

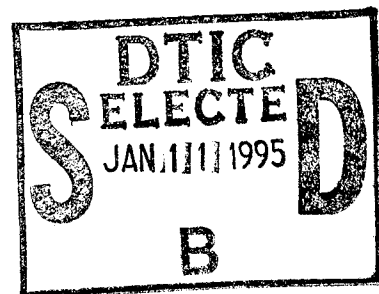
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RESEARCH ON PGI_2 AND TXA_2 EFFECTS AT TIMES OF
HYPERBARIC OXYGENATION OF DOMESTIC RABBITS
WITH ACUTE CEREBRAL ISCHEMIA
REIRRIGATION DAMAGE

by

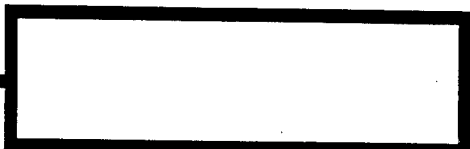
Teng Yansheng, Gao Guangkai, et al.



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HUMAN TRANSLATION

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ABSTRACT 33 New Zealand white rabbits were taken and randomly divided into a control group, a hyperbaric air group, and a hyperbaric oxyengation (HBO) group. All were reirrigated types following the creation of acute, incomplete cerebral ischemia. Respective measurements were taken of the overall carotid artery and interior jugular vein blood gases as well as cortical brain tissue homogenate amounts of 6-Keto-PGF_{1 α} and TXB₂ contained. In conjunction with this, pathological investigations were made. The results were that: the amounts of 6-Keto-PGF_{1 α} contained for the HBO group were clearly greatly increased ($P < 0.01$). TXB₂ clearly dropped ($P < 0.05$). Blood PO₂ in the HBO group clearly went up ($P < 0.01$). Pathological investigations showed that the HBO groups brain tissue damage was relatively light. Conclusion: there were clear effects on PGI₂ and TXA₂ with HBO when there was reirrigation after acute cerebral ischemia in the domestic rabbits. This is possibly one mechanism of HBO therapy for acute cerebral ischemia.

KEY TERMS Oxygenated 6-Keto-PGF_{1 α} TXB₂

Acute cerebral ischemia is a very great threat to the functions of the central nervous system of patients and even to their lives. Applications of HBO therapy have achieved definite therapeutic results^(1,2). However, as to its mechanisms, there is still a shortage of relatively in-depth studies. The experiments in question are aimed at the influences of PGI₂ and A₂(TXA₂) in observations of HBO after reirrigation of domestic rabbit acute cerebral ischemia or anoxia, in order to investigate the mechanisms in HBO treatment of acute cerebral ischemia.

MATERIALS AND METHODS

I. Experimental Animals and Methods

33 male New Zealand white rabbits, with body weights from 2.50-3.45 kg (average 2.96 kg), were randomly divided into a control group (12 rabbits), a hyperbaric air group (9 rabbits), and an HBO group (12 rabbits). All the experimental animals were anesthetized using 20% urethane (1g/kg). The two sides of the overall carotid artery or arteria carotis communis anterior were separated as well as the interior jugular vein or vena jugularis interna and the right side femoral artery or arteria femoralis. Using one end of a polyethylene tube, this was stuck into the femoral artery. The other end was connected to a blood pressure guage in order to monitor arterial blood pressure. From veins on the edge of the ears, slow injections were made of Xiaopuna (a nitric compound of sodium) (concentration 10ng/L). Researchers waited for blood pressures to drop to 5.33kPa (40mmHg). Then, use was made of arterial clips to cut off both sides of arteria carotis communis anterior. In this period, through regulating the speed of the injection of the nitric sodium compound (xiaopuna), one took the average arterial pressure and controled it at 5.99 ± 0.97 kPa (45 ± 7 mmHg). The blockage lasted 20 minutes. Then, the arterial clips were released. At the same time, the injections of the nitric sodium compound (xiaopuna) were stopped. Approximately 20-30 seconds after the drug injections were stopped, blood pressures went back up to normal levels. The experimental methods with the 3 groups of animals were different. The control group animals were taken and put into a pressurization chamber, causing their autonomic respiration of air at normal pressure. The hyperbaric air pressure group was taken and put in a

pressurization chamber. A 10 minute pressurization was used to 0.25MPa(2.5ATA). After a stayover of 90 minutes, there was a reduction to normal pressure at a uniform speed during 20 minutes. During the period inside the chamber, they were made to breathe through face guards an artificially regulated mixture of oxygen and nitrogen gases (oxygen concentration 8.4%). The HBO group animals, inside the chamber, breathed through face guards pure oxygen (oxygen concentration 99.92%). Their pressure-time program was the same as that with the hyperbaric air group.

When reirrigation had reached 120 minutes, blood gas specimens were taken from arteria carotis communis anterior and vena jugularis interna. Following this, 40% urethane was used to put the animals to death. Their skulls were opened, and cortical tissue from the area of the brain with the ischemia was quickly taken out. 1 piece of tissue was taken. The surface was rinsed of blood with low temperature saline solution, and it was placed in liquid nitrogen and quick frozen. Two other pieces were taken and, respectively, put into solutions of 10% methyl aldehyde or formaldehyde and 2.5% precooled (4°C) glutard aldehyde in order to prepare them for optical and electron microscope pathological examinations.

II. Specimen Titration Methods

Using a Corning 168 blood gas analyzer (US) direct titration tests were done on animal arterial and venous blood pH values, PO_2 and PCO_2 . Use was made of the preventive titration medicine kit supplied for the basic medical research of the Chinese Academy of Medicine as well as the 2107 fluid scintillation counter device (Xian) to do determinations of the amounts of 6-Keto-PGF_{1 α} and

TXB₂ contained in cortical brain tissue homogenate. The extraction recovery rates for 6-Keto-PGF_{1α} and TXB₂ were respectively 99.6±0.2% ($\bar{x} \pm s$, n=6) and 94.1±0.8% ($\bar{x} \pm s$, n=5). Coefficients of variability were respectively 11.7% and 10.5%. Brain tissues used HE dyes and took an OLYMPUS phase difference photo microscope (Japan) to make optical lens investigations. The brain tissues were taken, and, using Epon 812 to cover them up, they were sliced up through the CQR-1 slicing device (Shanghai), double dyed with uranium and lead, and, using the H-7000 electron microscope (Japan) to make electromicroscopy examinations.

III. Statistical Treatment

In blood gas analyses, titration results for the amounts of 6-Keto-PGF₁ and TXB₂ contained gave variance analyses. The result meanings, respectively, were that differences were not obvious ($P > 0.05$), obvious ($P < 0.05$), and exceptionally obvious ($P < 0.01$).

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RESULTS

I. Blood Gas Analysis Results:

The arterial and venous blood pH value differences associated with the three groups of animals had no obvious significance ($P > 0.05$). The arterial and venous blood PO₂ of the HBO group was obviously higher than the control and the hyperbaric air group ($P < 0.01$). However, the control group and the hyperbaric air groups did not differ in a clearly significant way ($P > 0.05$). The arterial and venous PCO₂ of the HBO group were higher than the other two groups ($P < 0.05$). However, the differences

between the control group and the hyperbaric air group had no clear significance ($P > 0.05$), Table 1).

① 组别	② 数量 (只)	③ 动脉血			④ 静脉血		
		pH	PO ₂	PCO ₂	pH	PO ₂	PCO ₂
⑤ 对照组	12	7.33±0.11	82.38±13.90	36.30±5.41	7.29±0.11	52.34±8.96	40.31±6.17
⑥ 高气压组	9	7.25±0.18	62.04±15.14	38.08±6.30	7.24±0.18	38.79±9.56	45.13±7.27
⑦ HBO组	12	7.24±0.33	362.72±69.57	45.48±12.84	7.16±0.27	88.19±31.07	52.88±11.44

Table 1 The Results of Blood Gas Analyses on the Three Groups of Animals ($\bar{x} \pm s, \text{mmHg}$) (1) Group (2) No. of Animals (3) Arterial Blood (4) Venous Blood (5) Control Group (6) Hyperbaric Air Group (7) HBO Group

II. Results of 6-Keto-PGF₁ and TXB₂ Titrations:

The amounts of 6-Keto-PGF₁ contained in the HBO group are higher than the other two groups ($P < 0.01$). Differences between the control group and the hyperbaric air group have no obvious significance ($P > 0.05$). Amounts of TXB₂ contained are lower than the other two groups ($P < 0.05$). However, differences between the control group and the hyperbaric air group have no obvious significance ($P > 0.05$, Table 2)

① 组别	② 数量 (只)	6-Keto-PGF ₁	TXB ₂
③ 对照组	12	278.08±155.24	762.92±269.42
④ 高气压组	9	222.33±123.84	753.56±272.96
⑤ HBO组	12	727.75±279.31	480.67±288.34

Table 2 6-Keto-PGF₁ and TXB₂ Titration Results for the Three Groups of Animals ($\bar{x} \pm s, \text{ng/L}$) (1) Groups (2) No. of Animals (3) Control Group (4) Hyperbaric Group (5) HBO Group

III. Results of Pathological Examinations

As seen in optical microscope examinations, mesenchyme brain tissues of the control group were clearly dropsical. Capillaries were expanded. Red blood cells presented agglomerations like a string of cash coins. Nerve cell membranes disappeared. Nuclear membranes, chromatin, and nucleoli were blurred and unclear, presenting the look of ground glass. There was clear proliferation of spongiocytes. Neurotropic phenomena were clear and obvious. The hyperbaric air group and the control group were generally the same. The HBO group mesenchyme was slightly dropsical. Capillaries were expanded. Some of the nerve cell membranes were disrupted. Nuclear membranes, chromatin, and nucleoli were clear. Spongiocyte proliferation was not obvious. As shown in electron microscope examinations, all cases showed capillary expansion or dilation. There were relatively numerous concave pits or depressions on the nuclear membranes of the control group cells. Double layer membrane structures were indistinct. Within neuron cytoplasm and in capillary endothelial cells as well as within axons, mitochondrial ridges (unclear) were blurred, presenting the look of denatured bone marrow or empty bubbles. The hyperbaric air group was basically the same as this. The nuclear membrane structures of HBO group cells were clear. Most mitochondrial structures were normal. A small number of ridges (unclear) were blurred.

DISCUSSION

I. Influences of HBO on Blood Gas Analyses

These experiments clearly prove that HBO has obvious influences on blood gases in periods of reirrigation after acute cerebral ischemia. The chief indications are, first of all, that HBO is capable of elevating blood PO_2 .

Oxygen moves from capillaries toward tissues. This is completed through diffusion effects dependent on the pressure differential gradient. The amount of the diffusion, its speed, and distance are directly proportional to PO_2 . These experiments' titrations of arteria carotis communis anterior PO_2 clearly show rises. At the same time, the arteria carotis communis anterior PO_2 which is recirculated from within the crania also clearly goes up. Therefore, this proves that the amounts of oxygen supplied to brain tissues markedly increases. A number of scholars also clearly demonstrated that HBO is capable of elevating the oxygen tension^(3,4) associated with brain tissues. This type of effect is beneficial for the restoration of reversible damage in ischemic areas lacking oxygen movement, causing nerve cell function to be improved. Besides this, we took titrated blood PO_2 and had it act as quality control index for the methods of the experiments in question. The PO_2 of the HBO group clearly goes up, showing that the effects of oxygen consumption are precise and definite. Second, HBO is capable of causing CO_2 retention. The possible causes are: (1) In an HBO environment, in blood plasma, the amounts of oxygen dissolved in physical form clearly increase. They are already capable of completely or basically satisfying the tissues' metabolic needs. Because of this, there is a reduction in the dissociation associated with oxygen and heme proteins. There is also a reduction in the original heme proteins. This leads to a reduction in the formation of carbonates of heme proteins giving rise to CO_2 retention. (2) These experiments involved taking animals after anesthesia and having them breath through face guards or covers. Because of respiratory weakness and increased respiratory drag forces, this leads to drops in the amounts of gas through the pulmonary alveoli causing a reduction in the

elimination of CO₂. Statistics clearly show that PCO₂ associated with the HBO group was higher than the other two groups. However, the hyperbaric air group's respiration through the same type of face guards or covers, by contrast, showed inconspicuous differences with the control group. Therefore, it is recognized that HBO is a primary cause of CO₂ retention. CO₂ retention will intensify acidosis and brain dropsy or edema. It is possible, through appropriate drops in pressure and reductions in respiratory drag forces, to improve flow through function for gases in order to improve this disadvantageous effect of HBO. Pathological examinations clearly show that brain tissue damage associated with HBO is relatively light and show the advantageous effects of HBO as taking a leading role.

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II. The Influences of HBO on PGI₂ and TXA₂

In recent years, the effects of PGI₂ and TXA₂ in the pathology of physiological processes associated with acute brain ischemia have received more serious attention with every passing day. It has already been clearly demonstrated that, within several minutes of ischemia, due to the fact that cell membranes suffer damage, under the influence of phosphatidase A₂, the ions of arachidonic acid AA released from membrane phosphatide materials then increase. As far as AA is concerned, besides numerous types of direct and indirect effects which it has on the functions of cell membranes, it is also capable, through cyclooxygenase, of transforming into a precursor of prostaglandin⁽⁵⁾. PGI₂ and TXA₂ are metabolic products of AA. PGI₂ possesses strong and violent effects associated with expanded or dilated blood vessels and inhibition of blood platelet aggregation. TXA₂, by contrast, is the opposite of this. The amounts of these contained as well as the dynamic

equilibrium between the two gives rise to key effects (6,7) in functions associated with the regulation of microcirculation. PGI₂ and TXA₂ have extremely short in vivo half lives. Their stable metabolic products are, respectively, 6-Keto-PGF_{1α} and TXB₂. A number of reports coming from clinical and animal experiments clearly prove that, in times of brain ischemia, TXB₂ increases. PGI₂ drops. And, PGI₂/TXA₂ is unbalanced. (8-10).

Our experimental results demonstrate that HBO is capable of causing 6-Keto-PGF_{1α} in the brain tissues of animals which have had reirrigation of acute brain ischemia to increase and TXB₂ to decrease. Under the influence of HBO, there are two types of physical factors which mix together, that is, hyperbaric air and hyperbaric partial oxygen or high partial pressure oxygen. In order to distinguish the functions of the two, we designed the hyperbaric air group to make the pressure-time process associated with the group in question inside the pressurized compartment be the same as that for the HBO group. The difference is that the group in question has a nitrogen-oxygen mixture of gases (oxygen concentration 8.4%) which is artificially formulated for animals to breath. According to Dalton's Law⁽¹¹⁾, $P_1 = P_x(C/100)$ calculates the gas which is breathed in by the hyperbaric group which is $PO_2 = 760 \times 2.5 \times (8.4/100) = 159.6 \text{ mmHg}$ (760 = mmHg no. for one atmosphere pressure; 2.5 = the pressure inside the chamber; 8.4% = the oxygen concentration in the mixture of gases). This is basically the same as for air. Statistical results clearly show that there are obvious differences between the HBO group and the other two groups. However, the differences between the hyperbaric air group and the control group are not obvious. Because of this, it is possible to eliminate the influences associated with the hyperbaric

group. And, it is the effects of the hyperbaric partial oxygen group which gives rise to the changes in 6-Keto-PGF_{1 α} and TXB₂.

How HBO gives rise to changes in 6-Keto-PGF_{1 α} and TXA₂ is, at present, still not clear. There are a number of scholars who cite HBO's ability to elevate the rate of utilization of glucose associated with damaged brain tissues⁽¹²⁾, to increase the activity of brain tissue mitochondrial ATPase⁽¹³⁾, and to improve microcirculation⁽¹⁴⁾. The experiments in question also clearly demonstrate that HBO is capable of causing blood PO₂ to obviously rise and increase the amount of oxygen associated with brain tissues. These are all capable of alleviating the damage to cell membranes from ischemia and anoxia. Therefore, they reduce the release of AA. Besides this, work already clearly demonstrates that Ca²⁺ is one of the substances⁽⁵⁾ associated with the creation of critical effects in the "cascade" reactions associated with AA's transition into prostaglandin after brain ischemia. HBO protects the integrity of cell membranes and increases the activity of ATPase. Therefore, maintaining the normal Ca²⁺ cross membrane gradient, preventing a large scale inflow of Ca²⁺ into the interior of cells and cutting off the Ca²⁺ activation of phosphatidase A₂ stage. This is only a deduction about the mechanism by which HBO influences PGI₂ and TXA₂. It is awaiting more detailed research. However, these types of effects associated with HBO are capable of being one type of mechanism for treating brain ischemia.

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