. Experimental exposures were presented to subjects according to a Latin square experimental design, which ensured that no two subjects experienced an identically ordered sequence of exposures.

PPB was initiated using the 'through the wall' method, as utilised by others (Goodman et al, 1993; Goodman et al, 1995). The hypobaric chamber was decompressed, such that the pressure within the chamber was lowered by an amount equal to the required PPB pressure (i.e. either 45mmHg or 70mmHg). Subjects could breathe air at either chamber pressure or the relatively higher pressure of ambient air outside the chamber. A bank of ganged two-way taps acted as a switchover mechanism, which could connect the subject's oxygen mask and CCPG, via gas hoses protruding through the chamber wall, to the relatively higher pressure ambient air, thus enabling simultaneous delivery of PPB and CCPG inflation. The two-way tap system was designed to allow rapid termination of PPB, if required. The FCAGTs were inflated from a compressed air

supply, via integrated control boxes (manufactured locally) linked to solenoid operated valves. The control boxes could be configured to enable the maintenance of any desired FCAGT inflation pressure, up to a maximum of 5 times PPB pressure.

Differential pressure transducers (Celesco transducers, model No. LCVR) measured the pressure in the subject's oxygen mask ('mask cavity pressure'), CCPG, FCAGTs, and in a reference pressure tube, which enabled the pressure differential between the chamber and ambient air to be monitored. The subject's arterial blood pressure and heart rate was recorded using a Finapres 2300 blood pressure monitor (Ohmeda Inc), with the finger cuff secured on the ring finger of the subject's left hand, which was held at heart level during the experimental exposures. The subject's respired gas composition was measured throughout all experimental exposures by a respiratory mass spectrometer (QP9000, Morgan Medical Ltd), configured to measure the relative concentrations of nitrogen, oxygen, carbon dioxide, and argon in the sampled gas. The outputs from the TCD sonograph, respiratory mass spectrometer, the pressure transducers, and the arterial blood pressure monitor, were displayed and recorded using an analogue to digital converter incorporating a data recording system (Maclab/S, ADInstruments) linked to a microcomputer (Apple PowerMac, Apple Computers).

During all PPB exposures, a suitably qualified Medical Officer accompanied the subject in the hypobaric chamber. Subjects could voluntarily terminate PPB at any time, via the use of a thumb-down signal. The Medical Officer terminated PPB if there was any evidence of impending syncope, or if the subject was considered unfit to continue PPB for any reason.

Data Acquisition and Statistical Analysis

Mean arterial blood pressure (MAP), heart rate, cerebral blood velocity, and estimated alveolar carbon dioxide tension data were obtained using dedicated analysis functions within the data recording/analysis software package (Chart, ADInstruments).

The data for each variable were averaged over 1-minute periods of each experimental condition. The data obtained from 45mmHg PPB experimental conditions (including the associated control condition) were separated from the data obtained from the 70mmHg PPB experimental conditions to form two distinct data sets. The mean values in each data set were subsequently analysed using a two-factor (FCAGT inflation pressure and time) analysis of variance with repeated measures. A significance level of $p<0.05$ was adopted as the cut-off point for all main effects. Where main effects were identified, post-hoc analysis (Newman Keuls test) was used to determine which experimental conditions differed from each other.

Phase 2

Six male subjects from the DERA staff gave informed consent to participate in this part of the study. All subjects were aged under 40 years, were medically screened and received positive pressure breathing (PPB) training prior to participation in the study.

Subjects were fitted with 3 electrodes to enable display of their electrocardiogram (ECG) using a standard 3-lead ECG configuration prior to donning the aircrew equipment assembly (AEA). Subjects wore a representative AEA comprising aircrew underwear, Royal Air Force (RAF) Mk14b aircrew flying coverall, a RAF Mk10b aircrew helmet, a modified RAF Type P/Q oronasal oxygen mask, representative FCAGTs, and a representative CCPG. The FCAGTs and CCPG were identical to those used in phase 1 of the study.

Subjects underwent experimental exposures at two levels of PPB (45mmHg for 2.5 minutes, and 60mmHg for 2.5 minutes), at four FCAGT inflation pressures (1 x PPB, 1.5 x PPB, 2 x PPB, and 2.5 x PPB). Thus, subjects completed eight individual PPB experimental conditions. In addition, subjects underwent two control conditions to provide a baseline comparison with data obtained during 45mmHg PPB exposures and 60mmHg PPB exposures. The control conditions involved normal breathing at ambient pressure, and were identical in all aspects to the PPB experimental conditions, save for the absence of PPB and counter pressure garment inflation.

Following garment fitting, subjects were seated on a chair positioned in a hypobaric chamber. On each visit to the laboratory, subjects underwent a maximum of three PPB experimental exposures per half day, with experimental exposures presented to subjects according to a Latin square experimental design, as described previously.

Arterial blood pressure and heart rate were recorded using a Finapres 2300 blood pressure monitor (Ohmeda Inc), with the finger cuff secured on the ring finger of the subject's left hand, which was held at heart level during the experimental exposures. Differential pressure transducers (Celesco transducers, model No. LCVR) measured the pressure in the subject's oxygen mask ('mask cavity pressure'), CCPG, FCAGTs, and in a reference pressure tube, which enabled the pressure differential between the chamber and ambient air to be monitored. The subject's respired gas composition was measured throughout all experimental exposures by a respiratory mass spectrometer (QP9000, Morgan Medical Ltd), configured to measure the relative concentrations of nitrogen, oxygen, carbon dioxide, argon, freon^{22}, and carbon monoxide^{18} in the sampled gas. The outputs from the respiratory mass spectrometer, the pressure transducers, and the arterial blood pressure monitor were displayed and recorded using an analogue to digital converter incorporating a data recording system (Maclab/S, ADInstruments) linked to a microcomputer (Apple PowerMac, Apple Computers) running a data recording and analysis software package (Chart, ADInstruments).

The PPB delivery and FCAGT inflation methods were identical to those used during phase 1 of the study. The experimental configuration during this phase of the study differed substantially to that employed during phase 1, with respect to provision of a facility to enable rebreathing manoeuvres to be performed during PPB. The modified RAF Type P/Q oronasal mask incorporated an occluded inspiratory port and a single common inlet/outlet pathway via the open expiratory port. A short section of rubber hose connected the expiratory port of the modified P/Q oxygen mask to a one-way non-rebreathing valve (PK Morgan), which acted as the junction between the inspiratory and expiratory limbs of a breathing circuit. A two-way tap, placed in the hose linking the mask and the one-way valve, functioned as a changeover mechanism between the breathing circuit and the rebreathing apparatus.

The rebreathing apparatus comprised a two-way tap, which enabled rebreathing bag filling/emptying, connected to a 200mm long metal pipe (of internal diameter 10mm), which extended through a hole in an airtight Perspex box and onwards into a 6-litre rubber rebreathing bag (PK Morgan). The mouth of the rebreathing bag was sealed around the metal pipe at the point where it entered the interior of the Perspex box, such that the pipe extended fully from the mouth of the bag to its distal end. The metal pipe was perforated with several holes, to prevent premature bag closure during inspiratory efforts in the rebreathing manoeuvres. The rebreathing gas was delivered to the rebreathing bag by a calibrated 7-litre capacity gas syringe (Hans Rudolph) that could be connected to the rebreathing bag via a filling/emptying two-way tap. A section of rubber hose connected the inside of the Perspex box to the air outside the chamber and, thus, the inside of the Perspex box was always exposed to the atmospheric pressure of air outside the chamber. This enabled the gas in the rebreathing bag to be pressurised to the same level as the gas delivered to the subject's oxygen mask, via the breathing circuit.

Subjects performed a rebreathing manoeuvre during the final 30 seconds of each experimental exposure. After pressure breathing for 2 minutes, subjects breathed out to residual lung volume, and then started rebreathing a quantity of gas (equal to 80% of their seated vital capacity) from the rebreathing bag. The rebreathing bag contained a gas mixture comprising approximately 3.5% freon^{22}, 10% argon, 0.3% carbon monoxide^{18} ($C^{18}O$), and 17.5% oxygen, in a balance of nitrogen. Subjects rebreathed at a frequency of 25 breaths per minute, for a period of 25 to 30 seconds duration. An audible metronome was used to assist subjects in the maintenance of the required breathing frequency during the rebreathing period. Subjects inhaled and exhaled the full volume of gas contained within the rebreathing bag throughout the rebreathing manoeuvre.

During all PPB exposures, a suitably qualified Medical Officer accompanied the subject in the hypobaric chamber. Subjects could voluntarily terminate PPB at any time, via the use of a thumb-down signal. The Medical Officer terminated PPB if there was any evidence of impending syncope, or if the subject was considered unfit to continue PPB for any reason.

Data Acquisition and Statistical Analysis

Mean arterial blood pressure (MAP) and heart rate data were obtained using dedicated analysis functions within the data recording/analysis software package (Chart, ADInstruments).

The records of argon, freon^{22}, C^{18}O, and carbon dioxide concentration during rebreathing manouevres were transferred from the Chart software to a semi-automated spreadsheet (Excel, Microsoft Corporation) function designed by the authors. Following input of the raw data, the argon, freon^{22}, C^{18}O, and carbon dioxide traces were represented as a series of graphs of gas concentration against rebreathing time. The argon trace was used to select two time intervals: the first equating to the peak inspired concentration of argon during the first inspiration from the rebreathing bag, the second equating to the time interval coincident with complete gaseous mixing between residual gas in the lungs and the gas within the rebreathing bag and associated apparatus. The data point equating to the peak inspired argon concentration was taken as the data point coincident with peak inspired concentration for freon^{22},and C^{18}O also. The argon, freon^{22}, and C^{18}O traces were then normalised with respect to their peak inspired concentrations, such that the plots were transformed into a series of graphs relating fraction of peak inspired concentration against time. The next stage of the analysis involved transforming these plots into graphs plotting the natural logarithm (ln) of the normalised freon^{22} and C^{18}O concentrations against time.

The carbon dioxide trace was used to select six end-tidal expiration sample points, starting with the first expiration following the point of complete gaseous mixing within the rebreathing 'system'. The time between the start of rebreathing and complete gaseous mixing never exceeded 10 seconds, and hence the final expired sample point occurred at a time interval no later than 23 seconds after the start of the rebreathing manoeuvre. The six sampling intervals determined from the carbon dioxide trace were used to obtain six data points from the ln freon^{22} and ln C^{18}O traces. The slope of a straight line plotted through the six data points represents the rate constant of decline in concentration (termed *k*) for the gas in question. Following determination of *k*, estimated values for the effective pulmonary blood flow and diffusing capacity of the lungs for carbon monoxide were calculated, in accordance with formulas described by Sackner (1987) and Cotes (1975), respectively.

The MAP and heart rate data were averaged over a 30-second period extending from 80 seconds following the start of each experimental condition. The data obtained from 45mmHg PPB experimental conditions (including the associated control condition) were separated from the data obtained from the 60mmHg PPB experimental conditions to form two distinct data sets. The mean values for heart rate, MAP, effective pulmonary blood flow, and diffusing capacity of the lungs for carbon monoxide in each data set were subsequently analysed using a single factor (FCAGT inflation pressure) analysis of variance with repeated measures. A significance level of $p<0.05$ was adopted as the cut-off point for all main effects. Where any main effects were identified, post-hoc tests (Newman Keuls) were used to identify which PPB experimental conditions differed from each other. A Dunnet's multiple pairwise comparison test analysed differences between PPB experimental conditions and the control condition.

Results

Phase 1

All experimental exposures were completed without untoward incident, with no evidence of pre-syncopal symptoms during any of the PPB exposures.

Cerebral Blood Velocity

Cerebral blood velocity during 45mmHg and 70mmHg PPB was significantly lower than cerebral blood velocity during the control condition, at all FCAGT inflation pressures. The level of FCAGT inflation pressure had no significant effect on the observed decrease in cerebral blood velocity during PPB. Figures 1 and 2 illustrate the cerebral blood velocity measured during 45mmHg PPB and 70mmHg PPB and associated control conditions.

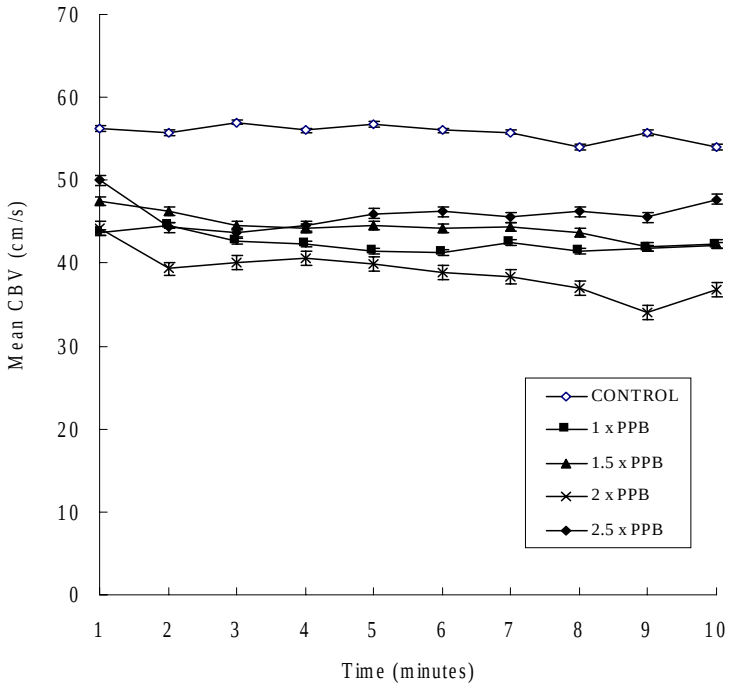

Figure 1: ***Cerebral blood velocity [mean (n=6) 6 SEM] during control condition and during 45mmHg PPB with FCAGTs inflated to various multiples of PPB pressure***

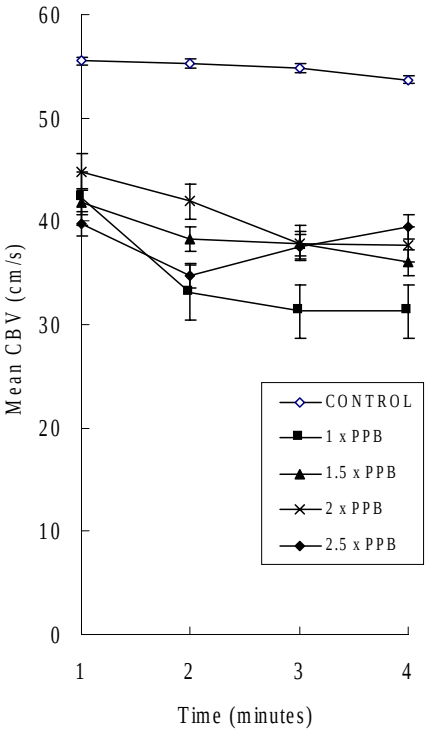

Figure 2: ***Cerebral blood velocity [mean (n=6) 6 SEM] during control condition and during 70mmHg PPB with FCAGTs inflated to various multiples of PPB pressure***

Heart Rate

Heart rate during 45mmHg and 70mmHg PPB with FCAGTs inflated to a pressure equal to PPB pressure was significantly greater than heart rate recorded during the corresponding control conditions. Heart rate during 45mmHg and 70mmHg PPB with FCAGTs inflated to 1.5 x PPB, 2 x PPB, or 2.5 x PPB was not, however, significantly different to heart rate during the control conditions. In addition, heart rate during the first minute of 45mmHg PPB was significantly lower than heart rate recorded at all other intervals during 45mmHg PPB, irrespective of FCAGT inflation pressure. Figures 3 and 4 illustrate the heart rate measured during 45mmHg and 70mmHg PPB and their associated control conditions.

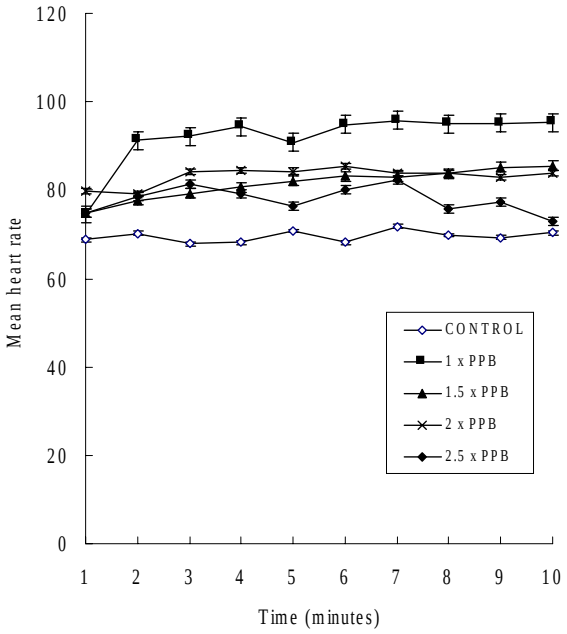

Figure 3: ***Heart rate [mean (n=6) ± SEM] during control condition and during 45mmHg PPB with FCAGTs inflated to various multiples of PPB pressure***

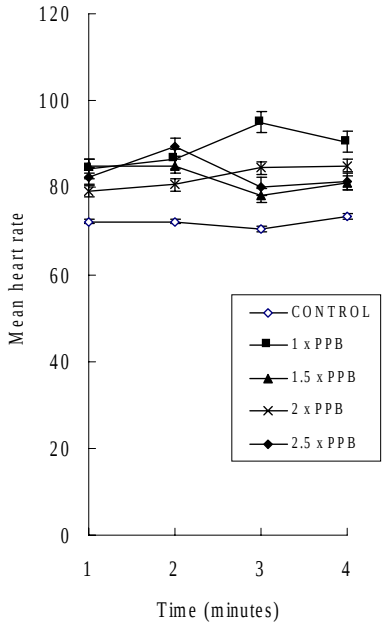

Figure 4: ***Heart rate [mean (n=6) ± SEM] during control condition and during 70mmHg PPB with FCAGTs inflated to various multiples of PPB pressure***

Alveolar Carbon Dioxide Tension

Alveolar carbon dioxide tension ($PACO_2$) during 45mmHg and 70mmHg PPB was significantly lower than $PACO_2$ during the control condition, at all FCAGT inflation pressures. During 70mmHg PPB with FCAGTs inflated to a pressure equal to PPB pressure, $PACO_2$ was significantly lower than the $PACO_2$ during 70mmHg PPB at all other FCAGT inflation pressures. In addition, $PACO_2$ during the first minute of 45mmHg and 70mmHg PPB was significantly lower than $PACO_2$ recorded at all other intervals during PPB, irrespective of FCAGT inflation pressure. Figures 5 and 6 show the $PACO_2$ measured during 45mmHg and 70mmHg PPB and their associated control conditions.

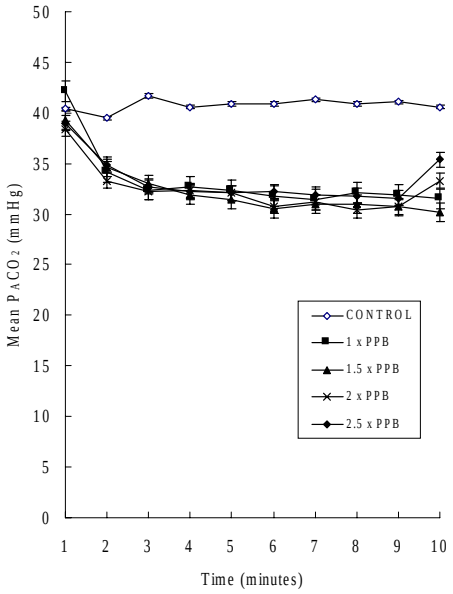

Figure 5: ***Alveolar carbon dioxide tension [mean (n=6) ± SEM] during control condition and during 45mmHg PPB with FCAGTs inflated to various multiples of PPB pressure***

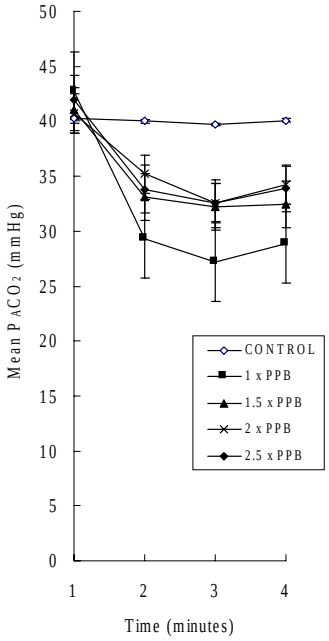

Figure 6: ***Alveolar carbon dioxide tension [mean (n=6) ± SEM] during control condition and during 70mmHg PPB with FCAGTs inflated to various multiples of PPB pressure***

Mean Arterial Pressure

Mean arterial pressure (MAP) recorded during 45mmHg and 70mmHg PPB was significantly greater than MAP recorded during control conditions, irrespective of FCAGT inflation pressure. The level of FCAGT inflation pressure had no significant effect on the observed increase in MAP during PPB. Figures 7 and 8 illustrate the MAP measured during 45mmHg PPB and 70mmHg PPB and associated control conditions.

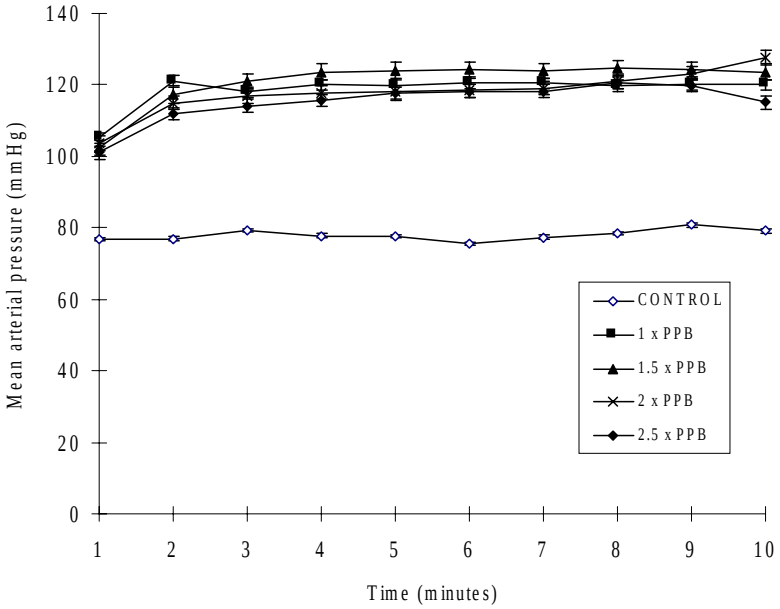

Figure 7: ***Mean arterial pressure [mean (n=6) ± SEM] during control condition and during 45mmHg PPB with FCAGTs inflated to various multiples of PPB pressure***

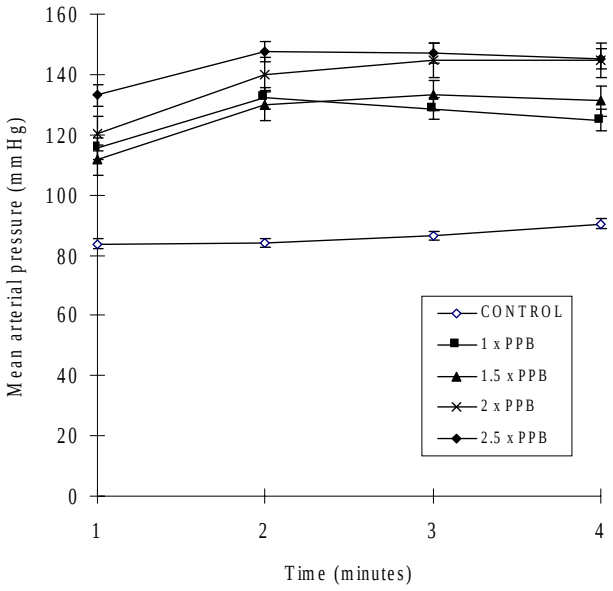

Figure 8: ***Mean arterial pressure [mean (n=6) ± SEM] during control condition and during 70mmHg PPB with FCAGTs inflated to various multiples of PPB pressure***

Phase 2

All experimental exposures were completed without untoward incident. Six subjects contributed heart rate and blood pressure data at the 45mmHg and 60mmHg positive pressure breathing (PPB) levels. Rebreathing data analysis revealed that two subjects, however, were unable to achieve a reliable mask seal whilst rebreathing during PPB, as evidenced by careful examination of mask cavity pressure records. Therefore, the rebreathing based data included in the statistical analysis were derived from only four subjects.

The diffusing capacity of the lungs for carbon monoxide ($D\mathrm{l}_{CO}$) data were transformed into diffusion coefficients for carbon monoxide (K_{CO}), an expression of $D\mathrm{l}_{CO}$ per litre of alveolar volume. The rebreathing lung volume during PPB was greater than rebreathing lung volume in the control condition, due to an increased residual lung volume (RV) during PPB. The $D\mathrm{l}_{CO}$ has been demonstrated to increase when measured at increased lung volumes (Stam, Hrachovina, Stijnen, and Versprille, 1994) and therefore, transformation of the data into diffusion coefficients prevented erroneous comparisons between $D\mathrm{l}_{CO}$ measured during PPB and $D\mathrm{l}_{CO}$ measured during the control condition.

Effective pulmonary blood flow

The effective pulmonary blood flow measured during PPB was not significantly different to the effective pulmonary blood flow recorded during the control condition, irrespective of FCAGT inflation pressure. Mean effective pulmonary blood flow during 45mmHg PPB is shown in figure 9; the results obtained during 60mmHg PPB are shown in figure 10.

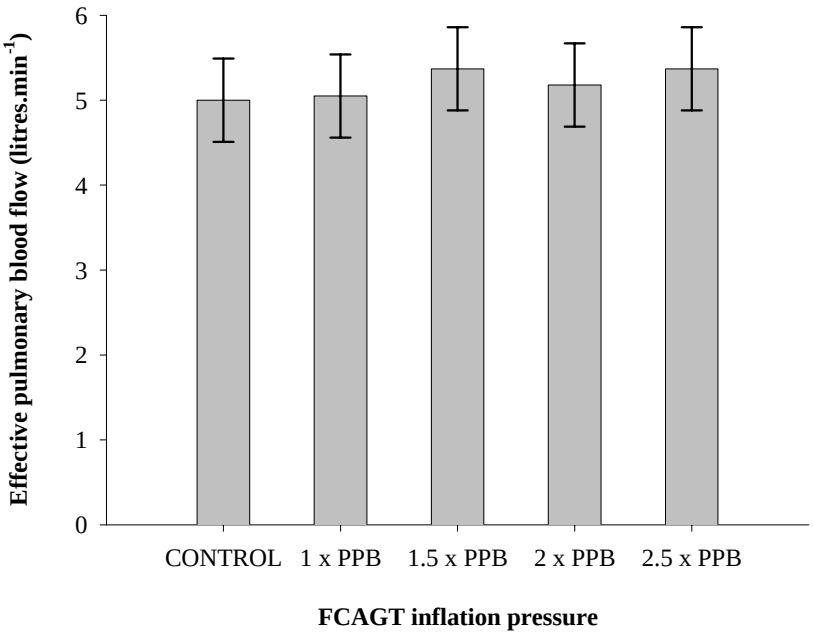

Figure 9: ***Effective pulmonary blood flow [mean (n=4) 6 SEM] during control and during 45mmHg PPB with FCAGTs inflated to various multiples of PPB pressure***

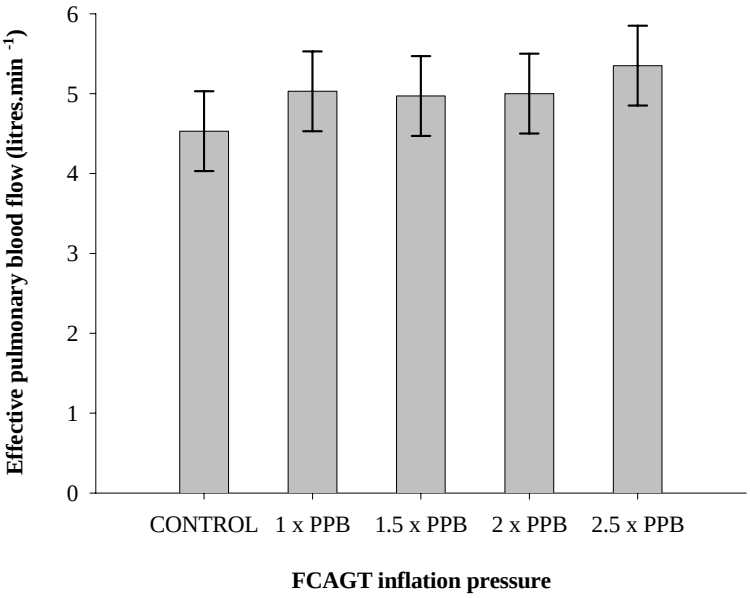

Figure 10: ***Effective pulmonary blood flow [mean (n=4) 6 SEM] during control and during 60mmHg PPB with FCAGTs inflated to various multiples of PPB pressure***

Diffusion Coefficient

The diffusion coefficient measured during PPB was not significantly different to the diffusion coefficient recorded during the control condition, irrespective of FCAGT inflation pressure. Mean diffusion coefficient during 45mmHg PPB is shown in figure 11; the results obtained during 60mmHg PPB are shown in figure 12.

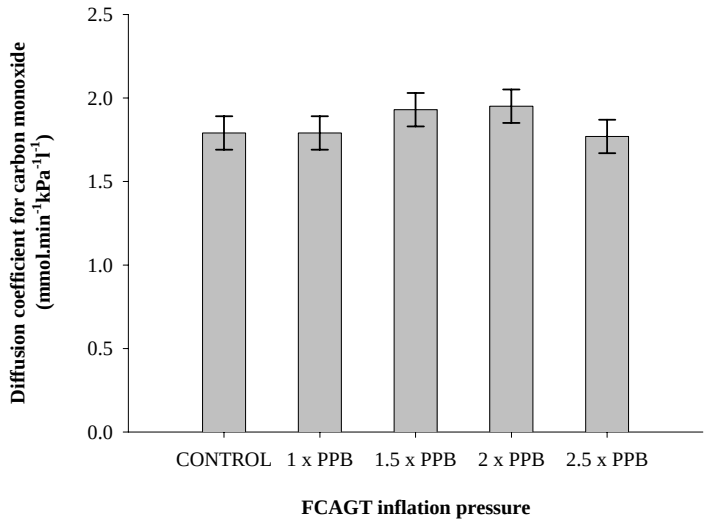

Figure 11: ***Diffusion coefficient for carbon monoxide [mean (n=4) 6 SEM] during control and during 45mmHg PPB with FCAGTs inflated to various multiples of PPB pressure***

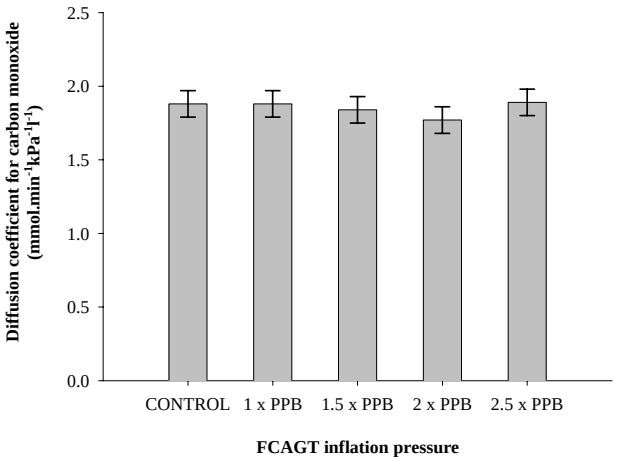

Figure 12: ***Diffusion coefficient for carbon monoxide [mean (n=4) ± SEM] during control and during 60mmHg PPB with FCAGTs inflated to various multiples of PPB pressure***

Heart rate

Heart rate measured during 45mmHg PPB with FCAGTs inflated to the same pressure as PPB pressure was significantly greater than heart rate recorded during the control condition ($p<0.05$). Heart rate during 45mmHg with FCAGTs inflated to 1.5 x PPB, 2 x PPB, or 2.5 x PPB was not, however, significantly different to heart rate during the control condition.

Heart rate measured during 60mmHg PPB with FCAGTs inflated to a pressure equal to PPB pressure was significantly greater than heart rate during the control condition ($p<0.01$). Heart rate during 45mmHg with FCAGTs inflated to 1.5 x PPB, 2 x PPB, or 2.5 x PPB was not, however, significantly different to heart rate during the control condition. In addition, heart rate during 60mmHg PPB with FCAGTs inflated to a pressure equal to PPB pressure was significantly greater than heart rate during 60mmHg PPB at all other FCAGT inflation pressures ($p<0.05$). Mean heart rate during experimental conditions at 45mmHg PPB and at 60mmHg PPB are shown in figures 13 and 14, respectively.

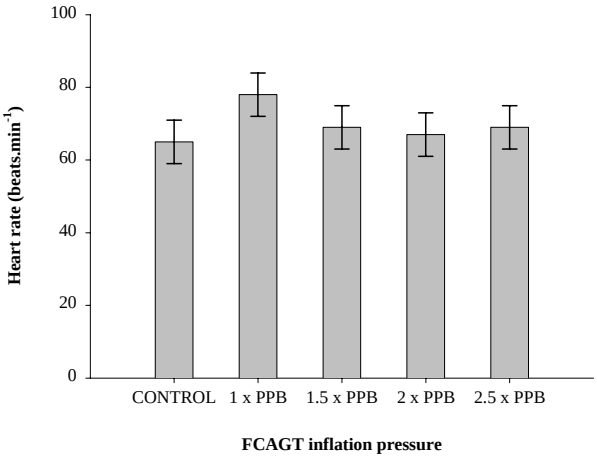

Figure 13: ***Heart rate [mean (n=4) ± SEM] during control and during 45mmHg PPB with FCAGTs inflated to various multiples of PPB pressure***

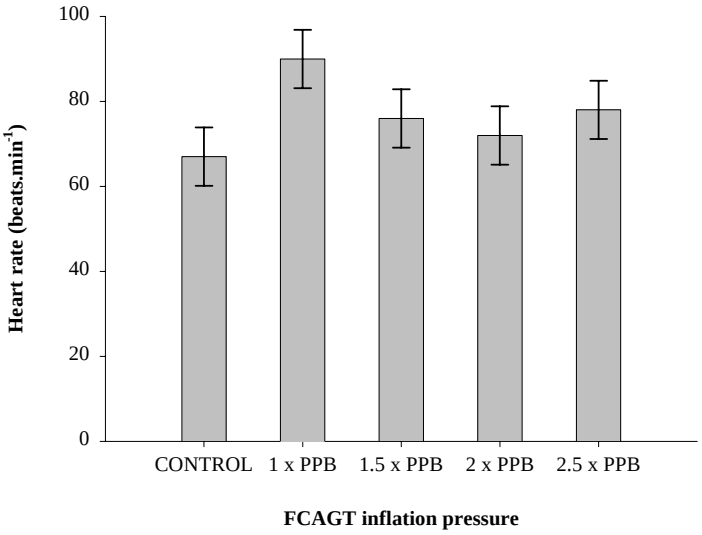

Figure 14: ***Heart rate [mean (n=4) ϭ SEM] during control and during 60mmHg PPB with FCAGTs inflated to various multiples of PPB pressure***

Mean Arterial Pressure

At both PPB levels, mean arterial pressure measured during PPB at all FCAGT inflation pressures was significantly greater than mean arterial pressure during the control condition ($p<0.01$).

Mean arterial pressure during the different experimental conditions conducted at 45mmHg PPB is shown in figure 15; the results obtained during experimental conditions at 60mmHg PPB are shown in figure 16.

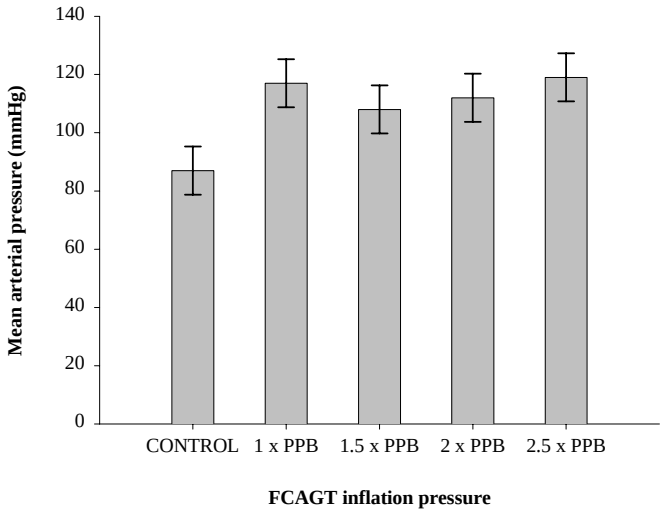

Figure 15: ***Mean arterial pressure [mean (n=6) ϭ SEM] during control condition and during 45mmHg PPB with FCAGTs inflated to various multiples of PPB pressure***

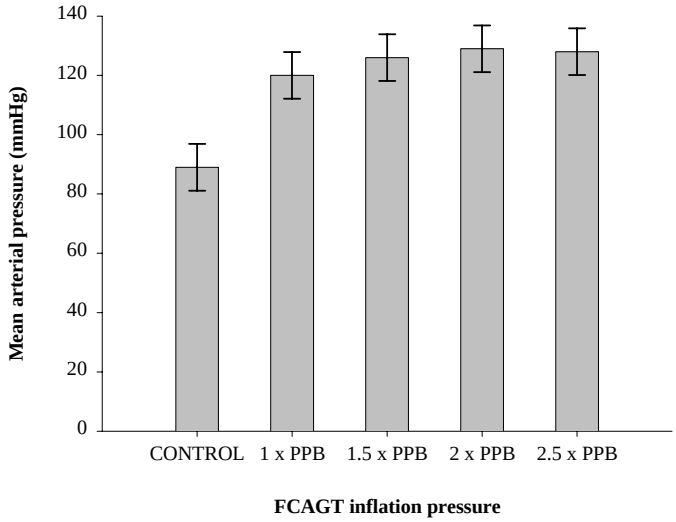

Figure 16: ***Mean arterial pressure [mean (n=6) ϭ SEM] during control condition and during 45mmHg PPB with FCAGTs inflated to various multiples of PPB pressure***

Discussion

This study aimed to investigate some of the physiological effects of positive pressure breathing (PPB) in subjects wearing a counter pressure assembly that incorporated full coverage anti-G trousers (FCAGTs) inflated to various multiples of positive breathing pressures. The results of the study show that FCAGTs inflated to 1.5, 2, or 2.5 times PPB pressure facilitated maintenance of near-normal heart rate during 45mmHg, 60mmHg, and 70mmHg PPB, in addition to near-normal effective pulmonary blood flow and diffusing capacity of the lungs for carbon monoxide during 45mmHg and 60mmHg PPB (see Figures 3, 4, 13, 14, 9, 10, 11, and 12). In contrast, during PPB conditions where FCAGTs were inflated to the same pressure as PPB, heart rate increased above control levels (see Figures 3, 4, 13, and 14). In addition, cerebral blood velocity (CBV) and alveolar carbon dioxide tension ($PACO_2$) during 45mmHg and 70mmHg PPB were consistently lower than CBV and $PACO_2$ measured during control conditions (see Figures 1, 2, 5, and 6), irrespective of FCAGT inflation pressure.

The Effect of Positive Pressure Breathing on Heart Rate and Blood Pressure

The increase in heart rate during PPB when FCAGTs were inflated to the same pressure as the PPB gas indicates that normal cardiovascular function was compromised under these conditions. Data from the four subjects who successfully completed rebreathing manoeuvres during PPB suggest that the effective pulmonary blood flow was unchanged during all PPB conditions, compared to that measured during the control conditions (see Figures 9 and 10). The effective pulmonary blood flow is a direct correlate of cardiac output since, during any period of time, the output from the left side of the heart – the cardiac output – must equal the output of the right side of the heart – the effective pulmonary blood flow plus anatomical and physiological shunts via non-ventilated regions within the lungs. Thus, these findings suggest that stroke volume was compromised during PPB when FCAGTs were inflated to a pressure equal to PPB pressure.

Several investigators have illuminated the mechanism underlying an increase in heart rate during PPB. Ernsting (1966) measured intra-esophegal pressure during PPB to demonstrate that a proportion of the increased airway pressure was transmitted to the intrathoracic cavity - the proportion of airway pressure transmitted to the intrathoracic cavity being dependent on the degree of lung distension induced by PPB. Ernsting demonstrated that the increase in intrathoracic pressure induced by PPB was followed by an increase in peripheral venous pressure, accompanied by an increase in peripheral limb volume, until

peripheral venous pressure equalled intrathoracic pressure. This observation confirmed that PPB induced displacement of blood from the thoracic cavity into the peripheral veins. Direct measurement of a subsequent decline in effective right atrial pressure (right atrial pressure minus intrathoracic pressure) led Ernsting to conclude that the observed increase in heart rate during PPB was a reflex mechanism initiated to maintain cardiac output in the face of a declining venous return. In a later study, Balldin and Wranne (1980) directly measured cardiac output (by the thermodilution method) and effective right atrial pressure during PPB at 30mmHg and 70mmHg. They confirmed that an increase in heart rate during PPB followed a decrease in effective right atrial pressure and a subsequent decline in stroke volume.

Recently, Goodman et al (1994) used radionuclide ventricular cardiography to demonstrate that increased heart rate during PPB was associated with a reduced end-diastolic left ventricular volume and decreased stroke volume. In summary, increased heart rate during PPB occurs subsequent to a fall in venous return, and hence cardiac preload, which results in a reduced stroke volume in accordance with the Starling mechanism.

In the present study, therefore, the observation of an increased heart rate during PPB when FCAGTs were inflated to a pressure equal to PPB pressure suggests that in these conditions, venous return to the heart was compromised. In a recent study, Goodman et al (1995) also observed that FCAGTs inflated to the same pressure as the PPB pressure were similarly unable to facilitate maintenance of normal heart rate during PPB. In addition, Goodman et al demonstrated that the increase in heart rate during these conditions was attributable to a reduction in end diastolic left ventricular volume and a subsequent fall in stroke volume. Therefore, it is likely that FCAGTs inflated to the same pressure as PPB pressure do not completely prevent accumulation of blood displaced from the thorax at the onset of PPB in the veins of the lower limbs. Thus, increasing the extent of lower body surface area bladder coverage alone is not sufficient to abolish the adverse cardiovascular effects of PPB observed in previous studies that employed standard coverage garments inflated a pressure equal to PPB pressure (Ernsting, 1966; Ackles et al, 1978).

When FCAGT inflation pressure equalled 1.5 times, 2 times, or 2.5 times PPB pressure, heart rate during 45mmHg, 60mmHg, and 70mmHg PPB was not significantly different to heart rate during the control condition (see Figures 3, 4, 13, and 14). Presumably, increasing FCAGT inflation pressure in excess of PPB pressure reduces the compliance of the veins within the lower limbs, via an increase in local tissue pressure. Therefore, during PPB, a peripheral to central venous pressure gradient can be restored without a significant increase in the volume of blood contained within the lower limb veins, thus preventing a decrease in circulating blood volume. The findings of the present study support the results of a recent investigation that showed that normal cardiovascular function during 70mmHg PPB can be facilitated by a counter pressure assembly incorporating FCAGTs inflated to 2 times PPB pressure (Goodman et al, 1995).

Mean arterial blood pressure was consistently increased from control levels during PPB, irrespective of FCAGT inflation pressure (see Figures 7, 8, 15, and 16). The increase in systemic blood pressure during PPB is a direct effect of increased intrathoracic pressure during PPB, as described earlier.

The control of systemic blood pressure during PPB is complex, and is thought to be influenced by a number of competing factors. In normal conditions, systemic blood pressure is mediated by baroreceptors located in the aortic arch and the carotid artery. These receptors are sensitive to ‘stretch’, and are thus affected by changes in transmural pressure across the walls of the vessels in which they are situated. If near normal cardiovascular function is maintained during PPB with counter pressure applied to the thorax, the aortic baroreceptors are not subjected to any change in transmural pressure, as the pressure within the heart and the intrathoracic cavity are increased by the same amount. The carotid baroreceptors, however, are located in an area that is not covered by counter pressure garments, and hence, they receive a hypertensive stimulus during PPB. Presumably, the carotid baroreceptors exert a vasodilatory influence during PPB, resulting in an overall increase in MAP that is slightly lower than the increase in intrathoracic pressure induced by PPB. This assumption is supported by the observations of Gradwell (1993), who showed that MAP during PPB with equal counterpressure applied to the thorax *and* neck increases to a level significantly higher than MAP during PPB with counter pressure applied to the thorax alone.

In previous studies (Ernsting, 1966; Gradwell, 1993; Goodman et al, 1995), PPB conditions that elicited an increase in heart rate from control conditions have been associated with a lower than expected increase in MAP. Presumably, relatively lower MAP in these conditions is a reflection of the reduction in venous return to the heart and concomitant reduction in stroke volume. Other investigators, however, have reported no significant differences in the MAP response between PPB experimental conditions, even when a significant difference in the heart rate response to different PPB experimental conditions was identified (Ackles et al, 1978).

The Effect of Positive Pressure Breathing on Effective Pulmonary Blood Flow

The effective pulmonary blood flow was maintained at control levels during 45mmHg and 60mmHg PPB, irrespective of FCAGT inflation pressure. When FCAGT inflation pressure equalled PPB pressure, however, the effective pulmonary blood flow was maintained at the expense of an increase in heart rate (see Figures 9, 10, 13, and 14).

The mechanism that initiates a compensatory increase in heart rate if stroke volume is compromised during PPB is poorly understood. In normal conditions, cardiovascular control is largely mediated by inputs to the cardiovascular control centre from arterial and cardiopulmonary baroreceptors that respond to changes in systemic and intrathoracic vascular pressure changes respectively (Victor and Mark, 1976). Thus, in normal conditions, these inputs are complementary, as a decrease in central venous pressure will reduce end diastolic volume, decrease ventricular contractile force in accordance with Starling's mechanism, and hence reduce systemic arterial pressure. Complementary inputs from arterial and cardiopulmonary baroreceptors will initiate a co-ordinated response in these conditions to increase peripheral resistance, heart rate and ventricular contractility to restore systemic arterial pressure (Victor and Mark, 1976).

As described earlier, the carotid baroreceptors sense an increase in transmural pressure during PPB, and would therefore exert a vasodilatory and bradycardic influence on the circulation, in an attempt to reduce peripheral resistance and cardiac output, and hence reduce carotid artery transmural pressure. Presumably, if venous return is decreased during PPB, cardiovascular control centres in the brain must receive additional inputs that override the carotid baroreceptor input, and initiate responses that attempt to facilitate maintenance of cardiac output, via an increase in heart rate and/or ventricular contractile force. The site of the receptors responsible for these inputs must reside in the intrathoracic cavity, probably within the heart itself or the pulmonary circulation, and these inputs must respond to a decrease in central venous pressure or atrial and/or ventricular distension during diastole.

Goodman et al (1994) recently provided evidence of a coordinated compensatory response to cardiovascular insufficiency during PPB. A Radionuclide ventricular cardiography technique has enabled these investigators to demonstrate that a reduction in end diastolic left ventricular volume during 70mmHg PPB is accompanied by an increase in heart rate *and* a decrease in end systolic left ventricular volume, thus providing evidence of an increase in ventricular contractility during PPB, which must be mediated by a compensatory reflex mechanism.

The Effect of Positive Pressure Breathing on Diffusion Coefficient for Carbon Monoxide

The diffusion coefficient for carbon monoxide (K_{CO}) was maintained at control levels during 45mmHg and 60mmHg PPB, irrespective of FCAGT inflation pressure (see Figures 11 and 12). This observation suggests that the capacity for diffusive gas exchange of carbon monoxide between the alveolar gas and the pulmonary capillary blood was not compromised during PPB, at all FCAGT inflation pressures.

The capacity for diffusive gas exchange of carbon monoxide between the alveolar gas and the pulmonary capillary blood is directly correlated with the capacity for diffusive gas exchange of oxygen between the alveolar gas and the pulmonary capillary blood (Piiper et al, 1979). Therefore, in the present study, PPB did not appear to impair the mechanisms that facilitate uptake of oxygen from the alveolar gas by the pulmonary blood – an observation that has particular relevance to the application of PPB as a procedure to prevent hypoxia in the event of cockpit depressurisation at altitudes exceeding 40,000 feet.

In addition, the maintenance of a normal diffusion coefficient for carbon monoxide suggests that PPB had no significant effect on the pulmonary capillary blood volume, at all levels of FCAGT inflation. The authors have adopted the assumption that PPB had no effect on the diffusing capacity of the alveolar capillary membrane – a proposition supported by Ernsting's (1966) measurement of the effects of PPB on the pulmonary capillary blood volume using Roughton and Forster's (1957) method.

The findings of the present study are, in this respect, unexpected. During PPB with FCAGTs inflated to the same pressure as PPB pressure, heart rate was increased from control levels, suggesting a reduction in venous return, and hence a diminution of thoracic blood volume, as described earlier. Presently, there is no adequate explanation for the observed maintenance of pulmonary capillary blood volume in these conditions.

A maintained pulmonary capillary blood volume during PPB with counter pressure has, however, been observed in chronically instrumented dogs (Williams and Horvath, 1959). These investigators observed that reductions in pulmonary capillary blood volume frequently occurred only when the reduction in *total* circulating blood volume was of sufficient severity to depress cardiac output.

Ernsting (1966) observed a decreased pulmonary capillary blood volume during PPB, but there are a number of significant differences between Ernsting's methodology and the methods employed during the present investigation. The subjects in Ernsting's study wore garments that applied counter pressure to the external surfaces of the thorax and abdomen only. These conditions are known to induce a significantly greater displacement of blood from the thorax than that observed during PPB with counter pressure applied to the external surfaces of the thorax, abdomen *and* lower limbs (Ernsting, 1966). In addition, Ernsting employed the breath hold method to measure $D\mathrm{l}_{\mathrm{CO}}$, a method that may reduce cardiac output during the measurement period (Gotshall and Davrath, 1999). Therefore, cardiac output was probably significantly decreased from control values during Ernsting's measures of pulmonary capillary blood volume during PPB.

The Effect of Positive Pressure Breathing on Cerebral Blood Velocity

Initially, observation of near-normal values for a number of cardiovascular variables during 45mmHg and 60mmHg PPB when FCAGTs were inflated to 1.5 times, 2 times, or 2.5 times PPB pressure appears to contradict the observed reduction in cerebral blood velocity during 45mmHg and 70mmHg PPB at the same FCAGT inflation pressures (see Figures 1 and 2). Even in experimental conditions where FCAGT inflation pressure equalled PPB pressure, the observed increase in heart rate was almost certainly sufficient to restore a near-normal cardiac output. Other investigators who have studied the cardiovascular effects of PPB in subjects wearing modern counter pressure assemblies have reported that a moderate increase in heart rate during PPB at, or below, 70mmHg is able to sufficiently compensate for any observed reduction in stroke volume, hence ensuring maintenance of a near-normal cardiac output (Goodman et al, 1994; Goodman et al, 1995).

Therefore, it is unlikely that the observed reduction in cerebral blood velocity during 45mmHg and 70mmHg PPB seen in the present study was caused by cardiovascular insufficiency induced by PPB itself. The consistently lowered alveolar carbon dioxide tension observed during all PPB experimental conditions in the present study (see Figures 5 and 6) is, therefore, probably responsible for a large proportion of the decrease in cerebral blood velocity during PPB. A reduction in alveolar carbon dioxide tension during PPB occurs as a result of hyperventilation, even in subjects with considerable experience of PPB (Ernsting, 1966).

The significance of hyperventilation during PPB, and the associated hypocapnia, lies in the effect of a reduction in arterial carbon dioxide tension on the cerebral circulation. Hypocapnia is known to reduce cerebral blood flow (Kety and Schmidt, 1948; Markwalder, Grolimund, Seiler, Roth, and Aaslid, 1984), presumably via vasoconstriction in the cerebral circulation. Therefore, the observed decrease in CBV during PPB in the present study may have been entirely attributable to the effects of hyperventilation induced by PPB.

Determination of the Most Effective FCAGT Inflation Pressure for use during Positive Pressure Breathing for Altitude Protection

The findings of the present study suggest that FCAGTs inflated to 1.5 times, 2 times, or 2.5 times PPB pressure are able to facilitate maintenance of near-normal physiological function during 45mmHg, 60mmHg and 70mmHg PPB. In addition, the physiological responses to PPB with FCAGTs inflated to 1.5 times PPB pressure did not significantly differ to the responses observed during PPB with FCAGTs inflated to 2 times or 2.5 times PPB pressure. Therefore, if discomfort and mobility problems are to be minimised, a FCAGT inflation pressure of 1.5 times PPB pressure would appear to be the most effective solution for use during PPB for altitude protection.

Conclusions

The results of the present study suggest that FCAGTs inflated to equal PPB pressure are incapable of facilitating maintenance of near normal cardiovascular function during 45mmHg, 60mmHg, and 70mmHg PPB. Increasing the FCAGT inflation pressure to 1.5 times, 2 times, or 2.5 times PPB pressure is, however, sufficient to abolish some of the adverse effects of 45mmHg, 60mmHg, and 70mmHg PPB observed when FCAGTs are inflated to a pressure equal to PPB pressure.

The observed reduction in cerebral blood velocity during 45mmHg and 70mmHg PPB is probably a direct result of hypocapnia caused by the hyperventilation induced by PPB. The practical significance of decreased CBV during PPB for altitude protection cannot be fully assessed until the effects of PPB when combined with a hypoxic stress on CBV are accurately determined.

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Decompression Sickness, Extravehicular Activities, and Nitrogen Induced Osmosis: Brian Hills Revisited

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Decompression sickness has been recognized as an environmental and occupational illness for over 100 years, yet we still today are trying to find ways to minimize its effects or prevent the illness altogether. As the International Space Station is being built over the coming years, new challenges arise in attempting to manage the demands of physical labor in space without producing decompression sickness. The etiology of decompression sickness has evolved over the past century from Boyle and Bert to Haldane to many of those reading this article. Oftentimes, it is interesting to return to earlier work and research and see how it may apply to today's problems. The purpose of this paper is to take a historical perspective on one researcher of yesteryear, Dr. Brian Hills. It is not to advocate any changes in decompression sickness preventive measures.

First of all, who was Brian Hills? An Australian electrical engineer, he became a physiology researcher who studied the biological mechanisms of DCS during the 1960s and 1970s at Duke University and the University of Texas Medical Branch, Galveston. His work contributed to research programs at the Ministry of Defence, the US Navy, and the US Air Force to name a few. A prolific writer, he was the primary author of over 50 published scientific papers in addition to texts.

One text in particular is entitled Decompression Sickness: the Biophysical Basis of Prevention and Treatment (1977). In this text he developed elaborate mathematical model of DCS based on thermodynamics that was the result of many of his bench level studies. In it, he elaborates on many principals, some of which today are obvious. These include:

1. The primary event and the critical insult in producing symptoms of DCS do not coincide.
2. The primary event is the activation of one or more of a reservoir of nuclei normally present in tissue into growth and hence the inception of a stable gaseous phase.
3. Gas separates from solution in extravascular sites and in static blood.
4. Limb bends are determined by pressure distorting nerve endings and are more dependent upon the gas volume separated from solution.
5. No more than one anatomical type needs to be involved in marginal cases of limb bends.
6. Much larger volumes of gas are deposited in fatty tissues and can be released into the venous system as bubbles which remain asymptomatic unless they fail to be trapped by the lungs.

Less known is a hypothesis that he developed: gas induced osmosis influences the distribution of body water. In this hypothesis, Hills preformed an elaborate experiment that demonstrated that the differential in the concentrations of gases induces osmosis across gross tissue sections. Transient gradients of inert gases are caused by a change in pressure or in the concentration of the breathing mixture. A decompression will allow maintenance of extravascular inert gas concentrations resulting in an osmotic shift of water out of the blood and into the cell or extravascular space. This further distorts the tissue and exacerbates the gas phase effects seen symptomatically. In other words, for short periods following the start of a rapid change in pressure, there can be substantial differentials in gas concentrations between blood and tissue, not necessarily across the capillary wall, but across more remote diffusion barriers such as the cell membrane. The imminence of limb bends depends

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upon the local pressure differential to bend a nerve ending which, in turn, is largely determined by the maximum volume of gas which can separate from solution in a unit volume of tissue. During a saturation state decompression, where there is a large reservoir of inert gas deep in tissue, this gas could exert a significant osmotic pressure tending to pull water out of the blood and so increase the tissue fluid pressure. Hills noted that regarding general fluid shifts, a reduction of extravascular fluid pressure is likely to decrease the threshold and even reverse a marginal bend. This he demonstrated clinically by administering low molecular weight dextran. Hills used the gas induced osmosis phenomenon to hypothesize the etiology of dry joints in extreme depth diving, the narcotic effect of the noble gases, and aseptic bone necrosis in diving.

It is not a surprise that DCS is a concern in both diving and EVAs. There are unique differences and concerns in the microgravity environment compared to the fluid environment. These include space adaptation syndrome, fluid shifts, and bone loss. There will be a considerable increase in the number of extravehicular activities expected to occur with the advent of International Space Station (ISS) construction. In turn, the likelihood of a decompression sickness case to occur increases proportionally. It brings up the important issues of how to treat a decompression sickness case versus a mission interruption and possible deorbit. What are ways to prevent or decrease the probability of decompression sickness from occurring? One question not asked is will it occur at all? Since the advent of space missions, no case of decompression sickness has been publicly acknowledged by US or former Soviet authorities. There have been occasional complaints of transient joint pains during EVAs while working, but these have been attributed to cramping or suit mechanical pressure and spontaneously resolved. There was an alleged pain only bends during a moon walk excursion. Is there a plausible explanation?

Thus far, what we are doing to prevent DCS seems to be working although we would all agree that it is probably only a mater of time before a case occurs. Decompression sickness preventive measures have been discussed at this meeting and include optimized pre-breathing schedules, exercise in general as well as potentially during the pre-breathing period, and overall fitness. Most of our data are based on earthbound experience and experiments. How does the microgravity environment change this, if anything? Could the microgravity environment be protective for decompression sickness? Current theories contend that adynamia or the lack of joint stress in the microenvironment versus gravity is a factor. Another is that the effect of weightlessness on the return blood flow from peripheral tissues improves denitrogenation and therefore decreases decompression sickness while in space. But does Hills' work also apply?

It is common knowledge that there is a fluid shift and diuresis over first 48 hours as the body equalizes fluid pressure levels. According to Hills', theory, this relative extravascular tissue water loss allows compensatory volume for osmosis of water into tissues and even larger gas phase bubbles during EVA decompression without producing symptoms due to nerve ending distortion. That is, the extravascular space, being decreased from the fluid shift, can now accommodate a bubble that would have to grow sufficiently large before exerting a nerve ending effect that would be symptomatic. It should be remembered that bubbles are present in the vasculature and tissues well before symptoms present, if at all.

If this is true, can we facilitate this protective effect in the event of an emergency before the 48 hour fluid shift has occurred? This brings us to a what was coined the "Smart Body Hypothesis" at the International Congress of Aviation and Space Medicine in 1985. Simply, the hypothesis states that a body when exposed to a changed environment will adapt such that it will optimize its function within the new environment. Facilitating the expected end point will also modify transient effects seen during the adaptation. Hence, if we can get to the endpoint faster, then we would reach this protective state sooner. One could probably facilitate the fluid shift end point by administering 50 mg of hydrochlorothiazide upon orbit insertion. This is one of the first diuretics approved for the control of high blood pressure in aviators. This may allow for an emergency EVA with decreased DCS probability after the medication induced diuresis. In addition, it may decrease or eliminate space adaptation syndrome symptoms as the transient fluid shifts play a part in this condition.

As a corollary, what about the alleged DCS in the man on the moon? If one looks at the physiology occurring, there was always an adaptation period allowed for the moon's gravity. One would have to assume that there would be a fluid shift back into the extravascular space, although of a smaller degree than with earth's gravity. Hence, the excursion on the moon's surface would not have as much protective effect. Considering the workload during these excursions, there would be an increased risk of DCS compared to the microgravity environment.

The work done by Dr Brian Hills may be instrumental in understanding and predicting the extent of decompression sickness seen during extravehicular activities. If his hypothesis on gas induced osmosis is correct, then the microgravity environment of space may actually be protective once the fluid shift has occurred. In addition, there may be an adjunctive mechanism to decrease DCS probability in an emergent event or decrease or eliminate the symptoms of space adaptation syndrome by facilitating fluid shift and diuresis by administering hydrochlorothiazide upon orbit insertion. It should be noted that the authors of this paper recognize the importance to continue preventive measures for decompression sickness in the diving and space environments and future research efforts to decrease DCS incidence. This paper is not intended to discount or ignore standard procedures that are currently in use or will develop in the future.

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Optimizing Denitrogenation for DCS Protection

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Introduction

Altitude decompression sickness (DCS) is caused by gas bubble formation resulting from tissue nitrogen supersaturation during decompression. Altitude DCS symptoms range from joint pain to neurological disfunction and respiratory distress. An important DCS countermeasure, other than adequate cabin pressurization, is prebreathing (preoxygenation), i.e. breathing 100% oxygen before decompression to denitrogenate body fluids and tissues. The inspiration of 100% oxygen excludes nitrogen and sets up a gradient in the tissues to allow tissue nitrogen to diffuse into the capillaries and be transported to the lungs for expiration. The longer this process is continued, the more effective the denitrogenation and the lower the incidence of DCS symptoms. The need for improvements in denitrogenation is driven by modifications in aircraft missions involving reduction or elimination of cabin pressurization, and development of new aircraft designed with pressurization systems that are inadequate to prevent DCS during some mission scenarios which the aircraft are capabile of performing.

Review of AFRL Studies Relevant to Increasing Denitrogenation

From 1-4 hours of prebreathing, the plot of male DCS incidence during a 4-h, 30,000-ft exposure versus prebreathe time is nearly linear (Fig. 1; data from Webb et al., 1996; Webb and Pilmanis, 1998; Webb et al., 1999). Both linear and logarithmic best fit regressions (MSExcel97 trendlines) show less than 10% additional protection for each hour of prebreathing up to four hours. After 4 hours the reduction in prebreathe effectiveness with each passing hour becomes more apparent as the logarithmic plot flattens to show only 80% protection from DCS after more than 12 hours of prebreathe. While we believe the logarithmic regression plot is too conservative, the linear regression plot depiction of a nine-hour preoxygenation as sufficient to provide complete protection from DCS at 30,000 ft (mild exercise) may overstate the effectiveness of resting preoxygenation. However, the difference between the linear and logarithmic plots with greater than 4 hours of preoxygenation is irrelevant due to the impracticability of doing an 8-12 hour prebreathe for NASA or USAF operations due to impact on crew fatigue and scheduling. Thus, alternatives to increases in traditional prebreathe time are of interest.

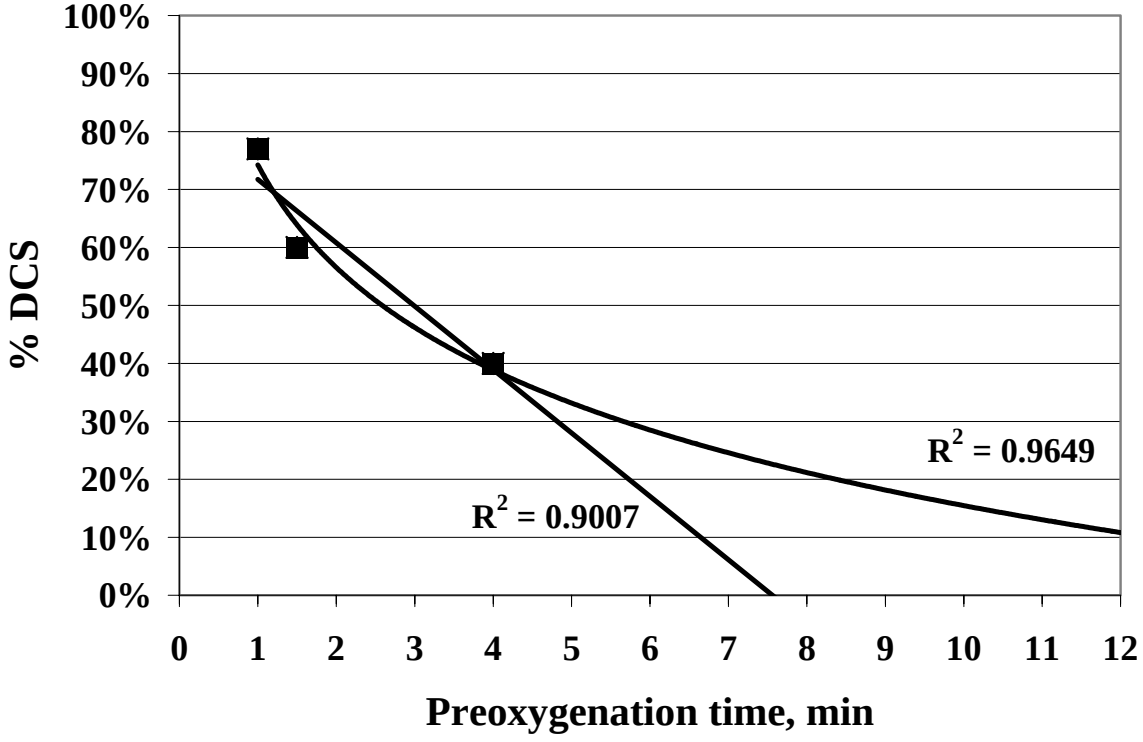

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Figure 1. Preoxygenation Time versus DCS Incidence

Research in the 1950s (Marbarger et al., 1956) showed that breathing 100% oxygen during a leveloff prior to final ascent would provide additional protection relative to a continued ascent; no leveloff. Due to differences in level of symptom severity acceptable today and the advent of non-invasive bubble detection technology, we repeated the work by testing inflight denitrogenation, i.e. staged decompression while breathing 100% oxygen, at altitudes up to 18,000 ft prior to a 4-h exposure to 29,500 ft. The hypothesis was that denitrogenation accomplished at altitude is as effective as prebreathe at ground level, allowing valuable time to be saved by "prebreathing" enroute. Our work demonstrated effective denitrogenation at altitudes up to 16,000 ft prior to a 4-hour, 29,500-ft exposure (Webb et al., In 2000; Fig 2). Due to the high level of venous gas emboli and one case of DCS at an in-flight denitrogenation altitude of 18,000 ft, use of in-flight denitrogenation altitudes above 16,000 ft was not recommended.

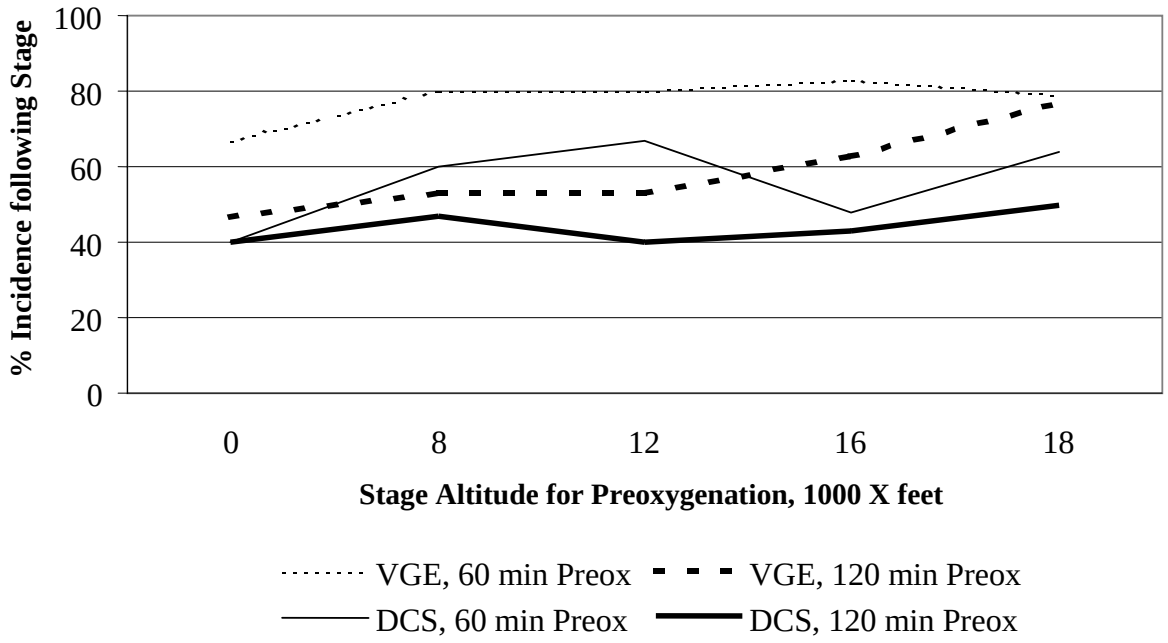

Figure 2. Inflight (Stage) Preoxygenation (Webb et al., 2000)

Another option to increasing prebreathe time is to enhance the effectiveness of prebreathe. This can be accomplished by beginning the prebreathe with 10 min of strenuous exercise, 75% of maximal oxygen uptake, that increases perfusion and ventilation. We demonstrated significant ($P<.03$) reduction in DCS incidence with this method (Webb et al., 1996; Fig. 3) and it has since been successfully tested operationally by one U-2 pilot (Webb, Hankins, and Pilmanis, 1999; Hankins et al., 2000) and incorporated in NASA's program to reduce prebreathe time prior to EVA for International Space Station construction (Gernhardt et al., 2000). Exercise-enhanced prebreathe can be used to reduce DCS incidence without increasing prebreathe time, or to reduce prebreathe time without increasing DCS risk, or, as in our study, achieve a combined reduction of both prebreathe time and incidence (Fig. 3; Webb et al., 1996; Webb and Pilmanis, 1998). Although various exercise devices were used by the U-2 pilot, the exercises all required upper and lower body aerobic exertion which did not cause significant residual fatigue (Hankins et al., 2000; Webb et al., 1999). No further symptoms have been reported by the U-2 pilot to date. However, one high flight involved a rapid response which disallowed use of adequate exercise intensity or duration. The result was DCS tolerated (unreported) for a short period prior to recovery without need for abort due to short duration of the specific mission.

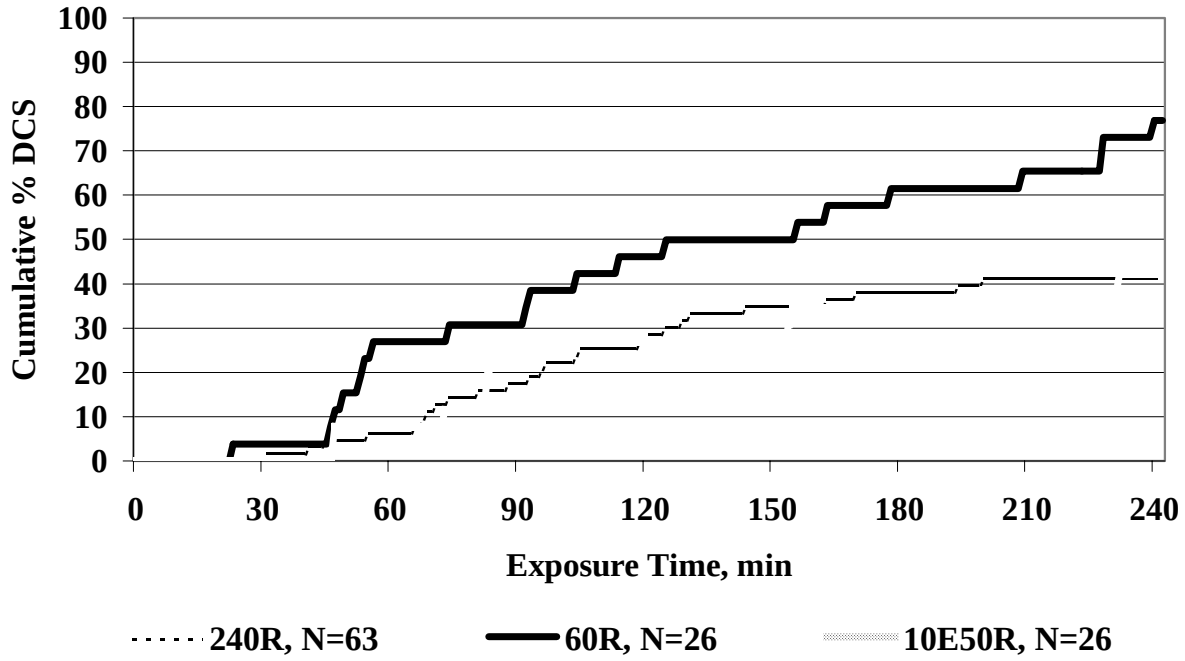

Figure 3. DCS Incidence following Resting Preoxygenation as compared with Exercise-Enhanced Preoxygenation

Comment

Continued efforts to optimize inflight denitrogenation and exercise-enhanced prebreathe should produce mission-compatible means of reducing the risk of DCS without jeopardizing mission effectiveness. These measures do require some time and equipment. The additional time and/or equipment involved with extending or enhancing prebreathe would generally not be necessary to prevent the significant altitude exposures which will be more common with development of aircraft designed with cabin pressurization systems inadequate to prevent DCS.

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Benefit of Acclimatization to Moderate Altitude on Arterial Oxygen Saturation Following Rapid Ascent to 4300 M

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Introduction

During long-term exposures (days-to-weeks) to high altitudes, humans compensate for the decreased inspired oxygen partial pressure (PIO_2) by progressively increasing ventilation (for a review see reference (4,14). For example, following rapid ascent to 4,300 m elevation, ventilation increases during the first 6-8 days (7). The rise in ventilation produces a decrease in arterial carbon dioxide partial pressure ($PaCO_2$) and a concomitant increase in PaO_2 (12).

The time course and magnitude for acquiring altitude acclimatization has been well described for unacclimatized lowlanders rapidly ascending to high altitudes. However, the magnitude of altitude acclimatization developed in lowlanders residing at moderate elevations (1,000 - 2,000 m) has not been well documented. Moreover, there is no comprehensive database that describes the degree to which acclimatization to moderate altitudes improves arterial oxygenation upon rapid ascent to higher altitudes. We propose that lowlanders acclimatized to moderate altitudes will maintain a higher level of arterial oxygenation when rapidly ascending to higher altitudes compared to lowlanders residing a low altitudes.

Numerous military installations housing large numbers of military personnel are located at moderate altitudes. Development of a database that describes the distribution of arterial oxygen saturation in lowlanders acclimatized to a range of moderate altitudes would provide commanders with ascent timetables to higher elevations that take full advantage of the personnel's acclimatization status. Furthermore, current limits on the time that aircrews of unpressurized aircraft may fly above 3,048 m without supplemental oxygen are based on studies of unacclimatized lowlanders. Altitude-acclimatized aircrews may be able to safely operate beyond these limits, thus enhancing operational capability.

The purpose of this study was to determine the distribution of arterial oxygen saturation following rapid ascent to high altitude (4,300 m) in military personnel residing at moderate (~2,000 m) altitude. These data were compared to similar measurements previously collected on men and women residing near sea level.

Materials and Methods

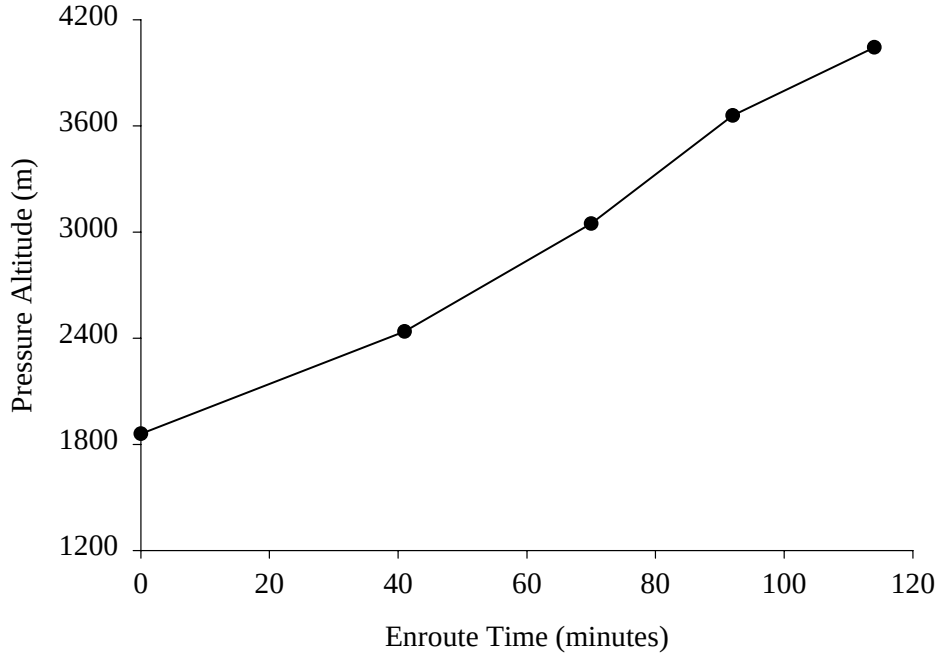
Studies were conducted on 38 military personnel (25 men, 13 women) assigned to the U.S. Air Force Academy (AFA group). All subjects had resided in the Colorado Springs, CO metropolitan area for at least 3 months prior to the study. All the subjects had passed their most recent military physical performance test, and were in good health. Women volunteers tested negative for pregnancy. The subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to U.S. Army Regulation 70-25 on the use of volunteers as subjects of research.

Paper presented at the RTO HFM Symposium on "Operational Medical Issues in Hypo- and Hyperbaric Conditions", held in Toronto, Canada, 16-19 October 2000, and published in RTO MP-062.

On the day of testing, subjects reported to an indoor test site located at the USAFA (terrestrial elevation 2,255 m, pressure altitude 1,860 m). At that site, several test procedures were performed: administration of an Environmental Background Survey and the Environmental Symptoms Questionnaire, and measurement of resting ventilatory parameters and forced vital capacity (FVC). After completion of these procedures, subjects entered a vehicle (van) and were transported to the U.S. Army Pikes Peak Research Facility on the summit (4,300 m terrestrial elevation) of Pikes Peak, CO via the Pikes Peak Highway. The vehicle stopped at the following pressure altitudes according to the prevailing barometric pressure: 2,438 m, 3,048 m, 3,658 m and on the summit 4,043 m. At each stop, the subjects remained in the vehicle at rest for approximately 5 min after which their resting SaO_2 and heart rate were recorded. Upon arriving at the summit, the same 5 min measurements were made after which the subjects entered the U.S. Army Pikes Peak Research Facility. The subject's resting ventilatory parameters were immediately measured. After about 1 h on the summit, the subjects were administered the Environmental Symptoms Questionnaire. The subjects then returned to the USAFA and were released from the study. The ascent profile is illustrated in Figure 1. Between 2,438 and 4,043 m, the average ascent rate was 66 m/min.

For each subject, all testing was completed on one day. The following test procedures were performed. At the USAFA lab, each subject's height and weight were measured. Then each subject completed the Environmental Background Survey (EBS). The EBS is a 57-item questionnaire designed to elicit information on test volunteer's previous experience in stressful climatic conditions in addition to epidemiologic, and medical history data. The presence of hypoxic-induced symptoms (dizziness, shortness of breath, alertness, etc) and the incidence of AMS were determined from information gathered using the Environmental Symptoms Questionnaire (ESQ). The ESQ is a self-reported, 68-question inventory used to document symptoms induced by altitude and other stressful environments (9). A weighted average of scores from cerebral symptoms (headache, lightheaded, dizzy, etc.) designated AMS-C and from respiratory symptoms (short-of-breath, hurts-to-breathe, etc.) designated AMS-R were calculated. AMS-C scores greater than 0.7 and AMS-R scores greater than 0.6 are defined as indicating the presence of AMS (9). Also, an alertness factor was calculated from the questionnaire (9). The ESQ was administered at the USAFA lab prior to starting the ascent and after about 1 hour on the summit.

Figure 1. Ascent profile from USAFA laboratory to U.S. Army Pikes Peak Research Facility. Elapsed time includes a 5 minute stop at each of the 3 intermediate altitudes.



Following completion of the questionnaires, each subject's resting minute ventilation ($\dot{V}E$), and end-tidal oxygen and carbon dioxide partial pressure ($P_{ET}CO_2$ and $P_{ET}O_2$) were measured using an open-circuit metabolic measurement system (SensorMedics Vmax229). Simultaneously, blood oxygen saturation (SaO_2) and heart rate (HR) were measured by pulse oximetry (Nellcor N-200), and blood pressure by auscultation. The subjects were studied after having fasted for at least 2 hr and having been seated at rest for 10 min. Resting ventilation was measured once at the USAFA and once upon arrival on the summit of Pikes Peak. The same measurement system was used to measure the subject's FVC and forced expired volume-1 s (FEV_1) after completing the resting ventilatory measurements at the USAFA.

Resting SaO_2 and heart rate were measured in the vehicle during each 5 min stop along the Pikes Peak Highway at pressure altitudes of 2,438 m, 3,048 m, 3,658 m and 4,043 m. The same finger pulse oximeter described in the resting ventilation studies was used.

Results

All data are reported as the group mean ($\overline{X}$) ± standard deviation (S.D.). The 38 subjects' age, height, weight, FVC and FEV_1 were: 35 ± 8 y, 176 ± 8 cm, 74.9 ± 13.8 kg, 5.1 ± 0.8 l and 4.2 ± 0.7 l. Based on analysis of the EBS, all subjects regularly participated in aerobic physical conditioning and nearly half in strength conditioning.

The resting ventilatory parameters are illustrated in Table 1. At the USAFA test site (1,860 m), $P_{ET}O_2$, $P_{ET}CO_2$ and SaO_2 were significantly ($p<0.05$) lower than normal values reported for lowlanders residing at sea level ($P_{ET}O_2$ 104 mmHg, $P_{ET}CO_2$ 40 mmHg and SaO_2 >96% (5). During the approximately 2 h ascent to 4,043 m, resting SaO_2 progressively decreased (Figure 2). The decrease in SaO_2 with increasing altitude was significant ($p<0.001$) at and above the 3,048 m elevation. There was no significant change in resting HR (Figure 2) during the ascent to 4,043 m.

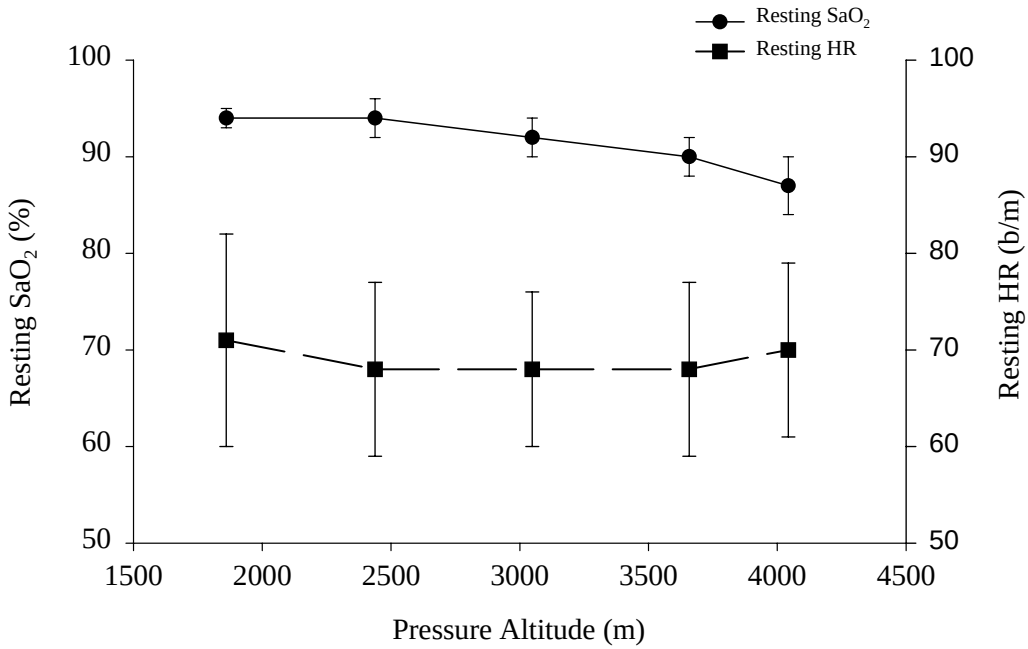
Table 1: Resting ventilatory parameters at residence altitude (USAFA) and during rapid ascent to 4,043 m.

Pressure Altitude (m)	$\dot{V}O_2$ (l/min)	$\dot{V}E$ (BTPS) (l/min)	$P_{ET}O_2$ (mmHg)	$P_{ET}CO_2$ (mmHg)	SaO_2 (%)
1,860	0.296 ± 0.051	10.7 ± 2.3	75.4 ± 4.9	33.6 ± 2.8	94 ± 1
4,043	0.284 ± 0.053	10.5 ± 2.6	51.5 ± 5.7	32.1 ± 4.5	86 ± 2

$\overline{X}$ ± S.D.

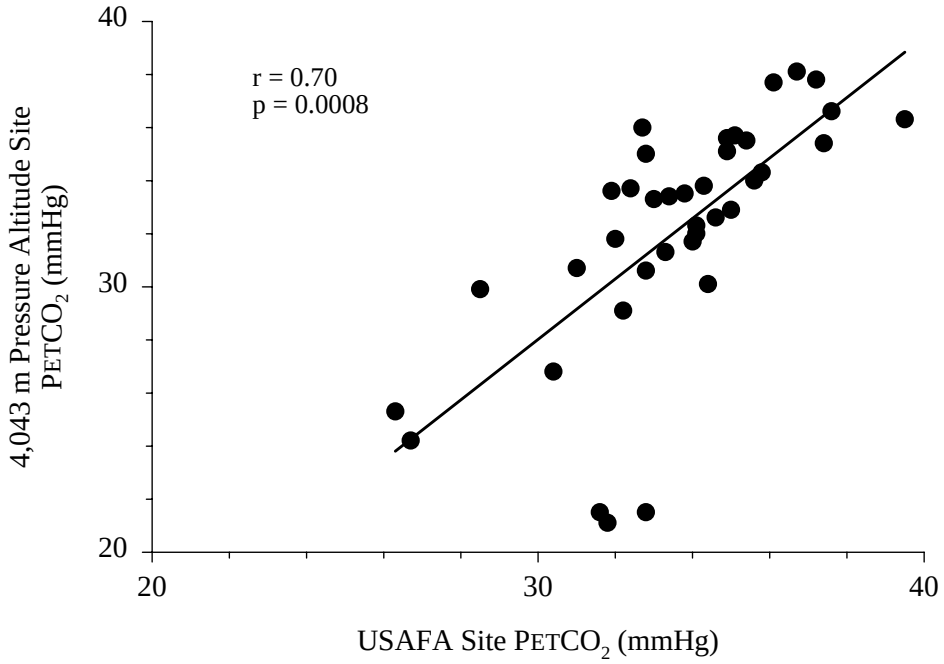
After arrival at 4,043 m, resting $P_{ET}O_2$, $P_{ET}CO_2$ and SaO_2 were significantly ($p<0.001$) lower compared to the measurements made at 1,860 m a few hours earlier (Table 1). The subjects' $P_{ET}CO_2$ at their residence altitude (1,860 m) correlated significantly ($r = 0.70$, $p<0.001$) with their $P_{ET}CO_2$ (Figure 3) and to a lesser degree with their SaO_2 ($r = 0.36$, $p<0.05$) measured at 4,043 m.

Figure 2. Resting SaO_2 and heart rate during vehicular ascent from the USAFA Laboratory to the U.S. Army Pikes Peak Research Facility.



None of the subjects reported ESQ symptom scores indicative of developing Acute Mountain Sickness. There were also no significant changes in the scores for alertness or fatigue following 1 h at 4,043 m.

Figure 3. Relationship between residence altitude resting $P_{ET}CO_2$ and resting $P_{ET}CO_2$ following rapid ascent to 4,043 m pressure altitude.



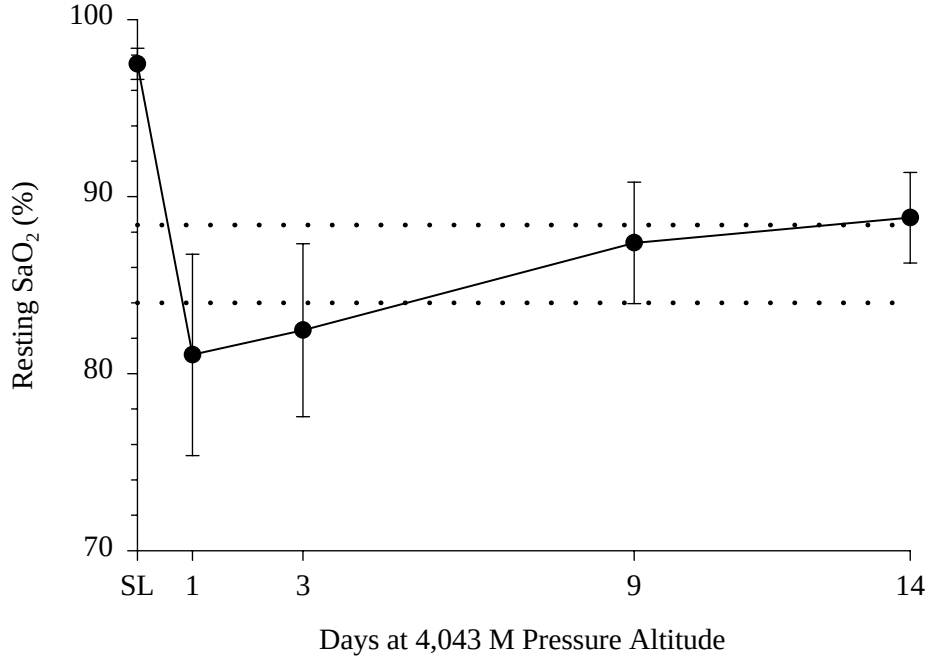
Discussion

This study demonstrated that military personnel residing at moderate altitude (~2,000 m) for greater than 90 days are mildly hypoxic at their residence altitude, and that the interindividual differences in the ventilatory response at higher altitude is related to differences among individuals at their residence altitude.

Previous studies have reported a large variation among individuals in the degree of ventilatory acclimatization at high altitude (10,11). Reeves et al., (8) reported that the variability in the degree of ventilatory acclimatization at high altitude, was related to the individual's sea level end-tidal $P_{ET}CO_2$. That is, the lower the individual's $P_{ET}CO_2$ at sea level, the greater their ventilation at high altitude. The current study extends this relationship to subjects residing a moderate altitude. It is clear that there is considerable inter-individual variability in the acute response to hypoxia, the rate of acclimatization to altitude and the vulnerability to mountain sickness. The latter finding may be potentially useful in predicting an individual's ventilatory response and subsequent well-being to a future high altitude exposure. Our study did not examine the relationship between arterial oxygen content at high altitude and susceptibility to high altitude illness, or physical and cognitive performance decrements. However, it is reasonable to expect that individuals maintaining higher arterial oxygen content will be less affected by the high altitude environment.

Another goal of this study was to determine the extent to which lowlanders acclimatized to moderate altitudes maintain their arterial oxygenation when rapidly ascending to higher altitudes compared to lowlanders residing a low altitudes. Numerous studies have reported the ventilatory response on arrival and during residence on the summit of Pikes Peak (2,3,6,7,13). The results of two of these studies (6,7), and our current study are illustrated in Figure 4. When sea level residents rapidly ascend to a pressure altitude of 4,043 m, on arrival their $P_{ET}CO_2$ is 34.9 ± 2.8 mmHg and their SaO_2 is 81 ± 5%. It takes 9-12 days of continuous residence at high altitude for the SaO_2 to rise to 88 ± 2%. By comparison, upon rapid ascent to 4,043 m, the AFA subjects resting SaO_2 was 86 ± 2%. These data suggest that personnel residing at ~2,000 m elevation for more than 90 days have acquired a level of ventilatory acclimatization equivalent to residing at 4,043 m for a week or more.

Figure 4. The USAFA personnel resting SaO_2 upon arrival to 4,043 m pressure altitude is illustrated by the two dotted-lines representing the mean ± 1 standard deviation. Also shown for comparison is the sea level residents resting SaO_2 upon arrival and the effect of ventilatory acclimatization on SaO_2.



Given the degree of ventilatory acclimatization achieved by personnel residing at the moderate altitude studied, we would expect such personnel to be less susceptible to Acute Mountain Sickness and decrements in cognitive and physical performance during rapid ascent to higher altitudes. Lowlanders who have achieved the level of acclimatization seen in our AFA group usually are not impaired by AMS symptoms, have complete restoration of cognitive performance and substantial improvements in physical work performance (1,14). Thus, we conclude that military personnel residing at moderate altitudes for a period of at least 90 days can be rapidly deployed to higher altitudes of up to 4,043 m with a low probability of developing AMS and experiencing significant performance decrements.

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Physiological and Clinical Findings During Latent Hypoxia in the Hypobaric Chamber

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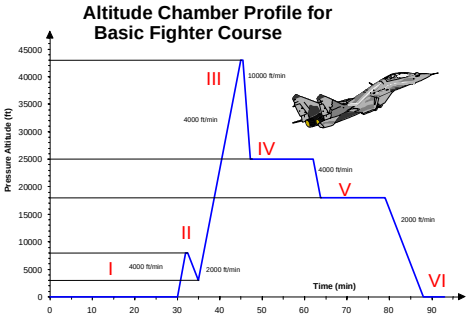
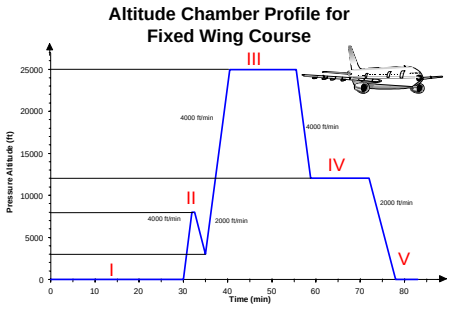
Introduction:

Since 1995 the hypobaric training of aircrew, in accordance with STANAG 3114, is performed in the highly sophisticated air conditioned hypobaric chamber of the German Air Force Institute of Aviation Medicine, Division II at Koenigsbrueck, Germany. It is a main part of overall 150 Physiological Training Courses per year.





Method:

Integrated in well known chamber profiles, demanded in the STANAG 3114, additional exposures in different pressure altitudes can be performed. Routinely six trainees, accompanied by one medical safety attendant, are monitored continuously by ECG, heart rate, breathing cycle, and oxygen saturation during their entire stay in the chamber. They will experience pressure breathing, starting at the pressure altitude of about 28.000 ft during the ascend of the chamber profile. Besides the mandatory demonstration of acute hypoxia at a pressure altitude of 25.000 ft there is a second demonstration of critical hypoxia at a pressure altitude of 18.000 ft for fighter aircrew and of mild hypoxia at 12.000 ft for transport aircrew during hypobaric chamber training.

At a pressure altitude of 25.000 ft, where acute hypoxia occurs, the trainees of basic courses should learn to experience at least one, or two of their personnel oxygen deficiency symptoms. They will have to recognise these symptoms later in the continuation training.

Because of this, it seems to be more important for operational reasons to experience the borderline exposure to hypoxia at the pressure altitude of 18.000 ft. This is the normal pressure altitude in the cockpit of fighter aircraft in flight altitudes above 40.000 ft. Future aircraft will be designed to fly routinely at altitudes up to 50.000 ft or 60.000 ft without full pressure garment. The pressurisation of the cockpit therefore will reach critical low

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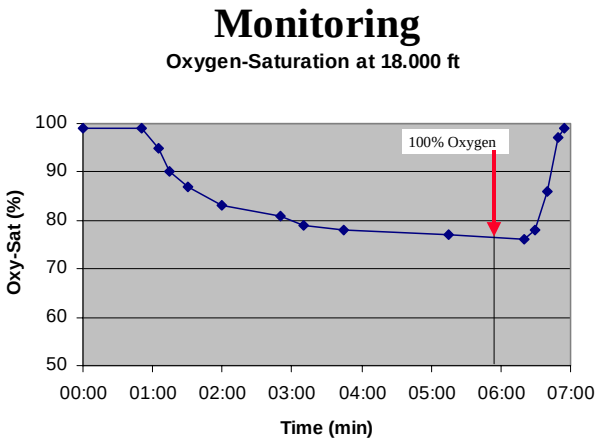
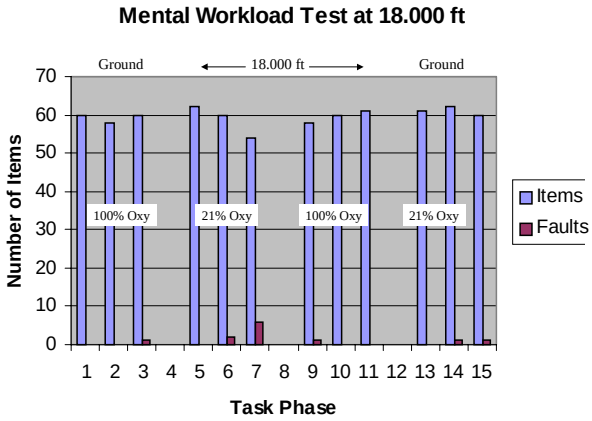
pressure values due to the maximum pressure difference of 5 PSI between the cockpit and the ambient atmosphere. Even short disconnection from the oxygen supply due to poorly fitting masks, leakage in the oxygen delivery system or removal of the oxygen mask will increase the risk of unrecognised hypoxia.

Therefore, in this "normal, operational" maximum cabin pressure altitude trainees perform mental workload tests, simulating normal tasks when flying the aircraft at high altitude, for example during surveillance missions. The mental workload test consists of 3 periods of 90 seconds each, in which the trainees have to calculate numbers. After the introduction and exercise period without data collection during the pre-breathing phase of the chamber training, the first three periods are performed at ground level when breathing 100% oxygen.



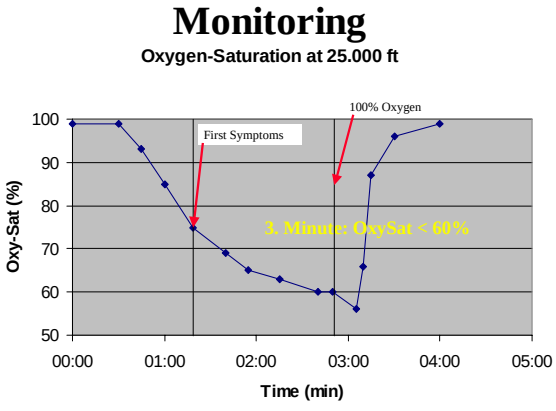


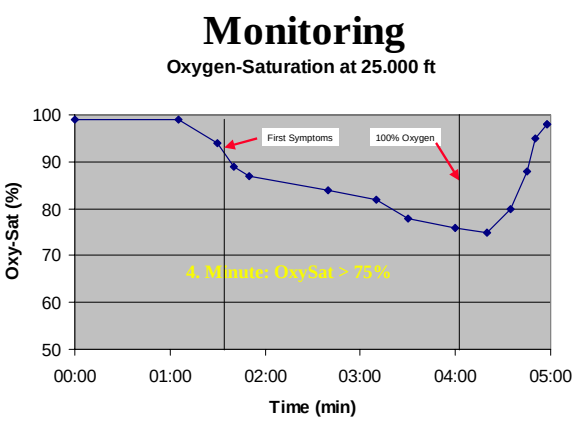
After the demonstration of acute hypoxia at 25.000 ft, the trainees descend to the pressure altitude of 18.000 ft. There they have to disconnect themselves from the oxygen supply. During the following three periods, lasting about five minutes, they are breathing ambient air (21% oxygen). Immediately after the last tasks they experience night vision demonstration in dimmed light, reading low level navigation maps. When connected to the oxygen system and breathing 100% oxygen again, they experience their colour vision deficiencies. In a second sequence they perform the same mental workload, now breathing 100% oxygen, to compare their individual results with the previous test. In addition to the findings of the results of this workload the ECG and the oxygen saturation curve (measured by a pulse oxymeter) will be individually discussed.

Results:

There is a broad variability in physiological responses to the exposure of hypoxia. The reaction of the heart rate varies from

- an ***increase*** up to 50 beats/min within seconds (stress reaction),
- gradual slight ***increase*** (physiological reaction to oxygen deficiency) and
- sudden ***decrease*** of the heart rate (warning symptom of hypoxia-induced loss of consciousness).





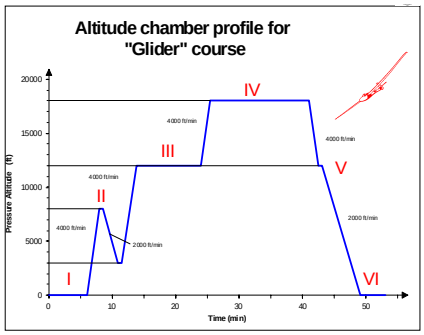
Dependent on gender, body-mass-index, and physical fitness, the time in which the trainees reach a critical oxygen saturation of 70%, varies from 90 seconds up to more than 5 minutes.

The steepness of hypoxia-induced decrease of oxygen saturation, especially during the operational hypoxia exposure at 18.000 ft, might be a symptom not only for individual dispersion but also for latent pathologic reasons. Typically, most of the trainees do not recognise hypoxia symptoms during their hypoxia exposure at 18.000 ft by themselves when distracted by the mental workload tests.

Some trainees re-connect themselves to 100% oxygen supply during the acute hypoxia exposure at a pressure altitude of 25.000 ft within less than 60 seconds, reaching an oxygen saturation level of 90% to 80%. But when distracted by mental workload at the pressure altitude of 18.000 ft breathing ambient air, they often do not feel hypoxia symptoms, although their oxygen saturation went down to 75% to 70%. The typically slower decrease in oxygen saturation might hinder the trainee to identify oxygen deficiency symptoms. During acute hypoxia at a pressure altitude of 25.000 ft an oxygen saturation level of 75% normally will be reached within one minute. While staying at a pressure altitude of 18.000 ft oxygen saturation decreases to 75% normally within 5 minutes. This might be explained by the comparison with the example: During sunset you may read a newspaper down to a very low ambient illumination. This will be recognised immediately after the light is switched on. In the same ambient illumination it might be impossible to read the newspaper, if the light previously was switched on. Human individuals may not recognise slow changes in their environment.

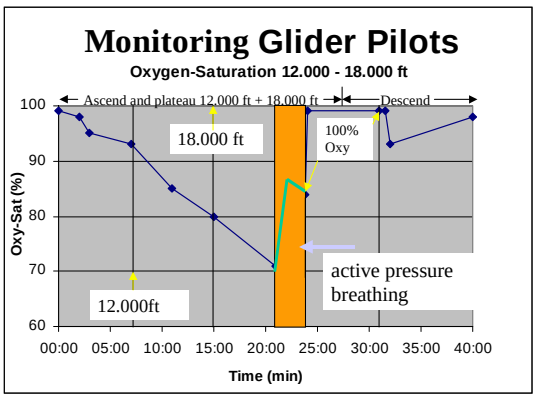
Lesson learned: The training results show the importance of situational awareness, when flying at altitudes, where the cockpit pressure altitude is above 12.000 ft. Situational awareness in this case means: watch your oxygen and cockpit pressure instruments during the cross checks, do not forget the PRICE-check. If this would kept in mind, a fatal accident, like the one of the crashed Lear Jet after a 5 hour ghost flight in October 1999 might have been avoided.

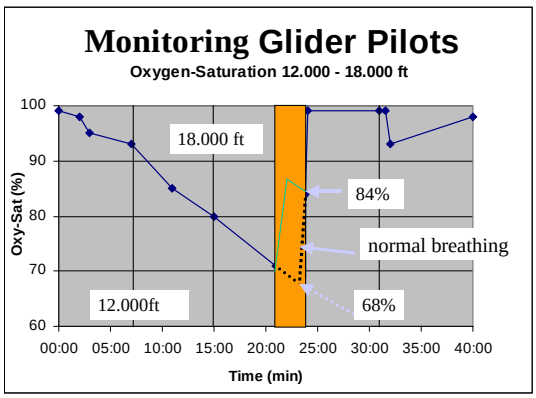
Active positive pressure breathing, performed as M-1 manoeuvre or Valsalva manoeuvre, increases the oxygen



saturation of the blood. The effectiveness of this method can be shown in the following example. At the pressure altitude of 18.000 ft, breathing ambient air (21% oxygen), the trainee reached an oxygen saturation of 70% . With active pressure breathing, the trainee is able to increase his oxygen saturation up to 84%. With this strength consuming breathing technique the evident higher oxygen saturation level can be stabilised up to about 60 seconds.

Without the pressure breathing technique the trainee would have reached 68% oxygen saturation in the same time.





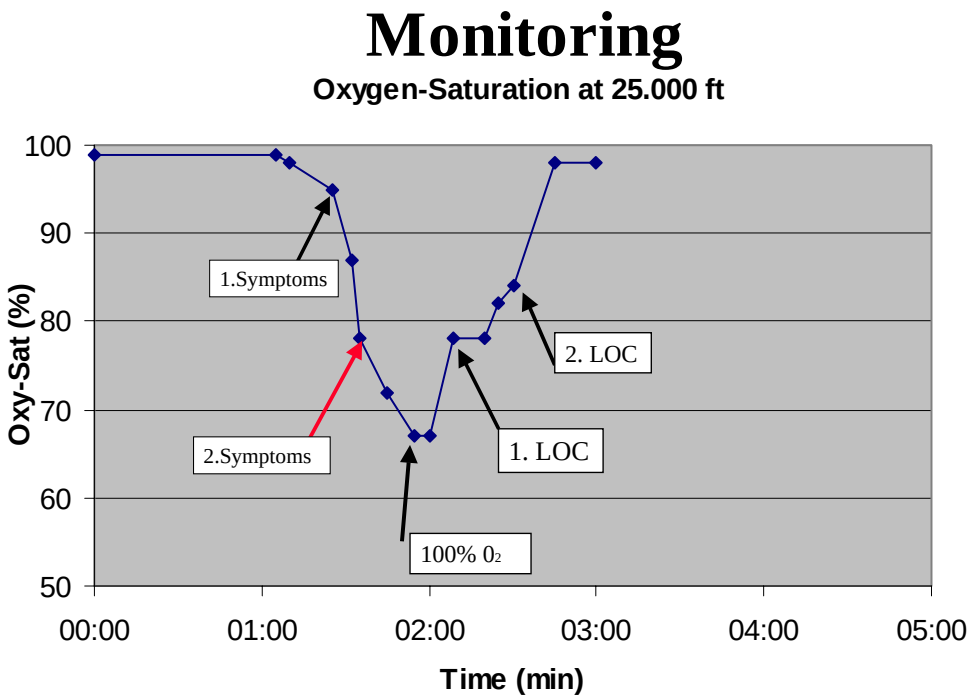
Other experiments showed, that it is important to reach safe pressure altitudes – or connection to a full bottle of oxygen – when performing this pressure breathing technique. We found, that the oxygen saturation of the blood decreases rapidly to a very low saturation level, when the trainee stopped the pressure breathing technique.

Therefore this technique should be used only as an emergency method when flying at high altitudes without sufficient oxygen supply.

Clinical aspects:

In former times - without any medical monitoring during physiological training in an altitude chamber - loss of consciousness occurred more than sporadic. Routinely these episodes were explained as a response to hypoxia only. Now - with the medical monitoring - we are able to differentiate between the reasons for loss of consciousness and even for imminent loss of consciousness.

The examples above underline, that it is an advantage to recognise signs of imminent hypoxia-induced loss of consciousness, even when the monitored oxygen saturation of the blood is greater than 75%. The sudden decrease of the heart rate during hypoxia exposure is a is typical omen of cardiac disturbance, presenting as bradycardia or even asystole.



Conclusion:

Biomonitoring during physiological training is not only helpful for the trainees' feedback by adding objective findings and numbers to subjective symptoms during acute and mild hypoxia, but also helpful for the safety crew of the hypobaric chamber to realise health problems of the trainees early enough.

Last but not least: pathological reactions and monitored findings in cardiac parameters are helpful to decide who should be examined further by a cardiologist. In addition, if for pulmonary reasons grounded aircrew should be cleared again for flying duty (waiver policy), monitored altitude and hypoxia exposure can be used for decision making.

Évaluation d'équipements de protection anti-fumées pour le personnel navigant technique

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RESUME

En cas d'émanations toxiques telles que les fumées dégagées par un feu à bord, les équipages d'avions de transport disposent de matériels de protection contre cette pollution accidentelle ; il s'agit de masques régulateurs à mise en place rapide. Ces masques assurent une protection respiratoire en cas de dépressurisation et aussi une protection anti-fumées. Ces masques sont très souvent associés à des lunettes pour la protection anti-fumées des yeux.

Le masque régulateur à mise en place rapide intègre au sein d'un même ensemble un régulateur d'oxygène miniaturisé, une coquille oronasale et un harnais gonflable et rétractable. Ce dernier dispositif maintient l'équipement sur le visage de l'utilisateur. Selon les modèles, les lunettes s'adaptent sur le masque, ou les deux éléments sont associés dans un même équipement. En cas de dépressurisation, la fonction « dilution », permet au régulateur de délivrer un taux inspiré d'oxygène asservi à l'altitude. En cas de pollution accidentelle, le régulateur par action d'une commande manuelle, alimente en oxygène les lunettes, qui se trouvent alors en légère surpression (+3 hPa), interdisant ainsi la pénétration de la pollution ambiante.

Ces équipement doivent répondre à des normes internationales (TSO C99 et AS 8031) pour obtenir leur qualification « aviation civile » et sont testés à cette fin au laboratoire de médecine aérospatiale, division du centre d'essais en vol (Brétigny sur Orge). Les essais sont réalisés sur une population composée de 12 hommes et 12 femmes. Quatre tests sont pratiqués par le laboratoire. Il s'agit de la rapidité de mise en place, l'évaluation du champ visuel, la fonction anti-pollution et la fonction protection contre l'hypoxie d'altitude.

Sur le plan ergonomique, l'équipement doit pouvoir être mis en place en moins de 15 secondes en cas de fumée et le test doit permettre de vérifier qu'il n'existe aucune gène à la mobilité de la tête pouvant nuire à la sécurité des opérations de pilotage. Par ailleurs, l'équipement compatible avec le port de verres correcteurs ne doit pas réduire l'acuité visuelle.

Concernant le champ visuel, l'équipement doit permettre une vision périphérique d'au moins 120° dans le méridien horizontal et 60° dans le méridien vertical.

La fonction anti-pollution de l'équipement est évaluée en plaçant les sujets dans une enceinte polluée par un gaz traceur dépourvu de tout risque toxique, le CF4, et en dosant la pollution comparativement dans l'enceinte, dans le masque et sous les lunettes. Les normes prévoient que le rapport entre la concentration de CF4 dans le compartiment testé et dans l'ambiance ne dépasse pas 10 % pour les lunettes et 5 % pour le masque.

Sur le plan de la protection contre les risques hypoxiques en altitude, le régulateur doit fournir réglementairement une concentration minimale de 69 % d'oxygène à 30 000 pieds (TSO C89) et de 95 % d'oxygène entre 35 000 et 40 000 pieds (FAR 25). Les essais, destinés à vérifier le taux d'oxygène au niveau du masque, sont effectués sur des sujets dans un caisson à dépression qui permet de simuler ces différents niveaux d'altitude.

Paper presented at the RTO HFM Symposium on "Operational Medical Issues in Hypo- and Hyperbaric Conditions", held in Toronto, Canada, 16-19 October 2000, and published in RTO MP-062.

1. INTRODUCTION

Différents incidents ou accidents de l'aviation commerciale sont la conséquence d'un feu à bord avec émanation de fumées toxiques. Le crash du Boeing 707 de la Varig en 1973 à Saulx les Chartreux a montré qu'un équipement de tête avait permis à l'équipage de conduire l'avion et de survivre. En revanche, les passagers avaient été tous fatalement victimes des émanations toxiques induites par la combustion des isolants thermiques et phoniques. Plus récemment, le vol SR 111 de la Swissair en 1998 à Halifax, Nouvelle Ecosse, Canada s'est terminé par un crash avec perte complète de l'aéronef (MD-11) et de ses occupants. Bien qu'à ce jour, l'enquête ne soit pas terminée, le feu dans le poste de pilotage apparaît être la cause la plus probable de l'accident.

Il est donc nécessaire que les équipages puissent disposer d'un équipement de tête assurant en fait plusieurs fonctions : la protection contre les émanations toxiques induites par un feu et la protection contre les risques hypoxiques. Par ailleurs, cet équipement de tête ne doit pas altérer les communications entre les différents utilisateurs.

Toutefois dans un avion de ligne, il faut distinguer l'équipage technique situé dans le poste avant et assurant ses fonctions essentiellement de façon sédentaire et l'équipage commercial devant intervenir auprès des passagers et ayant l'obligation de se déplacer pour assurer sa mission.

Ces deux activités très complémentaires ont amené les équipementiers à développer deux types d'équipements très différents dans leur concept. Pour l'équipage technique, l'équipement de protection peut être relié à une source d'oxygène fixe. Cette solution garantit l'approvisionnement en oxygène pendant une durée prolongée. Pour l'équipage commercial, l'équipement de protection, utilisé par un personnel mobile, doit être à la fois autonome en terme l'approvisionnement en oxygène et en terme de contrôle de la concentration de gaz carbonique. Son autonomie reste limitée.

L'objet de ce travail est de faire un bilan des essais nécessaires à la qualification des équipements de tête développés pour l'équipage technique. Il est lié aux efforts d'un industriel français, la société Intertechnique qui a développé dans le passé le masque MC 10 qui s'est imposé dans l'aviation commerciale. Cet équipementier souhaite actuellement certifier de nouveaux équipements plus performants.

MASQUES TESTES DANS CETTE EXPERIMENTATION		
TYPE	**CARACTERISTIQUES DES LUNETTES**	**OBSERVATIONS**
MF 20	Intégrées	
MC 10 XX	MXG	Evolution de l'actuel MC 10
MC 20	MXG	Evolution du harnais de l'actuel MC10
MRA	MXG	Nouveau masque régulateur
MLD 20	MXG	Nouveau masque régulateur

Il a confié au centre d'essais en vol certains travaux de certification qui ont été réalisés au sein du laboratoire de médecine aérospatiale.

La certification est basée sur un ensemble d'essais validant les impératifs fixés par plusieurs normes :

- le règlement TSO-C99,
- la FAR 25.

2. REGLEMENT DE CERTIFICATION

La réglementation de certification présentée ci-après fait l'objet, dan le chapitre suivant, d'un développement technique montrant les difficultés rencontrées.

2.1. Règlement TSO-C99

Le règlement TSO-C99 s'applique aux équipements de protection respiratoires. Il est basé sur les exigences définies par la « Society of automative engineers » (SAE) sous le numéro AS 8031. Ces exigences sont intitulées « système de protection personnel des membres d'équipage de l'aviation de transport contre les atmosphères toxiques et irritantes ».

Ces exigences s'appliquent aux équipements utilisés lors de situation d'urgence en vol. Il s'agit donc non seulement de protéger les équipages contre un risque induit par une atmosphère toxique ou irritante pour les voies respiratoires mais aussi contre un risque hypoxique. De plus, il est nécessaire que l'équipage puisse utiliser ces équipements dans une ambiance « de stress » induite par l'environnement évoqué précédemment.

En fait, ces réglementations concernent différents aspects des équipements. Elles définissent en particulier :

- régulateurs à la demande,
- microphones,
- systèmes optiques utilisés dans ces équipements.

Les sous composants des équipements doivent répondre à des critères de :

- résistance à la combustion,
- résistance à la dégradation par l'ozone,
- résistance à la dégradation par les ultraviolets,
- résistance à l'usure et au déchirement (abrasion),
- résistance aux réactions de la peau,
- compatibilité avec l'oxygène,
- odeurs,
- résistance à la déformation due au stockage,
- résistance au vieillissement,
- résistance au bris,
- qualité optique.

Il est stipulé dans cette norme, que l'équipement devra assurer une protection pendant au moins quinze minutes à une pression correspondant à une altitude de 2488 m (8000 pieds) avec une ventilation respiratoire de 30 l/min BTPD.

En fait, les équipements doivent pouvoir être utilisés dans des situations de décompression cabine à des altitudes plus élevées et faisant l'objet de la norme FAR 25 1443.

2.2. Norme FAR 25 1443 et TSO C89

La norme FAR 25 (part 25) et le règlement TSO C89 définissent les caractéristiques des régulateurs ou les objectifs à atteindre en terme de pression partielle d'oxygène, de fraction d'oxygène dans les gaz inhalés.

Il est demandé que les équipements puissent fournir une pression partielle d'oxygène trachéale inspiratoire minimale ($P_{TI}O_2$) de 161 hPa (122 mmHg) à des altitudes de 10 668 et 12 192 mètres (35 000 pieds et 40 000 pieds).

La fraction inspiratoire d'oxygène (F_IO_2) doit être**, au minimum** :

* selon le règlement TSO C89 de :
  - 0,69 à 9144 m. (30 000 pieds),
  - 0,98 entre 10 668 et 12 192 m. (35 000 et 40 000 pieds),
* selon la FAR 25 de :
  - 0,95 à ces diverses altitudes.

3. TESTS DE CERTIFICATION ET DIFFICULTES RENCONTREES

Les tests de certification pratiqués au laboratoire ont concerné :

- des essais ergonomiques de mise en place,
- la mesure du champ visuel,
- l'évaluation de la fonction anti-pollution,
- l'évaluation de la protection contre le risque d'hypoxie d'altitude.

3.1. Essai ergonomique de mise en place

Sur le plan ergonomique, l'équipement doit pouvoir être mis en place en moins de 15 secondes et le test doit permettre de vérifier qu'il n'existe aucune gène à la mobilité de la tête pouvant nuire à la sécurité des opérations de pilotage. L'équipement est installé dans une boite de rangement disposant d'un accés facilité par deux petites portes fermées sur des systèmes à ergo et dotées d'évidements permettant de placer les doigts. Ainsi, l'utilisateur récupère l'équipement en le prenant à travers ces évidements. De plus, il le prend en activant naturellement la commande de gonflement du harnais.

Pour l'évaluation, l'équipement est positionné de façon à reproduire la disposition réelle dans l'avion. Le sujet sort de sa boite le masque régulateur et le met en place d'une seule main. Il sort ensuite les lunettes de leur sac et les mets en place lorsque celles-ci sont indépendantes du masque. Un ajustement permettant une bonne adaptation et un meilleur confort est autorisé. Le temps nécessaire à la mise en place est chronométré. Des mouvements de tête dans toutes les directions sont effectués afin de vérifier qu'il n'existe aucune gène à la mobilité pouvant nuire à la sécurité des opérations de pilotage.

Ce test n'a pas présenté de difficultés majeures. Toutefois, il a été nécessaire que les sujets se familiarisent avec l'équipement et s'entraînent à sa mise en place. Les tests ont montré que les équipements testés répondaient à ce critère. En revanche, il est impératif que les éventuels utilisateurs soient entraînés à sa mise en place.

TYPE	TEMPS DE MISE EN PLACE	OBSERVATIONS
MF 20	3.4 ± 0.7 s	Tous < 5 s
MC 10	10.6 ± 1.4 s	Tous < 15 s
MC 20	10.5 ± 1.4 s	Tous < 15 s
MRA	11.7 ± 1.5 s	Tous < 15 s
MLD 20	8.5 ± 2.5 s	Tous < 15 s

3.2. Mesure du champ visuel

La mesure du champ visuel est réalisé à l'aide d'un campimètre de Goldmann. Cet appareil, utilisé en ophtalmologie, permet de détecter des scotomes visuels. Il s'agit d'une demi-sphère de 30 cm de rayon, rétro-éclairé et disposant à sa partie centrale d'un trou. A l'intérieur de cette hémisphère, est projeté un spot lumineux. La position du spot est repérée par un système de pantographe sur un support papier quadrillé. Les personnes examinées disposent d'un repose menton et d'un repose front ajustables pour amener l'œil examiné en face d'un trou centré au milieu de l'hémisphère. Ce trou que la personne doit regarder en vision monoculaire, permet à l'examinateur de s'assurer que l'œil regarde le centre de l'hémisphère. Lors de l'examen, le technicien marque sur le support quadrillé l'endroit où la personne commence à percevoir le spot lumineux. A la détection du spot lumineux, la personne examinée tapote sur la table pour renseigner l'examinateur de la détection. Cette disposition méthodologique évite à la personne examinée de parler et de déplacer la mandibule et donc la face et l'œil. L'examen est effectué tous les 15 degrés d'angle. Pour s'assurer d'une détection optimale, le spot est déplacé à deux reprises de la zone « aveugle » à la zone de détection.

Dans le cadre de l'évaluation des équipements aéronautiques, la mesure du champ visuel s'effectue avec et sans équipement. Toutefois, en raison de l'encombrement de l'équipement, il est impossible au sujet d'utiliser le support de menton et de front du campimètre. De plus, cette évaluation s'effectue en vision binoculaire et non pas en vision monoculaire. Il a donc été nécessaire de supprimer le support de front et de modifier le support du menton en tenant compte de l'épaisseur éventuelle de la lèvre inférieure du masque. L'examinateur, sensibilisé sur cette difficulté méthodologique doit s'assurer que la face du sujet est centrée sur le support et que le front est bien positionné. Une

autre personne s'assure que, sans maintien, le sujet ne déplace pas sa tête durant l'examen. En cas d'obtention de valeurs aberrantes, il est prévu de refaire l'examen.

Sachant que le champ visuel doit être de 60° de part et d'autre du point central selon le plan horizontal et de 40° au-dessus et 20° en dessous sur l'axe vertical, les résultats ci-après montrent que les équipements développés par la société Intertechnique sont conformes aux exigences de la norme.

Ensemble masque-lunettes Intertechnique MF20

TYPE	CHAMPS VISUEL (°)		
	HORIZONTAL	VERTICAL	VERTICAL
		Hommes	Femmes
MF 20	180	67	67
MC 10	180	68	73
MC 20	180	72	70
MRA	180	71	72
MLD 20	180	74.5	72.5

Par ailleurs, l'équipement compatible avec le port de verres correcteurs ne doit pas réduire l'acuité visuelle. Les tests d'acuité visuelle ont été réalisés avec une échelle optométrique « ELLA » pour des sujets porteurs de verres correcteurs. Ils ont été effectués de façon comparative avec et sans équipement. Ces tests ont montré que les lunettes de protection anti-fumées n'altéraient pas l'acuité visuelle.

3.3. Evaluation de la fonction anti-pollution

La fonction antipollution de l'équipement est évaluée en plaçant les sujets dans une enceinte polluée par un gaz traceur dépourvu de risque toxique et en dosant la pollution comparativement dans l'enceinte, dans le masque et sous les lunettes. La norme prévoit que le rapport entre la concentration de CF4 dans le compartiment testé et celle de l'ambiance ne dépasse pas 10% dans les lunettes et 5 % pour le masque. Ces valeurs doivent être respectées au minimum sur 80 % de la durée de l'essai. Le gaz traceur est le CF4.

L'enceinte est un caisson en bois de 1.2 m^3 de volume, dotée de deux fenêtres permettant de surveiller le sujet et d'une porte étanche verrouillée par un système à ouverture rapide. Cette enceinte est équipée d'un système de tuyauterie à travers la cloison qui permet d'injecter le gaz traceur et de prélever les échantillons de mesure de ce gaz. A l'intérieur de l'enceinte, le sujet est assis sur un siège, face à la porte.

Il est équipé du masque respiratoire et des lunettes anti-fumées. Le masque est raccordé à une bouteille d'O_2 de 3.3 dm^3 à une pression de 15 MPa. Après vérification du fonctionnement nominal de l'équipement, le masque est mis en fonction surpression, l'enceinte est fermée et le CF4 est injecté. Le test débute quand la concentration dans l'ambiance atteint 5 %. Des points de prélèvements de gaz étant prévus dans l'ambiance, le masque et les lunettes, la mesure est effectuée toutes les 20 secondes en utilisant un spectromètre de masse. L'essai dure 15 minutes. Durant les 5 premières minutes, on demande au sujet de réaliser des mouvements de tête 5 fois vers le haut, le bas, la gauche et la droite. Entre la cinquième et la dixième minute, le sujet doit lire un texte préalablement fourni. A l'issue des 15 minutes, il enlève les lunettes et les place dans l'ambiance. La mesure effectuée alors permet de s'assurer de façon comparative à celle de l'ambiance que les mesure effectuées étaient correctes. La pesée de la bouteille d'oxygène au début et à la fin de l'essai permet de connaître la consommation d'oxygène, donc la ventilation moyenne du sujet. Cette évaluation est effectuée uniquement à titre indicatif pour le constructeur.

La réalisation de ce test s'est appuyée sur la longue expérience du laboratoire en mesure de gaz respiratoire par spectrométrie de masse. Par ailleurs, le choix du gaz traceur, le CF4, utilisé à une concentration où il n'est pas toxique, est basé sur son poids moléculaire. Celui-ci est relativement faible (86) et le ventilateur installé dans l'enceinte permet d'assurer une concentration homogène du gaz traceur. Plusieurs tests « à vide » effectués préalablement ont permis de vérifier qu'il n'y avait pas de biais métrologiques induits par une stagnation du gaz traceur. Ces tests préalables ont permis de positionner de façon optimale le ventilateur.

Les essais ont permis de détecter les éventuelles pollution du masque ou des lunettes comme ceci est présenté ci-après.

POURCENTAGE DE POLLUTION RETROUVE (%) SUR 24 SUJETS		
TYPE	**MASQUE**	**LUNETTES**
MF 20	0	18 cas : 0 6 cas dont valeur maximale < 1.6
MC 10	0	11 cas : 0 13 cas dont valeur maximale < 5
MC 20	O	12 cas : 0 11 cas dont valeur maximale < 2
MRA	5 cas, traces < 0.1	3 cas : 0 13 cas dont valeur maximale < 0.1 6 cas dont valeur entre 0.1 et 0.5 2 cas dont valeur entre 0.6 et 0.9
MLD 20	0	9 cas : 0 7 cas dont valeur maximale < 0.1 7 cas dont valeur entre 0.1 et 0.5 1 cas dont valeur : 0.8

N.B Sur les 10 sujets porteurs de verres correcteurs, l'étanchéité et l'acuité visuelle sont conservées.

3.4. Evaluation de la protection contre le risque hypoxique

L'évaluation de la protection contre le risque hypoxique est menée à l'aide du caisson d'altitude du laboratoire. Ce caisson comporte deux chambres connectées de 60 et 10 m^3 de volume. La mesure des gaz est effectuée par un spectromètre de masse de la marque Spectra situé à l'extérieur.

Le sujet est installé à l'intérieur de la grande chambre, tenu sur son siège par un harnais, en face d'un hublot à travers lequel il est surveillé. Il dispose d'un altimètre et du matériel mis en œuvre par un technicien de mesure l'accompagnant. Il s'agit pour ce dernier de connecter les différentes tuyauteries nécessaires à la mesure des gaz.

Il est équipé de l'équipement de tête en évaluation. Cet équipement dispose d'une tuyauterie d'essais permettant de prélever des échantillons de gaz à l'intérieur du masque.

Les essais sont effectués au sol, à 9 144, 10 668 et 12 192 m. (30 000, 35 000 et 40 000 pieds).

L'asservissement de la F_IO_2 à l'altitude est réalisé automatiquement par la fonction "dilution". La fonction "surpression antipollution" peut être activée manuellement ou non par l'utilisateur pour éviter embuage et pénétration de gaz extérieurs dans le mélange inspiré. Les mesures ont été effectuées avec cette surpression activée et non activée pour en connaître l'influence.

La surveillance du sujet est effectuée de façon visuelle, phonique, et par le suivi d'une variable physiologique.

La surveillance visuelle est assurée à travers un hublot du caisson d'altitude. Une liaison phonique permet au responsable de s'assurer de l'état psycho-physiologique du sujet et de donner des directives.

Un oxymètre de doigt type Nelcor permet de s'assurer que le sujet a une saturation artérielle d'oxygène suffisante pour séjourner à cette altitude.

La pression partielle d'oxygène dans le masque est mesurée de façon précise par spectrométrie. Cette méthode de mesure a été choisie car elle permet de suivre l'évolution instantanée de la concentration de gaz. Cette mesure instantanée a pour avantage d'évaluer les concentrations en fin d'inspiration et en fin d'expiration des gaz contenus à l'intérieur du masque. Par là même, elle permet d'évaluer les caractéristiques de fonctionnement du régulateur.

Cette mesure est rendue délicate en altitude du fait du volume massique de l'air. Le responsable a été confronté à cette difficulté durant toute la phase de mise au point.

Pour assurer une mesure correcte, il a été nécessaire d'effectuer pour chaque altitude, un étalonnage avec des concentrations connues de mélange. Le responsable a été de surcroît confronté à des problèmes de maladie de décompression. Les personnes se trouvant en altitude ont présenté des « bends » et les essais ont été interrompus dès leur apparition. Ces manifestations ont été ultérieurement prévenues par une dénitrogénation d'une durée d'une heure et demi.

L'évaluation de la fonction « protection contre l'hypoxie » de ces régulateurs a été la plus difficile à assurer, étant donné les précisions demandées et les risques potentiels encourus. En revanche, elle a permis au laboratoire de fournir à l'industriel les caractéristiques de ses équipements. Les résultats présentés ci-après montrent les valeurs obtenues au cours de ces différentes altitudes. Ils montrent que la technologie employée permet d'assurer les critères de certification.

FRACTION INSPIRATOIRE EN OXYGENE (valeurs extrêmes sur 3 sujets**)**			
Type	**Altitude** (pieds)	**Surpression non activée**	**Surpression activée**
MF 20	30 000	0,943 et 0,957	
	35 000	0,969 et 0,989	0,976 et 0,99
	40 000	0,956 et 0,979	0,964 et 0,983
MRA	30 000	0,948 et 0,975	
	35 000	0,946 et 0,965	0,968 et 0,979
	40 000	0,942 et 0,961	0,964 et 0,966
MLD 20	30 000	0,79 et 0,90	
	35 000	0,825 et 0,98	0,980 et 0,99
	40 000	0,765 et 0,97	0,975 et 0,99

4. CONCLUSION

Le laboratoire de médecine aérospatiale a mené des essais de certification d'équipements respiratoires utilisés par les équipages techniques de l'aviation commerciale.

Ces essais de certification comportaient une évaluation ergonomique et du champ visuel, des tests d'étanchéité et le contrôle de la fonction « protection contre l'hypoxie d'altitude ».

Ces essais ont nécessité des développements technologiques ou méthodologiques spécifiques à l'environnement aéronautique. L'évaluation de la dernière fonction s'est révélée toutefois la plus difficile car la mesure devait être effectuée de façon précise en haute altitude.

Les équipements développés par la société Intertechnique ont passé avec succès tous ces essais de certification.

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