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THE TRENDELENBURG POSITION AFTER CEREBRAL AIR EMBOLISM IN DOGS: EFFECTS ON THE SOMATOSENSORY EVOKED POTENTIAL, INTRACRANIAL PRESSURE, AND BLOOD-BRAIN BARRIER

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The experiments reported herein were conducted according to the principles set forth in the current edition of the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This technical report has been reviewed by the NMRI scientific and public affairs staff and is approved for publication. It is releasable to the National Technical Information Service where it will be available to the general public, including foreign nations.

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Medical personnel routinely recommend placing the victim of dysbaric or nosocomial cerebral air embolism in the Trendelenburg position. This maneuver is expected to reduce the chance of subsequent cerebral air emboli and to hasten clearance of bubbles trapped in the cerebral circulation. The Trendelenburg position will also increase intracranial pressure and reduce cerebral perfusion pressure; this may have an adverse effect on recovery of the injured brain. We placed 8 dogs in the left lateral decubitus, 45° Trendelenburg position for 1 h following cerebral air embolism and transient hypertension, then treated the animals with compression on a modified U.S. Navy Treatment Table 6A (head-down or HD group). We compared somatosensory evoked potentials (SSEP), intracranial pressure and pressure-volume index (PVI), brain water, and blood-brain barrier function assessed by extravasation of Evans Blue to these variables in 9 embolized and hypertensive dogs maintained in a

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head-up (sphinx) position as controls (horizontal or HZ group). At the end of the treatment, the HD group recovered less (27.3% ± 23.2% (mean ± SD)) of their baseline SSEP amplitude than the HZ group (53.9% ± 4.6%, $p<0.01$). In the HD group the intracranial pressure and the PVI were higher (indicating increased cerebral blood volume), and the degree of the blood-brain barrier damage was significantly greater, while the amount of brain water was almost the same. We conclude that the changes in intracranial pressure and cerebral perfusion produced by the extreme Trendelenburg position in dogs negates any possible benefits of this technique, and would recommend that this not be considered a standard position for initial therapy or transfer of the air embolized victim.

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INTRODUCTION

Many physicians recommend that the victim of cerebral arterial gas embolism (CAGE) be immediately placed in the extreme Trendelenburg (head-down, legs raised to 30-60° above horizontal) position, and that the casualty remain in this position until definitive recompression therapy can be provided (1,2,3). The use of Trendelenburg position (also known as Durant's maneuver: positioning the patient on his left side with the head-down) is clearly effective in the treatment of venous air embolism, because in this position venous air can be trapped in the right atrium, thus reducing the risk of potentially fatal pulmonary air embolism (4,5,6). Van Allen et al. (7) originally suggested that the buoyancy of the arterial gas bubble would cause it to distribute away from dependent portions of the circulation, thus protecting the patient in the Trendelenburg position from embolizing the brain. The buoyancy effect might further hasten the clearance of bubbles from the cerebral venous circulation once they have passed through the capillary network (1). The Trendelenburg position is associated with dilation of the cerebral venous system as well, and might therefore encourage transcapillary clearance of air from the brain (8,9,10). One diver who suffered an air embolism related to pulmonary barotrauma recovered completely upon being placed head-down (1), and air emboli appeared to clear more rapidly from the cerebral circulation in cats placed in the head-down position after arterial air injection (10).

The potential benefits of the Trendelenburg position on CAGE may not be fully realized for several reasons. The buoyancy of the bubble will effect redistribution of emboli away from the brain in the Trendelenburg position only if there is reembolization

after the initial ischemic event. Although the head-down position might prevent brain injury in certain surgical cases (11,12), it is unlikely to help after pulmonary barotrauma, since the pressure differential that causes alveolar rupture is eliminated by surfacing. Several investigators have observed that the effect of buoyancy on the distribution of bubbles is negligible in the face of normal arterial blood pressure (13,14,15). Cerebral venous dilation caused by the Trendelenburg position leads to increased intracranial pressure, and decreased cerebral perfusion pressure (9). The perfusion pressure decrease, and perhaps the increase in venous pressure itself, may lead to the increased formation of cerebral edema (16).

We decided to study the effect of the extreme Trendelenburg position on recovery after air embolism. We used a previously established animal model of internal carotid air embolism combined with transient severe hypertension that reliably produces late deterioration of brain function despite hyperbaric treatment (17). In order to simulate the circumstances surrounding transfer of a diving accident victim to a hyperbaric chamber, we first embolized the dog, then exposed it to the Trendelenburg position for 1 h, and proceeded to treat the animal with a modified U.S. Navy Table 6A. At the end of treatment, we assessed outcome as the percent of baseline somatosensory evoked response amplitude recovered, measured brain water, and quantified the extent of Evan's Blue extravasation as an index of blood-brain barrier function. In addition, we continuously monitored the intracranial pressure and periodically tested cerebrospinal fluid dynamics with compliance measurements.

MATERIALS AND METHODS

Anesthesia and Respiration

The local Animal Care and Use Committee reviewed the protocol prior to the experiment and certified that the procedures met the standards set forth in the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council, U.S. Department of Health and Human Services, Publication No. (NIH) 86-23. We began the experiments in 24 dogs (Canis familiaris), weighing 9.1-15.1 Kg. We tranquilized the dogs with a subcutaneous injection of xylazine (1.1 mg/Kg) and atropine (0.05 mg/Kg) and induced surgical anesthesia with 13.5 mg/Kg pentobarbital IV, followed in 20 min with 6.25 mg/Kg IV. We gave 1.6 mg/Kg 1V every 20 min thereafter, or as necessary to maintain the dog without a corneal response.

We intubated the dogs and instituted controlled ventilation with a Bird respirator connected to the built-in-breathing system of a Bethelem Steel hyperbaric chamber, and modified so that the respiratory rate could be varied with the chamber sealed. We monitored expired CO_2 and maintained it at a fraction equivalent to 4.0% ± 0.5% at the surface.

Vascular Access, Temperature Control and Somatosensory Evoked Response Monitoring

We catheterized both femoral arteries and veins for continuous blood pressure monitoring, arterial blood sampling, and administration of drugs and fluids. We connected the catheters to ports in the chamber wall for use at depth. We cannulated the right internal carotid artery with a PE-50 catheter calibrated so that 0.18 ml of saline would fill it. We continuously monitored rectal temperature and maintained it at

38 ± 0.5 ° C with heating pads during the surface preparation and with warm water circulated through copper heating coils during the therapeutic recompression.

We inserted stainless screw electrodes into holes drilled through the outer table of the skull for recording the cortical somatosensory evoked potential (SSEP) evoked by stimulation of the left median nerve by subcutaneous needle electrodes. We positioned the active electrode 1 cm off the midline at a point 1/3 of the nasion-inion distance in front of the inion, and placed the reference electrode in the nasal bone. We used a Nicolet CA-1000 evoked response system with a HGA-200 physiologic amplifier (gain 10,000x) to record responses, setting the low linear filter at 30 Hz, the high linear filter at 3000 Hz, and delivering 13-19 mAmp stimuli with a 100 μsec duration at 1.9 stimuli per second. We averaged 40 stimuli for each recording. We measured the amplitude from the first major positive peak latency to the next most negative peak using the cursor on the CA-1000. We left the first cursor at the latency obtained prior to any air injection, and referred all subsequent amplitude measurements to this latency.

Intracranial Pressure (ICP) and Pressure-Volume Index (PVI)

We inserted an 18-gauge spinal needle with a flattened bevel designed to avoid brain stem trauma percutaneously into cisterna magna and connected the needle by IV extension tubing to a Gould-Statham pressure transducer, the output of which was continuously monitored on the physiograph. We ended the experiment at this point in 3 dogs of the original 24 that developed bloody cerebrospinal fluid and unstable blood pressure, probably due to penetration of the brainstem by the needle. We clamped the pressure transducer to the frame that supported the dog in such a way that the height of

the recording diaphragm remained at the level at which the spinal needle penetrated the skin. A Y-connector at the junction of the pressure transducer and the extension tubing with a valve on the side arm permitted us to infuse 0.8-1 ml of normal saline at intervals for determination of intracranial compliance. We used a Sage infusion pump to deliver the saline at a constant rate of 1 ml/min. We expressed the intracranial compliance as the pressure-volume index, calculated as:

$$PVI(ml) = \frac{V}{\log Pp/Po}$$

where V is the infused volume (ml), Pp is the peak of ICP after the infusion, and Po is the ICP before the infusion (18,19). We were unable to measure PVI while the animal was in the chamber, and report measurements before air embolism, immediately after air embolism, following 1 h at the surface, and after surfacing from the therapeutic recompression.

Baseline Recordings, Cerebral Air Embolism, and Hypertensive Episode

We recorded the average amplitude of 5 SSEP's and values of controlled physiological parameters, including arterial blood pressure, pH, pO_2, pCO_2, hematocrit, temperature, and ICP. We measured the PVI twice, allowing 20 min between determinations. All of the subsequent evoked response measurements are reported as the percent of the average baseline amplitude.

We opened the stopcock on the internal carotid catheter to verify blood backflow, then flushed 0.4 ml of air through the catheter with 0.6 ml of warm saline. In two dogs we could not verify blood back flow, and we gave no air to these animals. We repeated the PVI in head-down and flat positions in these animals as unembolized control subjects. We immediately performed a SSEP to demonstrate the effect of the embolus on the amplitude, and eliminated 2 more animals of the original 24 from the experiment at this point because the air failed to suppress the SSEP amplitude below 10% of baseline.

In the remaining adequately suppressed animals, we gave a single IV bolus of norepinephrine (10 μg/Kg). The protocol to this point is identical to that previously reported with one minor exception (the measurement of PVI) and one critical difference (the interval between the air embolism and the injection of norepinephrine). Our previous results show that the combination of air embolism and a transient burst of hypertension produces a very severe cerebral injury with a poor response to recompression and a tendency to deteriorate over time (17).

Experimental Groups

At this point the procedures for the experimental groups diverge. We had, prior to obtaining baseline values, secured with bars in the external ear canal 9 animals in a frame that held them with the head upright, above the heart level, resting lightly on the sternum ("sphinx" position). This position is identical to that used in previous series, and forms the horizontal control (Hz) group. We had secured 8 animals in the left lateral decubitus position on a different frame that left the head at the same level as the heart

and supported the rear legs of the animal as well as holding the head with ear bars. After the air embolism and hypertensive episode, we lowered the head of this frame to a position of 45° from horizontal (Trendelenburg position or HD group). The dogs remained in their designated positions for 1 h, while we recorded evoked potentials at 10-minute intervals and repeated measurements of controlled physiologic parameters. We then returned the HD group animals to horizontal, left lateral decubitus position, and placed them and the Hz group animals into the hyperbaric chamber.

Recompression Treatment

We recompressed both groups on a treatment table closely modeled on the U.S. Navy Treatment Table 6A (20). The dive profile is shown in Fig. 1. After the initial compression to 6 ATA on air for 30 min, we decompressed the dogs to 2.8 ATA, where they completed three 20-minute periods on O_2, with 5-minute air breaks between each O_2 breathing period. We slowly brought the dogs to 1.9 ATA after the last air break while they breathed O_2 for 30 min. The dogs remained at 1.9 ATA for 75 min, breathing O_2 for the last 60 min at this stop (Fig. 1). We then surfaced the chamber. The treatment lasted 214 min, and we continuously monitored and controlled physiologic parameters, and recorded SSEP's at 10-minute intervals. We gave the maintenance dose of pentobarbital (1.6 mg/Kg) every 20 min during the dive without fail, since we were unable to check the corneal reflex while the dog was in the chamber. Upon surfacing, we wiped any accumulated serous fluid or blood from the skull electrodes, and recorded a final evoked response and PVI. We then euthanized the animal with 50 cc of a saturated KCl solution injected into the right ventricle via a previously placed catheter.

Measurement of Wet and Dry Weights and Fluorescence Microscopy

Immediately before leaving the 1.9-ATA depth, we gave the animals 3 mls/Kg of 2% Evans Blue in saline IV.

After euthanasia, we removed the brain in less than 5 min and froze it in liquid Freon maintained at -70 ° C over liquid nitrogen. We took 2 white and 2 gray matter samples from each hemisphere of the frozen forebrain, weighed them, then dried them to constant weight after two days at 110 ° C. We calculated the percent of brain water as:

$$\text{Brain water (\%)} = 100\% \times (\text{wet-to-dry weight})/\text{dry weight}$$

The final value reported is the average of the determinations in the 2 samples.

We divided the remaining brain roughly into thirds. From each third we cut at least three 12μ sections on an American Optical cryostat microtome. When all the frozen brains had been cut, we examined the sections for Evans Blue by epifluorescence excitation and measurement of the emitted light intensity with a photomultiplier-tube-based microdensitometry system (Carl Zeiss UMSP system with manual stage and computer controlled linearization). We estimated the area of observation with the selected magnification and photomultiplier aperture (magnification 16x, aperture 2.5 mm) as 0.0192 mm^2. The excitation light came from a 100-Watt high pressure mercury lamp and the photomultiplier had a useful detection wavelength range from 230-850 nM. We examined the same areas (two cortical gray and two subcortical white) in each section, then expressed the result as the average of the 9 fluorescence

measurements for the gray and white in each hemisphere. We performed all fluorescence measurements for both experimental groups on the same day after establishing the linear response of the system on a single slide. This method reduces the problems of obtaining an exact recalibration of the system, and allows us to express all fluorescence intensities as an dimensionless number relative to the linear calibration of the system. This number is proportional to the relative concentrations of Evan's Blue in the brain tissue.

The results are expressed as mean ± standard deviation. We used the Wilcoxon Rank Sum test to compare results in the two treatment groups when testing parameters at a single time, and 2-way analysis of variance (ANOVA) to summarize data trends over time. We applied the least squares method to obtain a regression of PVI versus intracranial pressure.

RESULTS

We condensed the results of continuous physiologic monitoring and intermittent measurements of blood gases throughout the experiment to the values shown in Table 1 for four different time points. We also show the average amount of fluid in, amount of urine output, average weights, and temperature at the final time point. We find no significant difference between groups for any variable at any time (Wilcoxon Rank Sum).

In previous studies, we have found that the interval between air embolism and h`ertension, the duration of the hypertensive phase, and the maximum level of the blood pressure are related to recovery. We record the group averages of these

parameters in Table 2, along with the average time between air embolism and reaching treatment depth. This last time includes the 1 h at surface in either head-down or upright position. As noted in the Methods section, we did not treat the 2 animals that failed to reach less than 10% of baseline evoked potential animals in the first 2 min following carotid air embolism. The HD group reached 2.6% ± 3.2% (N = 8) of baseline amplitude after air, and the control group reached a statistically identical 3.2% ± 3.3% (N = 9) of baseline (Wilcoxon Rank Sum).

Evoked Potential Results

Figure 2 displays the mean ± 95% confidence limits of percent of baseline evoked response amplitude recovery at 15-minute intervals during the experiment. Table 3 presents the results of the 2-way ANOVA comparing the treatment and time effects during various phases of the experiment. There is a significant difference between the HD and Hz groups when all time points are considered, and when the hyperbaric treatment phase is considered alone. The graphs of the recovery during the pre-hyperbaric treatment phase show steady recovery, as indicated by the significant time effect on the ANOVA, but no difference between groups. The adverse effect of HD positioning only becomes apparent as the treatment proceeds. The Hz group recovered 53.8% ± 13.7% of baseline SEP amplitude upon arriving at the surface following the treatment table, as opposed to 26.5% ± 23.2% recovery in the HD group ($P \leq 0.01$, Wilcoxon Rank Sum).

Brain Water and Extravasation of Evans Blue Albumin

We present the results of the wet-to-dry weights in Table 4, expressing them as the

percent of wet weight that is water. There is no significant difference between any of the groups, in any area of the brain. The results of the fluorescence microscopy are the averages of three determinations in three different coronal slices of brain. We picked roughly similar anatomic areas in the left and right cortex for each determination. We express the results in Table 5 as a dimensionless number that is the fluorescence of the sample on a linear scale relative to the highest and lowest fluoresences recorded during the single recording session. We were unable to repeat any recordings because of bleaching of the sample. Higher numbers represent a relatively greater intensity of fluorescence from a known area of brain and thus reflect an increase in the amount of Evans Blue in the brain.

ICP and PVI

We present results of continuous monitoring of ICP and cerebral perfusion pressure at selected time points in Table 6. When measured in the 45° head-down position just prior to treatment, the ICP was 28.8 ± 7 mmHg compared to the average pressure of these animals when returned then to the horizontal position of 22.2 ± 5.3 mmHg. The pressure rises steadily immediately after the air injection in both groups, and, although it declines again, remains elevated above baseline throughout the experiment. The ICP is significantly higher, and the cerebral perfusion pressure is significantly lower in the HD group in the both baseline and end of treatment time periods, probably because of an increase in sagittal sinus venous pressure in the left lateral decubitus position, as opposed to the head-up position. Although there is a clear mechanical explanation for the group differences in ICP, the increased pressure might contribute to the poor recovery in the

HD group. This point is emphasized by the significant correlation of the ICP level with the amount of Evans Blue extravasation in the injured hemisphere (Fig. 3).

We measured the PVI in the baseline period, after air embolism, and at the end of treatment, and present the results in Table 7. The PVI correlates very well with the intracranial pressure measured before starting the PVI injections (Fig. 4), and is at its highest in the period immediately following the air injection. The PVI is also higher in the HD group at all time points.

DISCUSSION

The head-down position increases cerebral venous cerebral blood volume, thereby increasing ICP and extravasation of blood-borne tracers through the blood-brain barrier. The raised ICP is associated with poorer recovery of electrical function of the brain as measured by the somatosensory evoked response. To recommend that patients be placed in the Trendelenburg position to reduce the risk of reembolization or to improve clearance of air from the brain is to disregard the effects of this position on ICP. Our study suggests that this is deleterious.

In previous studies we have shown that the combination of air embolism and a brief, intense, "spike" of increased blood pressure leads reliably to late deterioration (17). We believe that this experimental combination mirrors the likely consequences of multiple air emboli in the clinical situation, some of which might distribute to the brainstem. Embolic ischemia of the brainstem leads to tremendous increases of blood pressure, ICP and circulating catecholamines (20). Even in the absence of brainstem ischemia, the

stress of acute brain ischemia or resuscitation maneuvers such as intubation may produce a similar spike of blood pressure (21). We used the amplitude of the cortical somatosensory evoked potential to assess neuronal function in these anesthetized animals. This amplitude is proportional to the number of cells that are still able to function following the embolus. We, and others, have shown that a reduction in evoked response amplitude is associated with reduced cerebral blood flow (17,22). A variety of factors can influence the amplitude of the evoked potential, including temperature and attention to the stimulus, so that it is difficult to base firm conclusions on this measurement in clinical studies. However, an effect on evoked potential amplitude in controlled situations such as the one we describe has been accepted as evidence of positive or negative influences of treatments (23).

The recommendation for using the head-down position is based largely on van Allen's studies that showed, after air embolism in dogs, the bubbles distributed away from the brain when the animal was in the head-down position (7). However, van Allen gave a large volume of air that often produced cardiac arrest, and it is in the animals with low or absent blood pressure that he saw redistribution of the bubbles. Kent and Blades repeated these experiments, taking care to preserve normal blood pressure, and found no influence of head-down position on the distribution of bubbles, stating: "It is fallacious to rely upon the head-down position to protect the brain from air embolus. Our findings indicate that, if the air reaches the left ventricle and passes into the aorta, there is nothing that can be done in the way of change of position of the patient to ward off access of air in to the arteries of the brain" (13). More recent studies confirm that

bubbles in the arterial circulation distribute exclusively with blood flow, and this distribution is not influenced by buoyant forces (14). Atkinsson reported a patient in whom the head-down position seemed to lead to recovery (10). He further investigated this phenomenon in six cats with cranial windows, showing that air in the cerebral arteries cleared when the animals were head-down 5 min after embolization (10). This study is not definitive because he did no control animals, although air clears rapidly from the pial vessels in most cases (24). We can find, therefore, no experimental support for the possible beneficial consequences of the head-down position on air embolism.

The head-down position may have deleterious effects other than those addressed in this study. With the use of mechanical ventilation in our experiments we saw no effect of the Trendelenburg position on respiration and arterial blood gases. It is known that the head-down position in humans with spontaneous respiration decreases the functional residual capacity, vital capacity, and pulmonary compliance (25,26,27). These changes lead to hypoxemia (28,29) that would clearly have a negative influence on cerebral recovery. With the initiation of the head-down position hydrostatic pressure is increased at the carotid and aortic baroreceptors (30). These receptors respond with a reflex eliciting systemic vasodilation and bradycardia, even if the initial mean arterial pressure is as low as 60 mmHg (31,32). The final result of the baroreceptor reflex is a decline in mean arterial pressure and carotid blood pressure. We did not observe this in our animals, possibly because anesthesia blunted the reflex response (33), or because of damage to the carotid bulb during catheterization of the internal carotid. Lower mean

blood pressure would lessen collateral circulation in the brain and lead to further deterioration of recovery.

The poor functional recovery in the head-down group is associated of an increase in the Evans Blue albumin fluorescence, but not with any change in the amount of brain water. This apparent contradiction is best explained by the fact that the brain water measurements represent an integral of all the water extravasation over the 5 h following the cerebral air embolism, whereas the Evans Blue measurement samples only events during the last 30 min of recovery. It is known that air embolism leads to immediate blood-brain barrier opening, but that this opening rapidly clears (34). At 4-5 h, the blood-brain barrier reopens because of progression of ischemic damage in the brain (35,36); it is this later event that is detected by the extravasation of Evans Blue. Both groups experienced roughly the same amount of endothelial damage with the initial bolus of air, but the head-down group had more severe ischemic consequences, as documented by the poor recovery of the evoked potential. The amount of edema in the brain following air embolism does not in any case correlate with the amount of recovery (37), and the change in Evans Blue extravasation is probably indicative of worsening ischemia, rather than a cause of the deterioration.

We hoped that the ICP and PVI measurements would help explain the reasons for the poor evoked response recovery, but this is not the case. The ICP is persistently higher in the head-down group because of a change in the relative head to heart position, but the values of this increase are well below those that might reduce cerebral perfusion pressure enough to influence blood flow to the brain. The change in ICP with

position in brain-injured humans is not predictable, so it cannot be concluded that a change in position is always innocuous (38). The PVI increases with increasing ICP, a result that at first seems contradictory (increase in ICP should logically lead to a decrease in compliance of the CSF spaces, and therefore, reduced PVI). However, in this experiment the ICP increase is due to relative engorgement of the distensible cerebral veins in the head-down group (9,39), not to edema or to the addition of blood or tumor mass to the brain. Thus, the PVI is increased because there is an increase in the volume of distensible and compliant venous structures in the animals in the left lateral decubitus position. These vessels can react easily to an injection of mock CSF by forcing more blood to the internal jugular, resulting in a smaller rise in the ICP. This concept is supported by observations that PVI tends to increase with an increase in cerebral blood volume (40). The influence of the cerebral venous volume on PVI is also demonstrated by the increase of PVI observed when blood pressure falls below the autoregulatory range (41,42). Under these conditions, the cerebral vessels are maximally dilated, and thus contribute more to the intracranial compliance measurement.

We noted that the recovery of the animals maintained in the horizontal position in this experiment was much greater than in our previous experiments (17), despite a delay of 1 h prior to beginning recompression. The significant difference between the current control group and the original animals is the delay between the air injection and the injection of norepinephrine to induce hypertension. The effect of hypertension is to further damage the endothelial lining of blood vessels already damaged by the air. The damage wrought by the hypertension depends on the sudden dilation of perfused blood

vessels that have lost the ability to autoregulate. If the blood pressure is increased very soon after the air injection, the endothelium is not affected by this event, because significant portions of the vulnerable arterial tree are blocked by air bubbles. In fact, raising the pressure when the vessels are still plugged with air may lead to a more speedy clearance of gas (43), thus leading to improved recovery.

We feel that the current recommendation of maintaining the victim of air embolism in the head-down position until recompression is based on inadequate evidence, and that those who advocate this position ignore the deleterious effects on ICP and recovery that we have shown here. The victim of air embolism is best transported flat, and, in our opinion, would not suffer if he or she is transported in the sitting position. We would not recommend the construction of special litters designed to maintain the Trendelenburg position for air embolism cases.

REFERENCES

1. Kruse C.A., "Air embolism and other skin diving problems." Northwest Medicine, Vol. 62, pp. 525-529, 1963.
2. Stonier J.C., "A study in pre-chamber treatment of cerebral air embolism, patients by a first provider at Santa Catalina island." Undersea Biomedical Research, Vol. 12 (Suppl 58), pp. 58, 1985.
3. Pearson R.F., "Diagnosis and treatment of arterial air embolism." In: Schilling C.W., Carlston C.B., and Mathias R.A., eds. The Physicians Guide to Diving Medicine. New York: Plenum Press, 1984, pp. 333-367.
4. Durant T.M., Long J., and Oppenheimer M.J., "Pulmonary (venous) air embolism." American Heart Journal, Vol. 33, pp. 269-281, 1947.
5. Durant T.M., Oppenheimer M.J., Lynch P.R., Ascanio G., and Webber D., "Body position in relation to venous air embolism: A roentgenologic study." American Journal of Medical Sciences, Vol. 227, pp. 509-520, 1954.
6. Oppenheimer M.J., Durant T.M., and Lynch P. "Body position in relation to venous air embolism and the associated cardiovascular-respiratory changes." American Journal of Medical Sciences, Vol. 225, pp. 362-373, 1953.
7. Van Allen C.M., Hrdina L.S., and Clark J., "Air embolism from the pulmonary vein." Archives of Surgery, Vol. 19, pp. 567-599, 1929.
8. Stangland K.J., Milde J.H., and Michenfelder J.D., "Canine cerebral function and blood flow after complete cerebral ischemia: Effect of head position." Anesthesiology, Vol. 64, pp. 430-434, 1986.

9. Toole J.F., "Effects of change of head, limb and body position on cephalic circulation." New England Journal of Medicine, Vol. 279, pp. 307-311, 1968.

10. Atkinson J.R., "Experimental air embolism." Northwest Medicine, Vol. 62, pp. 699-703, 1963.

11. Bagdonas A., Stuckey J., Dennis C., Piera J., Domingo R., and Cappelletti R., "The role of position in the development of cerebral air embolism following air injection at the base of aorta." Surgical Forum, Vol. 10, pp. 653-656, 1960.

12. Bagdonas A., Stuckey J., Dennis C., and Piera J., "Studies of the effects of position on the development of cerebral air embolism during open-heart surgery." Surgery, Vol. 52, pp. 487-493, 1962.

13. Kent E.M. and Blades B., "Experimental observation upon certain intracranial complications of particular interest to the thoracic surgeon." Journal of Thoracic Surgery, Vol. 11, pp. 434-455, 1942.

14. Butler B.D., Laine G.A., Leiman B.C., Walters D., Kurusz M., Sutton T., Katz J., "Effect of the Trendelenburg position on the distribution of arterial air emboli in dogs." Annals of Thoracic Surgery, Vol. 45, pp. 198-202, 1988.

15. Moore R.M. and Braselton S.W., "Injections of air and carbon dioxide into a pulmonary vein." Annals of Surgery, Vol. 112, pp. 212-218, 1940.

16. Kapuscinski A., "Further studies on postischemic brain edema: Contribution by disorders of central circulation and respiratory mechanical difficulties." Advances Neurology, Vol. 20, pp. 321-332, 1978.

17. Dutka A.J., Hallenbeck J.M., and Kochaneck P., "A brief episode of severe arterial hypertension induces delayed deterioration of brain function and worsens blood flow after transient multifocal cerebral ischemia." Stroke, Vol. 18, pp. 386-395, 1987.

18. Shapiro K., Marmarou A., and Shulman K., "Characterization of clinical CSF dynamics and neural axis compliance using the pressure volume index: 1. The normal pressure volume index." Annals of Neurology, Vol. 7, pp. 508-514, 1980.

19. Marmarou A., Shulman K., and Rosende M., "A non linear analysis of the cerebrospinal fluid system and intracranial pressure dynamics." Journal of Neurosurgery, Vol. 48, pp. 332-344, 1978.

20. Evans D.E., Kobrine A., Weatersby P., and Bradley M., "Cardiovascular effects of cerebral air emboli." Stroke, Vol. 12, pp. 338-344, 1981.

21. Ropper A.H., Kennedy S.K., and Zervas N.T., "Neurological and Neurosurgical Intensive Care." Baltimore: University Park Press, 1983, pp. 59-62.

22. Branston N., Symon L., Crockard H., and Pasztor E., "Relationship between cortical evoked potential and local cortical blood flow following acute middle cerebral artery occlusion in the baboon." Experimental Neurology, Vol. 45, pp. 195-208, 1974.

23. Ropper A.H., "Evoked potentials in cerebral ischemia." Stroke, Vol. 17, pp. 3-5, 1986.

24. Fries C.C., Levowitz B., Adler S., Cook S., Karlson K.E., and Dennis C., "Experimental cerebral gas embolism." Annals of Surgery, Vol. 145, pp. 461-470, 1957.

25. Wilcox S. and Vandam L.D., "Alas, Poor Trendelenburg and his position! A critique of its uses and effectiveness." Anesthesia and Analgesia, Vol. 67, pp. 574-578, 1988.

26. Case E.H. and Stiles J.A., "The effects of various surgical positions on vital capacity." Anesthesiology, Vol. 7, pp. 29, 1946.

27. Nunn J.F., Coleman A.J., Sachithandan T., Bergman N.A., and Laws J.W., "Hypoxemia and atelectasis produced by forceful expiration." British Journal of Anaesthesia, Vol. 37, pp. 3, 1965.

28. Scott D.B., Lees M.M., and Taylor S.H., "Some respiratory effects of the Trendelenburg position during anaesthesia." British Journal of Anaesthesia, Vol. 38, pp. 174-178, 1966.

29. Scott D.B. and Slawson K.B., "Respiratory effects of prolonged Trendelenburg position." British Journal of Anaesthesia, Vol. 40, pp. 103-106, 1968.

30. Tomaselli C.M., Kenney R.A., Frey M.A., and Hoffler G.W.L., "Cardiovascular dynamics during the initial period of head-down tilt." Aviation, Space and Environmental Medicine, Vol. 58, pp. 3-8, 1987.

31. Sibbald W.J., Paterson N.A., Holliday R.L., and Baskerville J., "The Trendelenburg position: hemodynamic effects in hypotensive and normotensive patients." Critical Care Medicine, Vol. 7, pp. 218-224, 1979.

32. Abel F.L. and Waldhausen J.A., "Influence of posture and passive tilting on venous return and cardiac output." American Journal of Physiology, Vol. 215, pp. 1058-1066, 1968.

33. Fluckiger J.P., Sonnay M., Boilat N., and Atkinson J., "Attenuation of the baroreceptor reflex by general anesthetic agents in the normotensive rat. European Journal of Pharmacology, Vol. 109, pp. 105-109, 1985.

34. Nishimoto K., Wolman M., Spatz M., and Klatzo I., "Pathophysiologic correlations in the blood-brain barrier damage due to air embolism." Advances in Neurology, Vol. 20, pp. 237-248, 1978.

35. Kuroiwa T., Ting P., Martinez H., and Klatzo I., "The biphasic opening of the blood brain barrier to proteins following temporary middle cerebral artery occlusion." Acta Neuropathologica, Vol. 68, pp. 122-129, 1985.

36. Suzuki R., Yamaguchi T., Kirino T., Orzi F., and Klatzo I., "The effects of 5-minute ischemia in Mongolian Gerbils: Blood-brain barrier, cerebral blood flow, and local cerebral glucose utilization changes." Acta Neuropathologica, Vol. 60, pp. 207-216, 1983.

37. Hallenbeck J.M., Leitch D.R., Dutka A.J., and Greenbaum L.G., "The amount of circumscribed brain edema and the degree of post-ischemic neuronal recovery do not correlate well." Stroke, Vol. 13, pp. 77-80, 1982.

38. Ropper A.H., Rourke D., and Kennedy S.K. "Head position, intracranial pressure, and compliance." Neurology, Vol. 32, pp. 1288-1291, 1982.

39. Wilkins R.W., Brandley S.E., and Friedland C.K., "The acute circulative effects of the head-down position (negative G) in normal man, with a note on some measures designed to relieve cranial congestion in this position." Journal of Clinical Investigation, Vol. 29, pp. 940-949, 1950.

40. Nyary I. and Vajda J., "Relationship of cerebral blood volume changes and estimated intracranial compliance." Intracranial Pressure, Vol. 5, pp. 316-318, 1983.

41. Gray W.J. and Rosner M.G., "Pressure-volume index as a function of cerebral perfusion pressure. Part 1: The effects of cerebral perfusion changes and anesthesia." Journal of Neurosurgery, Vol. 67, pp. 373-376, 1987.

42. Gray W.J. and Rosner M.G., "Pressure-volume index as a function of cerebral perfusion pressure. Part 2: The effects of low cerebral perfusion pressure and autoregulation." Journal of Neurosurgery, Vol. 67, pp. 377-380, 1987.

43. Gorman D.F., Browing D.M., and Parsons D.W., "Redistribution of cerebral arterial gas emboli: A comparison of treatment regimens." In: Bove A.A., Bachrach A.J., and Greenbaum L.J., eds. Underwater and Hyperbaric Physiology IX. Proceedings of the Ninth International Symposium on Underwater and Hyperbaric Physiology. Bethesda: Undersea and Hyperbaric Medical Society, 1987, pp. 1031-1050.

TABLE 1

Results of physiologic monitoring of animals. All results mean ± SD.

	Hz Group (N = 9)	HD Group (N = 8)
Mean Arterial Pressure (mmHg)		
baseline	129 ± 19	118 ± 19
pre-treatment	111 ± 20	99 ± 14
post-treatment	128 ± 17	116 ± 17
Heart Rate (BPM)		
baseline	116 ± 22	103 ± 23
pre-treatment	127 ± 23	116 ± 32
post-treatment	137 ± 26	130 ± 21
Hematocrit (%)		
baseline	43 ± 4	42 ± 8
pre-treatment	42 ± 4	42 ± 7
post-treatment	42 ± 3	41 ± 6
Arterial pH		
baseline	7.39 ± 0.5	7.40 ± 0.1
pre-treatment	7.43 ± 0.2	7.39 ± 0.5
post-treatment	7.40 ± 0.5	7.35 ± 0.3
Arterial pO_2 (mmHg)		
baseline	88 ± 10	93 ± 7
pre-treatment	98 ± 6	97 ± 5
post-treatment	94 ± 5	92 ± 4
Arterial pCO_2 (mmHg)		
baseline	37 ± 4	36 ± 3
pre-treatment	33 ± 3	35 ± 4
post-treatment	37 ± 3	40 ± 3
Weight (kg)	12.8 ± 1	11.7 ± 1
Amount of pentobarbital given (mls of 50 mg/ml)	12 ± 2	11 ± 2
Fluid in (saline or ringers lactate, mls)	625 ± 319	524 ± 343
Urine out (mls)	160 ± 69	115 ± 82
Temperature at end of experiment (° C)	38.6 ± 0.4	38.1 ± 0.6

TABLE 2

Timing and intensity of hypertension induced by norepinephrine, and treatment delay.

	Hz Group (N = 9)	HD Group (N = 8)
Minutes from Air to Levophed Injection	2.2 ± 0.6	3.3 ± 0.9
Maximum Mean Arterial Pressure, mmHg	300 ± 98	263 ± 48
Cerebral Perfusion Pressure at Maximum MABP, mmHg	250 ± 96	191 ± 70
Minutes while Systolic Blood Pressure was > 200 mmHg	4.9 ± 3.3	3.5 ± 1.4
Minutes from Air to Treatment Table	72 ± 8.2	77 ± 3.0

TABLE 3

Two-way analysis of variance reports for evoked potentials, head-down versus control at various times.

1. All time points except for 2 minutes post air

Source	DF	Sum-Squares	Mean Square	F-Ratio	Prob > F
A (RXGROUP)	1	27514.95	27514.95	80.73	0.0000
B (TIME)	18	13832.21	768.4561	2.25	0.0029
AB	18	5068.11	281.5617	0.83	0.6690
ERROR	285	97134.47	340.8227		
TOTAL (Adj)	322	144428.1			

2. 2-way anova for pre-hyperbaric treatment phase only

Source	DF	Sum-Squares	Mean Square	F-Ratio	Prob > F
A (RXGROUP)	1	278.1636	278.1636	1.31	0.2567
B (TIME)	3	3871.385	1290.462	6.08	0.0011
AB	3	127.2081	42.40271	0.20	0.8960
ERROR	60	12725.57	212.0928		
TOTAL (Adj)	67	17036.88			

3. 2-way anova during treatment period only

Source	DF	Sum-Squares	Mean Square	F-Ratio	Prob > F
A (RXGROUP)	1	31710.71	31710.71	84.53	0.0000
B (TIME)	14	1460.387	104.3134	0.28	0.9957
AB	14	466.9752	33.35537	0.09	1.0000
ERROR	225	84408.91	375.1507		
TOTAL (Adj)	254	118117.7			

TABLE 4

Wet-to-Dry Weight Measurements: % of wet weight of the brain that is water. Mean ± SD.

Non-Embolized Animals (N = 2)	
Right Cortex	80.4 ± 0.75
Left Cortex	81.4 ± 0.10
Right Centrum Semiovale	64.5 ± 0.71
Left Centrum Semiovale	65.4 ± 0.67
HZ Group (N = 9)	
Right Cortex	82.4 ± 1.44
Left Cortex	81.6 ± 1.52
Right Centrum Semiovale	67.6 ± 2.25
Left Centrum Semiovale	67.6 ± 2.19
HD Group (N = 7)	
Right Cortex	81.4 ± 0.84
Left Cortex	81.5 ± 1.27
Right Centrum Semiovale	66.8 ± 0.90
Left Centrum Semiovale	67.3 ± 2.25

TABLE 5

Evans Blue Fluorescence Measurements.

	Hz Group (N = 6)	HD Group (N = 8)
Left Hemisphere		
Cortical Gray	62.5 ± 6.7	103.7 ± 33.4
Subcortical White	28.3 ± 4.2	45.5 ± 17.7
Right Hemisphere		
Cortical Gray	66.4 ± 7.5	97.9 ± 33.4
Subcortical White	28.2 ± 3.4	46.9 ± 19.3

TABLE 6

Intracranial pressures and cerebral perfusion pressures in HD and Hz groups.

	Hz Group (N = 9)	HD Group (N = 8)
Baseline	2.6 ± 2.4	10.3 ± 6.1
2 minutes after air embolism	17.6 ± 7.6	33.0 ± 18.0
Prior to recompression	14.4 ± 7.7	22.3 ± 5.5
After recompression	8.2 ± 2.8	21.5 ± 11.2
Cerebral Perfusion Pressure mmHg		
baseline	126 ± 20	108 ± 22
pre-treatment	97 ± 22	76 ± 13
post-treatment	119 ± 17	77 ± 37

TABLE 7

Pressure volume index at various times in the experiment, in mls, mean ± SD.

	Hz Group (N = 9)	HD Group (N = 8)
Baseline	0.86 ± 0.15	1.43 ± 0.54
10' after air embolism	1.41 ± 0.31	1.75 ± 0.54
20' after air embolism	1.48 ± 0.31	1.73 ± 0.72
30' after air embolism	1.49 ± 0.31	1.81 ± 0.31
End of Treatment	1.05 ± 0.16	1.53 ± 0.55

FIGURE LEGENDS

Figure 1: This figure gives the depth and time profile for the hyperbaric treatment used for both head-down and horizontal groups. It differs from the U.S. Navy Treatment Table 6A in that it is 90 min shorter; this table eliminates 1 h of oxygen breathing at 30 fsw, and the slow ascent to surface from 30 fsw.

Figure 2: Percent recovery of evoked response, at 15-minute intervals after injection, head-down and control (horizontal) groups, mean ± 95% confidence limits.

Figure 3: Final intracranial pressure versus fluorescence microscopy relative values. This is a significant correlation as indicated by the regression line.

Figure 4: Relationship between pressure-volume index and intracranial pressure; in both groups, before and after air embolism. This indicates that cerebral venous dilation is the likely cause of ICP increase in head-down group.

Figure 1

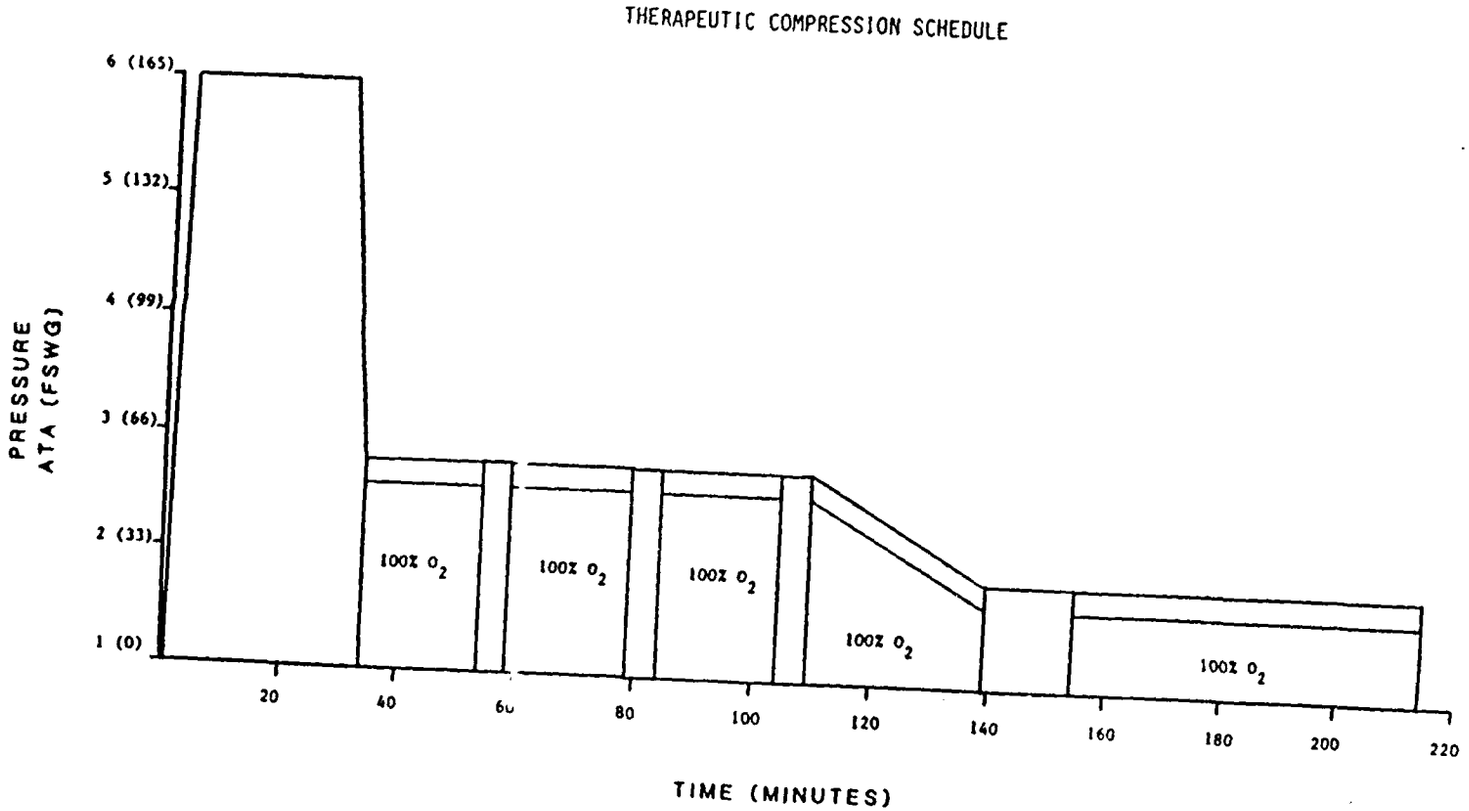

THERAPEUTIC COMPRESSION SCHEDULE
PRESSURE ATA (FSWG)
6 (165)
5 (132)
4 (99)
3 (66)
2 (33)
1 (0)
100% O2
100% O2
100% O2
100% O2
100% O2
20
40
60
80
100
120
140
160
180
200
220
TIME (MINUTES)

Figure 2

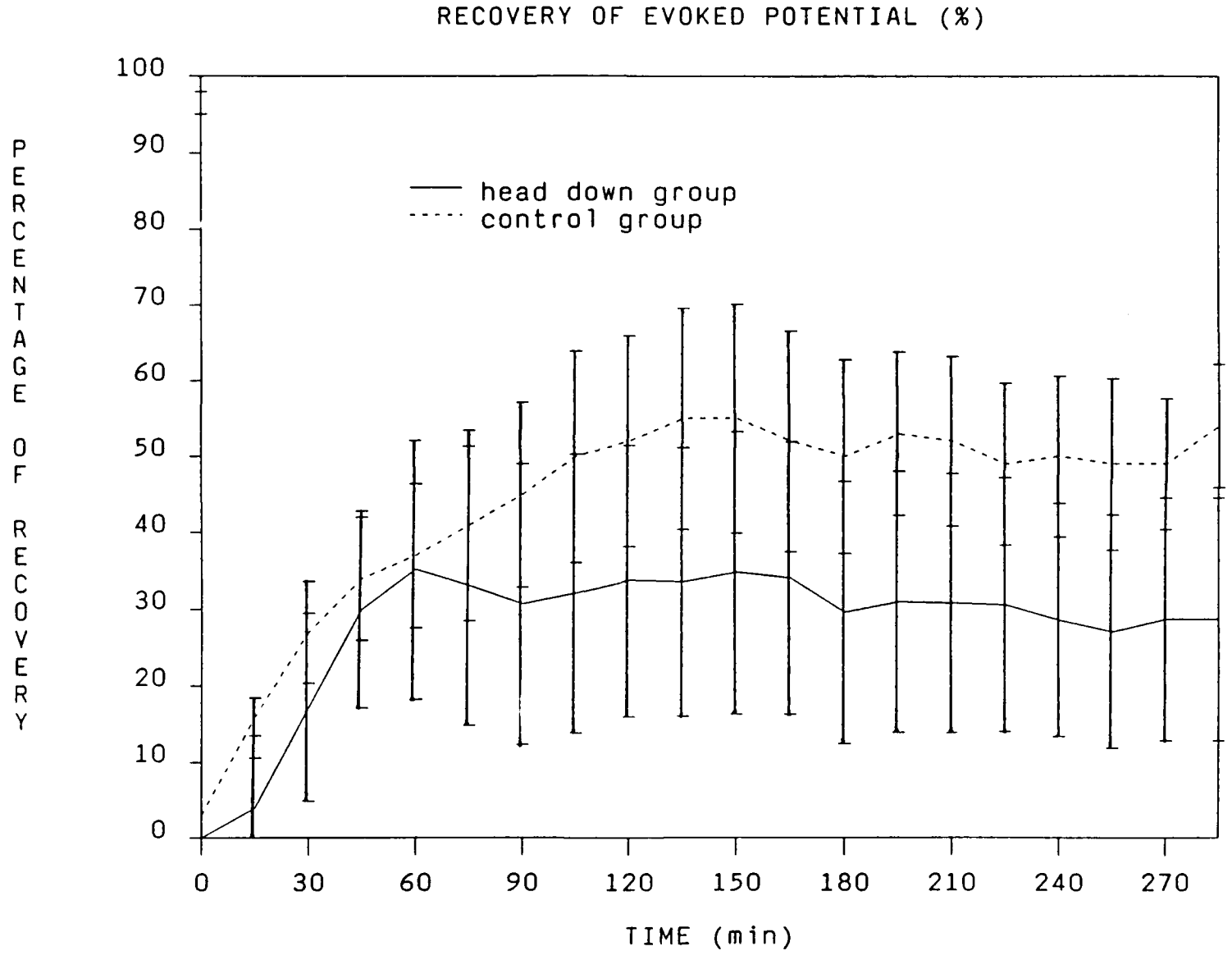

RECOVERY OF EVOKED POTENTIAL (%)
PERCENTAGE OF RECOVERY
100
90
80
70
60
50
40
30
20
10
0
head down group
control group
0
30
60
90
120
150
180
210
240
270
TIME (min)

Figure 3

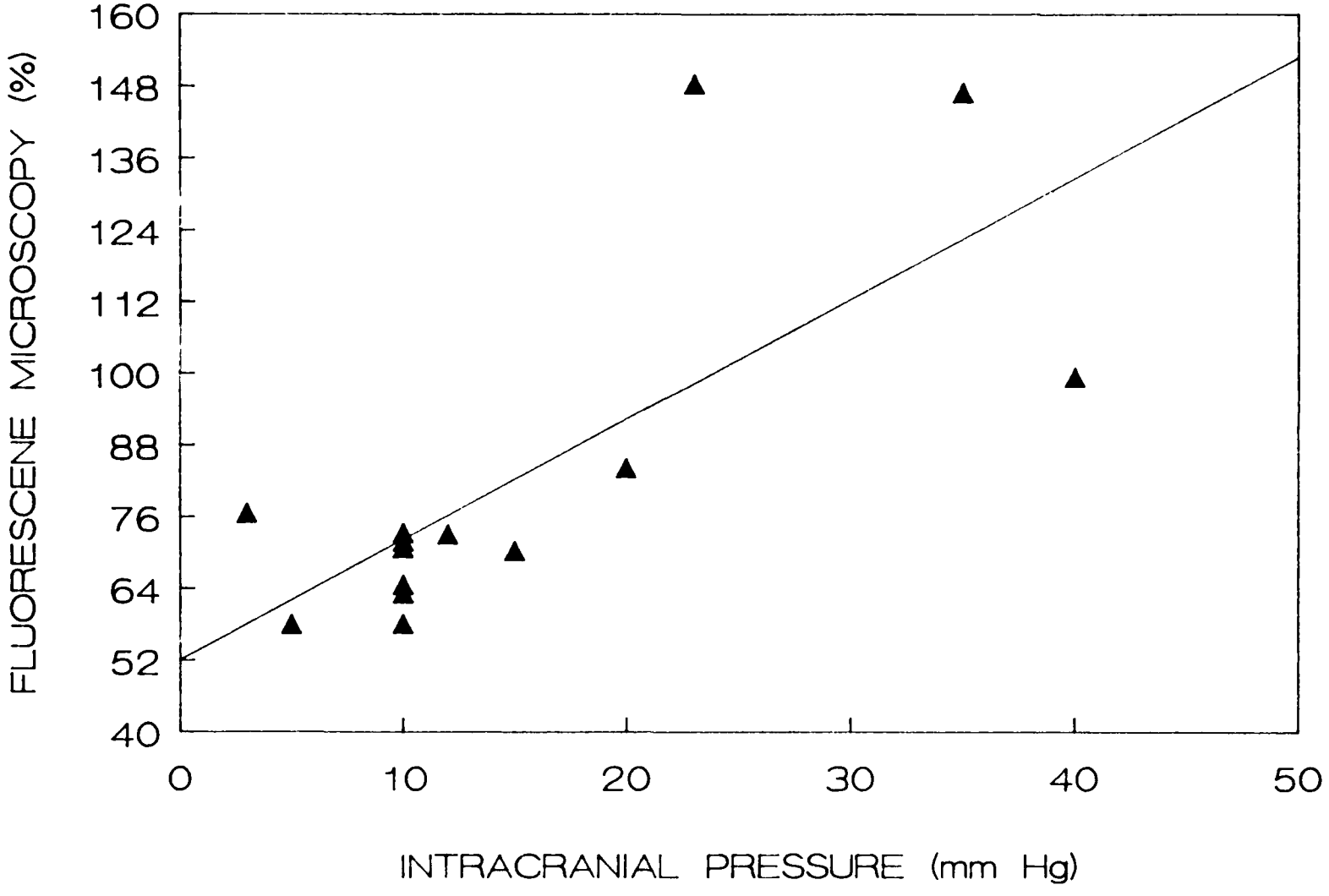
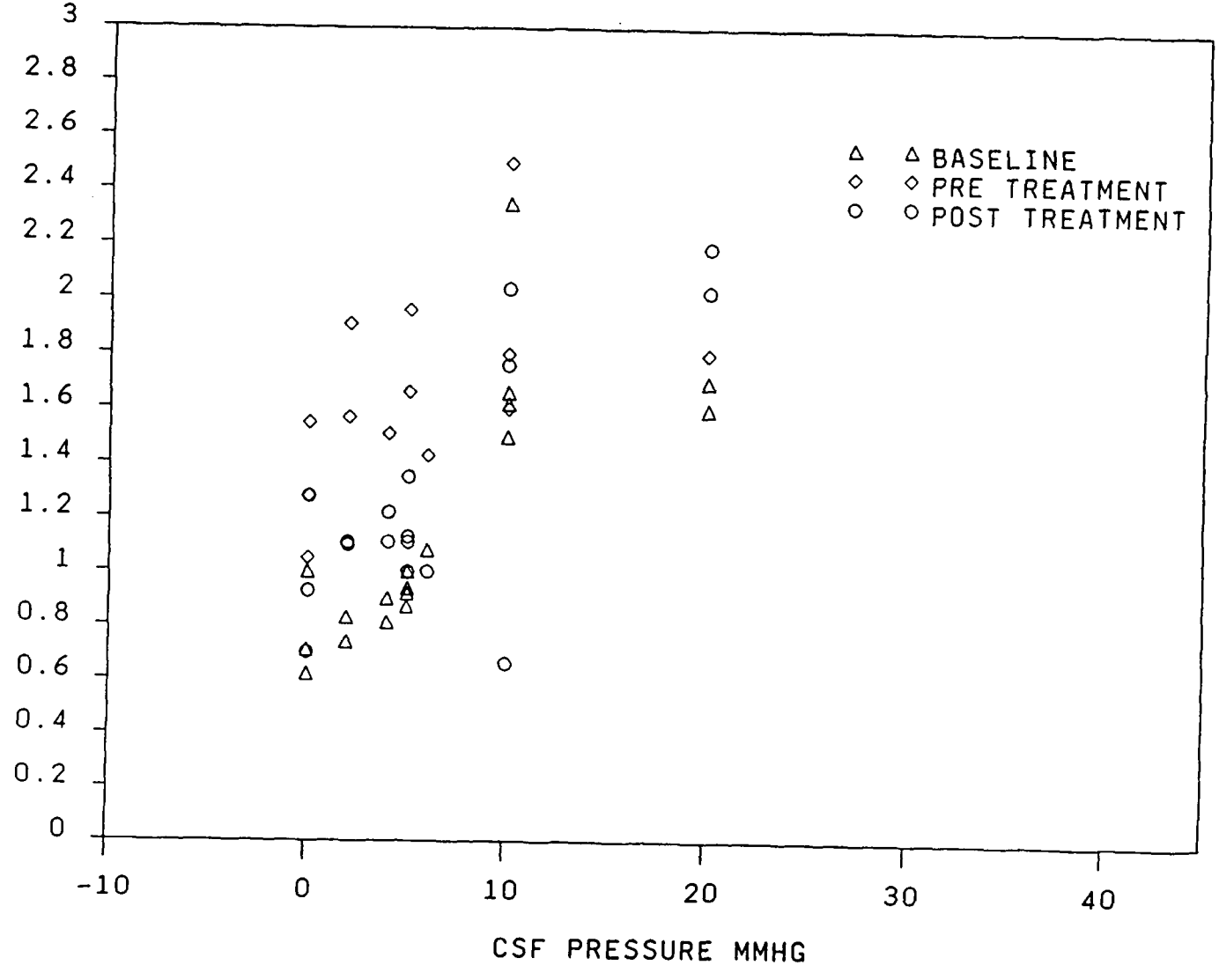

160
148
136
124
112
100
88
76
64
52
40
FLUORESCENE MICROSCOPY (%)
0
10
20
30
40
50
INTRACRANIAL PRESSURE (mm Hg)

Figure 4


3
2.8
2.6
2.4
2.2
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-10
0
10
20
30
40
CSF PRESSURE MMHG
BASELINE
PRE TREATMENT
POST TREATMENT