Effect of Isovolemic Hemodilution on Cerebral Blood Flow Following Experimental Head Injury*

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The pathophysiology of head injury results from a complex set of interrelated and interdependent factors such as concussion, changes in intracranial pressure and cerebral blood flow, cerebral edema, and cerebrospinal production and absorption. This report is primarily concerned with alterations in cerebral blood flow during acute compression of the brain and in the hours thereafter. While other studies have been carried out on blood flow during various types of head injury and increased intracranial pressure, few have investigated the beneficial effects of increasing blood flow during poor flow conditions. This investigation utilizes our model of extradural compression previously described. The model furnishes a relatively controlled means of altering brain compression, brain distortion, and intracranial pressure. It also lends itself to greater reliability in studies of mortality and morbidity in a series of animals.

This study was carried out in three parts:
1. Changes in cerebral blood flow and arteriovenous oxygen difference induced by extradural compression.
2. Alterations in cerebral blood flow with isovolemic hemodilution.
3. Effects of hemodilution and hemodilution plus hyperbaric oxygenation on mortality and morbidity following cerebral injury.

Material and Methods

Blood Flow Studies. Twenty-six mongrel dogs were used, varying in weight from 26 to 35 lbs. Under sodium pentobarbital anesthesia (10 mg/lb), extradural balloons were placed over the frontal cortices bilaterally, the right utilized for compression and the left for recording intracranial pressure. Silver electrodes were placed over the parietal cortices for bipolar recording of the EEG. A femoral arterial catheter was inserted to the descending aorta for obtaining blood gas samples and for recording systemic blood pressure. A pneumatactic device measured respiratory rates, and a Beckman Dynograph recorder with Statham strain gauges was used for recording data. A PE 90 polyethylene catheter was inserted 1 cm into the anterior superior sagittal sinus for obtaining venous blood samples.

A right neck dissection was carried out as described by Rosomoff and Holaday in which the external carotid vessels were tied off from the common carotid artery, thus isolating the flow to the internal carotid artery. The right vertebral artery was isolated as it branched from the right subclavian artery. Previous India ink injection studies we performed indicate that approximately 95% of the blood flow in these vessels is limited to the intracranial circulation. More precise measurements of cerebral flow could have been obtained by using primate animals which have fewer anastomotic channels with the external carotid system than the dog. The dog was used, however, since more animals could be used for a survival study with the available funds, and relative changes in flow were of greater importance than absolute flow values. Square-wave Carolina electromagnetic flow probes were used to measure flow in the vertebral and common carotid vessels. Probes were calibrated on isolated perfused vessels using whole blood at varying hematocrits. As recording was only performed on the vessels of the right side, the sum of flow in the right vertebral and carotid arteries was doubled to approximate total cerebral blood flow. Arterial and venous blood samples were analyzed for PO₂.

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PCO₂, and pH with a Beckman physiological gas analyzer (Model 160).

Expansion of the right extradural balloon was carried out with 0.1 to 0.2 cc increments of water over a 1½- to 2-hr period, to the point of a self-sustained rise in intracranial pressure and blood pressure and a bilaterally flat EEG for 3 min. Periodic sagittal sinus and arterial blood samples were drawn for blood gas analysis. After decompression of the expanding balloon, dogs were monitored for approximately 8 hrs.

Eight dogs were studied under condition of spontaneous respiration. A No. 30 endotracheal tube was employed to maintain an airway. In eight other dogs, controlled respirations were used. A Bird respirator, which used room air, maintained a PaO₂ of approximately 80 mm Hg and a PaCO₂ of 30 mm Hg.

A third group of 10 animals was prepared and compressed as above and then subjected to isovolemic hemodilution within 10 minutes of deflation of the extradural balloon. Hemodilution was carried out over a 10-min period using a 5 mm diameter polyethylene catheter inserted to the inferior vena cava via the femoral vein. It was performed by rapid withdrawal of 50 cc of venous blood and replacement of 50 cc of 6% dextran in normal saline (Gentran-MW 75,000)* until the hematocrit was reduced from a mean value of 47 to 20. This required 450 to 500 cc exchanged in all animals. Hemoglobin concentration was reduced to between 7 and 8 gm%. Flow measurements and arterial and venous blood gases were monitored over the next 4 hrs. Flow probes were previously calibrated with whole blood at a hematocrit of 45 and with whole blood diluted with Gentran to a hematocrit of 20.

Survival Studies. Fifty dogs were included in this series. All were subjected to extradural compression as described above to the point of spontaneously rising intracranial pressure and a flat EEG bilaterally for 3 min (Cal 50 μV = 5 to 10 mm). These animals were allowed spontaneous respiration during the compression period. Following deflation of the extradural balloon, 20 animals were utilized as controls, 20 were subjected to isovolemic hemodilution as described above, and 10 after hemodilution were placed in a hyperbaric oxygen chamber pressurized to 2 atmospheres with 100% O₂. The latter group were left in the chamber for 4 hrs and received no further oxygen therapy after this time.

Results

Blood Flow Studies. Figure 1 demonstrates graphically the changes in the eight dogs studied under spontaneous respiration. The rate of rise in intracranial pressure is primarily dependent on the rate of expansion of the extradural balloon. However, it should be noted that nearing the point of maximal compression, smaller increments of fluid, added at less frequent intervals, were used to raise the pressure. The steeper slope near this point reflects the increasing loss of compensatory accommodation to the expanding intracranial mass.

Blood pressure and pulse showed the typical "Cushing response" to increased intracranial pressure; that is, a rising blood pressure and slowing pulse as the intracranial pressure is elevated. After deflation of the compression balloon, only a slow spontaneous rise in intracranial pressure was noted in these animals, never to exceed 20 mm Hg.

Cerebral blood flow (CBF) started to decrease after a pressure of approximately 40 mm Hg (520 mm H₂O) had been reached and continued to decline until deflation of the expanding balloon. With deflation there was a surge of flow followed by a subsequent decline in flow over the next 8 hrs, which was not associated with a decrease in blood pressure or increase in the intracranial pressure (ICP). It should be noted that as the point of maximal compression was approached, periodic waves were noted in the ICP and blood pressure. Figure 2 shows the synchronization of these waves with respiration and the concomitant rise in blood flow with the rise in blood pressure. Figure 1 plots the flow at the basal levels, rather than at peaks of these "vasopressor" waves, so that as maximal compression was approached the peaks of these waves accounted for some recovery of flow according to their frequency.

Cerebral arteriovenous (A-V) O₂ difference, calculated from the PaO₂ and sagittal
sinus $P_vO_2$ ($SSP_vO_2$), showed an increase with increasing intracranial pressure until appearance of the vasopressor waves, when it decreased. This reflected the burst of increased flow during these episodes. Following deflation, the A-V $O_2$ difference was initially low, corresponding to the surge of flow upon decompression, and was followed by a widening value as flow later decreased.

Oxygen consumption, being the product of blood flow and A-V $O_2$ difference, was also affected (Fig. 1); in early phases of increased pressure, slowing of the circulation was compensated by widening of the A-V $O_2$ difference. Later, compensation was no longer evident with decline in the cerebral $O_2$ consumption. This appeared to be correlated with a decrease in the EEG amplitudes. After
deflation, O₂ consumption became stable; however, as noted above, there was a gradual decline in blood flow and gradual increase in A-V O₂ difference. The death of the animal appeared to occur when the decrease in blood flow could no longer be offset by an increasing O₂ extraction. All animals died rather abruptly within 36 hours from respiratory arrest, without significant recovery of consciousness.

Eight animals were studied under controlled ventilation to investigate changes during the vasopressor waves. With controlled ventilation, these waves were more
sustained in character rather than occurring in bursts triggered by periodic respiration (Fig. 3). This allowed more time for obtaining blood samples during such episodes. Figure 4 demonstrates a recording of an animal with controlled ventilation nearing the point of maximal compression; blood pressure is rising slowly with concomitant rise in the blood flow, and intracranial pressure is being increased gradually with increments of 0.1 cc water. Blood gas measurement at point 1, 2, and 3 reflected a rising SSP, O₂, being 48, 54, and 59 respectively. The vasoconstrictor waves at the point of maximal compression were always associated with a narrowing of the A-V O₂ difference. Figure 5 indicates the changes in cerebral blood flow and A-V O₂ difference in ventilated animals. Blood flow was not so markedly decreased as in non-ventilated animals, but showed a gradual deterioration after the period of compression. A-V O₂ difference changes were similar to those described for the non-ventilated animals. These animals all died within 24 hours. They all tended to have a greater intracranial pressure reached faster following deflation of the extradural balloon than that of the group studied under spontaneous respiration.

Figure 6 compares the changes in blood flow and A-V O₂ difference induced by hemodilution over control values. Cerebral blood flow was improved 61% in the immediate post-compression period, but only 10% after approximately 4 hours. Figure 7 demonstrates a flow record from the right internal carotid artery during the period of deflation of the extradural balloon and subsequent hemodilution period. Figure 8 is a record of an animal subjected to hemodilution and showing resultant stabilization of the intracranial pressure, improvement in respiration, and restoration of the EEG. Little change was noted in the systemic arterial blood pressure with hemodilution.

Survival Studies. In the control group of

Fig. 3. Record of a dog with spontaneous rise in intracranial pressure, blood pressure, and blood flow in right internal carotid artery. Respiration controlled with respirator. Time scale = 1-min interval during slow record, 1-sec interval during fast record.
20 dogs, 19 died within 36 hours. The surviving dog made a relatively good recovery by the 10th day.

In the group of 20 animals in which hemodilution was carried out after compression, nine animals survived and were sacrificed on the 10th day. One dog died on the 6th day from meningitis. All but one of these surviving dogs were walking and able to maintain an adequate oral intake by the
second day. Vision and hearing were intact. All had evidence of weakness on the left side for several days and several had evident weakness of the hindquarters. One dog, though surviving 10 days, was lethargic and dull during this period, appearing to have greater neurological damage than the rest of the surviving animals.

In the group of 10 animals treated with both hemodilution and hyperbaric oxygen conjointly, by the 10th day seven had made a good recovery and one a poor recovery.

In summary, the mortality of the control group was 95%; of the group subjected to hemodilution, 50%; and of the group with both hemodilution and hyperbaric oxygen, 20%. Most of the surviving animals were in good condition.

Discussion

Slowing of the cerebral circulation during periods of increased intracranial pressure has been described previously by numerous workers.\(^6,7,17,21\) This appears to be related to compression and obstruction of subarachnoid veins with cuffing at the superior sagittal sinus. After a certain level of increased pressure is attained, reflex increase in the blood pressure occurs. This has been labeled the “vasopressor response,” or “Cushing response.” It is effective in partially restoring blood flow. Ryder, et al.,\(^16\) and Langfitt, et al.,\(^7,8\) have postulated that near this point there is also dilation of the cerebral vasculature secondary to loss of vasomotor tone which serves to increase the intracranial blood volume and in turn escalate the intracranial pressure. This vicious cycle continues until the intracranial pressure equals the blood pressure and all cerebral flow ceases. It might also be noted that the partial restoration of flow by the vasopressor response and in the immediate period after deflation of the expanding balloon is marked by narrowing of the cerebral A-V O\(_2\) difference. This appears to be the result of blood flow through either metabolically depressed tissue, or flow through preferred channels and
A-V shunts that have remained open. Although the presence of A-V shunts in the cerebral circulation has never been widely accepted, Rowbotham and Little\(^6\) have demonstrated their existence in the pial circulation. It would seem likely that the narrow A-V \(O_2\) difference would be a reflection of flow through these anatomical shunts as well as metabolic shunting through inert areas. This finding of narrowing of the A-V \(O_2\) difference can be correlated with the “red veins” described by Ecker\(^3\) and Feindel and Perot\(^5\) following cerebral trauma or epileptic seizures. Studies of the microcirculation by Gelin\(^4\) have also indicated that defective flow and sludging in the capillary bed predisposes to A-V shunting.

While changes in blood flow during the period of acute brain insult are important, it is the time period following injury which is of vital importance to therapeutics. Little is known about flow in this period. Recently Ames, \textit{et al.},\(^1\) in studying cerebral ischemia have noted endothelial and perivascular astrocytic swelling following interruption of blood flow to the brain. This appears to be secondary to blood stasis and breakdown of the \(Na^+\) pump mechanism and results in extrusion of fluid into the perivascular space. This results in encroachment upon the vascular lumen, which progresses to sludging of the blood flow after reestablishment of the circulation. One could postulate a similar mechanism to account for the decreasing flow noted in the present study after relief of the extradural compression. More specifically, the ischemia during the acute insult may result in damage and swelling of the vasculature which gives rise to a circulatory defect after the initial injury. Observation of pial vessels after cerebral injury has revealed spasm at the arteriolar level, which also contributes to decreased flow in this period.\(^20, 21\)

Post-compression isovolemic hemodilution was carried out as a means of preventing the progressive deterioration of blood flow in this period. While it may be possible to alter blood flow by changes in blood pressure and increase in the cross-sectional area of the microcirculation, we chose to alter the blood viscosity. Elevation of the blood pressure, or dilation of the cerebral vessels (they may already be maximally dilated) would lead to deleterious increase in intracranial pressure.

Race, \textit{et al.},\(^12\) have shown that normovolemic hemodilution in dogs with Gentran to
the level used in this study results in an increase in cardiac output of approximately 100%, with a 129% and 71% increase in the vertebral and carotid artery flow respectively. This appears to be the result of a decrease in blood viscosity and thereby a decrease in the peripheral resistance. Further, Dedichen, et al., have shown that it is a decrease in viscosity after dilution which lowers peripheral resistance rather than vasodilation secondary to tissue anoxia. Since vessels less than 100 μ in size, or the microcirculation, account for 90% of the peripheral resistance, it can be assumed that lowering the blood viscosity improves the flow at this point. It has been noted that hemodilution is particularly effective in reducing blood viscosity at low shear rates and is therefore more effective in regulation of the slow flow of the microcirculation. Sundt and Waltz have made observations in the pial circulation following occlusion of the middle cerebral artery in monkeys and the changes induced by hemodilution. They have noted increase in velocity of flow in veins with dislodgment and decreased aggregation of erythrocytes and platelets in areas affected by the vascular occlusion.

Low-molecular-weight dextran (Rheomacrodex, MW 40,000), which in addition to hemodilution acts by altering the red blood corpuscle charge and agglutination properties, was not used since it has an osmotic effect on the brain. This may lower the intracranial...
pressure with beneficial results not attributable to improvement in the microcirculation. Dextran (MW 75,000) was therefore used, being strictly a diluting agent with an osmotic effect similar to that of plasma.

Reduction of the hematocrit to 20 was found to reduce the hemoglobin concentration to 7 to 8 gm%. Although this results in a severe reduction in the oxygen-carrying capacity of the blood, it is adequate for basal oxygen requirements at normal flow rates and temperature.12 The fact that the A-V $O_2$ difference is less than might be expected after hemodilution, may reflect the low oxygen-carrying capacity of the blood and the inability to extract further oxygen in low flow areas. More likely, the narrow A-V $O_2$ in the initial period following hemodilution represents increased flow through areas previously ischemic and rendered metabolically inert and depressed by the build-up of lactic acid and its accompanying acidosis. While the reduction in oxygen-carrying capacity may offset some of the beneficial improvement in flow, in terms of $O_2$ delivered to the brain, the capacity to move other important metabolites and metabolic products is not so severely altered. It may be in this sphere that the beneficial results occur. Alternatively, it may be that, while the oxygen-carrying capacity is reduced, the oxygenated blood that is present is being more widely distributed.

In the third phase of this study, hyperbaric oxygen was used to compensate for the loss in oxygen-carrying capacity of the blood following hemodilution. At 2 atmospheres pressure, approximately 4.6 cc $O_2$/100 cc blood can be physically dissolved and compensate for the loss of approximately 3.5 gm% hemoglobin. Recent studies by Sukoff, et al.,18 have shown a decrease in cerebral edema following head injuries treated with hyperbaric oxygen. Recently, Moody, et al.,19 have studied the effects of hyperbaric oxygen alone on animals subjected to the same type and level of injury used in this study. They have found a 50% survival in these animals. The greater improvement with hemodilution would appear to be the effect of better distribution of the hyperoxygenated blood.

The fact that the majority of dogs that survived in the experimental groups had little gross neurological deficit after 10 days indi-cates that irreversible neuronal damage had not occurred with the present level of insult. The initial damage seems to be to the vasculature rather than neuronal parenchyma. With reestablishment of the circulation the animals made a remarkable recovery. There was little gradation between good survival and death. Ames, et al.,1 in their studies of cerebral ischemia have also proposed that viable neuronal parenchyma may still be present when severe and even irreversible vascular damage has occurred. If this be true, greater attention to blood flow and oxygenation in human cases may result not only in less mortality, but less morbidity as well. While it is certain that many severe head injuries have suffered immediate irreversible neuronal damage, there may be an additional group in which damage is primarily to the vasculature, which may lead to irreversible neuronal damage if uncorrected.

The method of isovolemic hemodilution has been presented primarily to demonstrate the concept of treating the microcirculation following head injuries. Decreased oxygen-carrying capacity and increased cardiac strain may prevent its use in the human subject. Hyperbaric oxygenation may resolve some of these difficulties, but in itself presents problems in terms of equipment and oxygen toxicity. Moreover, hemodilution leads to reduction in plasma-clotting factors, and increased capillary circulation makes control of bleeding a major problem, although it was overcome in these experimental animals with meticulous hemostasis. Further work along these lines using other techniques to lower blood viscosity and maintain blood oxygenation may lead to a technique suitable for human use.

Summary

Basic measurements of cerebral blood flow and oxygen consumption were made on dogs subjected to cerebral injury from an expanding extradural balloon. Of primary importance was the decline in blood flow after deflation of the balloon, which was attributed to an increasing cerebral vascular resistance. Isovolemic hemodilution was advantageous in lowering the blood viscosity and overcoming this increasing vascular resistance. Hyperbaric oxygen was utilized to compensate for the loss in hemoglobin following he-
modulation. Hemodilution was found to reduce mortality from 95% to 50% in animals given similar levels of injury. Hemodilution coupled with hyperbaric oxygenation further reduced this mortality to 20%. Since morbidity was minimal in surviving animals, it is possible that vascular damage may precede irreversible neuronal damage.

References