Only prospective randomized studies can establish quantitatively the risk-benefit ratio of such therapy. Extreme caution must be exercised when embarking on simultaneous aspirin-warfarin therapy in a given patient. Once begun, very close and careful followup of the patients’ prothrombin times and clinical status is essential.

References

The Effects of Extreme Hemodilutions on the Autoregulation of Cerebral Blood Flow, Electroencephalogram and Cerebral Metabolic Rate of Oxygen in the Dog

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SUMMARY The effects of profound (hematocrit value, Ht 20%) and extreme (Ht 5%) hemodilutions on the relationship between the mean arterial pressure (MAP) and the cerebral blood flow (CBF) were studied in pentobarbital-anesthetized dogs. A regression line was found between the CBF and Ht values during normotensive hemodilution (MAP 100 torr): CBF(ml/100g min) = -98.9 log Ht (%) + 195.5 (p < 0.001). The CBF was increased by hemodilution, but the range of its autoregulation was narrowed, suggesting a progressive susceptibility of CBF to blood pressure with hemodilution. The electroencephalogram (EEG) was not significantly changed by hemodilution within the range of the CBF autoregulation, below which it became slowed. In contrast, the cerebral metabolic rate of oxygen (CMRo₂) was decreased by hemodilution even within the range of the CBF autoregulation, while there were no significant differences in CMRo₂ values between MAPs of 100 and 40 torr. Thus, the brain function in terms of the EEG seemed to correlate more with the autoregulatory mechanism of the CBF than with the CMRo₂ value in the hemodilated states.

Hemodilution is frequently noted in clinical practice. It occurs most often during transfusion of fluids for treatment of acute hemorrhage and sometime in autotransfusion, or in therapeutic hemodilution for brain ischemia. Previously, we have found that the dog can survive extreme hemodilution of down to 3–5% of hematocrit (Ht) values for more than an hour when the systolic arterial pressure is maintained at above 100 torr. However, the abnormal electroencephalogram (EEG) patterns were frequently noted in such an extremely hemodiluted state.

The autoregulation of the cerebral blood flow (CBF) has been shown to be affected by several factors, such as hypoxia, hypercapnia, and halothane-anesthesia. The distortion of the autoregulation of the CBF may lead to disturbances of brain functions. However, there have been no available data about the autoregulation of the CBF during profound hemodilution.

The present study was undertaken to investigate the effects of profound and extreme hemodilutions on the autoregulation of the CBF and on the relationship between the brain function in terms of the electroencephalogram (EEG) and CBF or the cerebral metabolic rate of oxygen (CMRo₂).
Methods

Eight mongrel dogs of both sexes, weighing 9 to 12 kg, were the subjects of this study. Anesthesia was induced with intravenous injection of thiamylal sodium (25 mg/kg) and maintained with intramuscular injection of pentobarbital sodium (10 ± 2 mg/kg). Anesthetic depth was judged by ongoing activities of electroencephalogram (EEG) and other vital signs. All measurements were carried out under a light surgical stage of pentobarbital anesthesia, monitored by the EEG pattern and vital signs. When any change was noticed in the vital signs, additional intravenous injections (2–5 mg/kg) were carried out. To facilitate the tissue oxygenation throughout the experiment, artificial ventilation was undertaken through an endotracheal tube with 100% oxygen. End-tidal CO\(_2\) (Fe\(_{\text{E}}\)CO\(_2\)) was monitored by the Godart Capnograph\(^\text{®}\) (MO-1) to eliminate hyper- or hypocapnia throughout the experiment, since carbon dioxide tension combined with anemia greatly affects the CBF. \(^2\) Both femoral arteries were cannulated for measurements of the MAP and for retransfusion of shed blood. The femoral vein was also cannulated for transfusion of Ringer’s solution during injections or retransfusion of shed blood. Muscle relaxation was achieved by intravenous administration of 4 mg of pancuronium bromide, which was supplemented as necessary.

The CBF was measured by a magnetic flowmeter based on the technique of the direct methods. \(^3\) The extracerebral vessels draining into the sagittal sinus were interrupted. The posterior portion of the sinus was exposed and wedged with a Teflon catheter which was connected to a magnetic flowmeter. The sinus caudal to the catheter was occluded. The isolation of sagittal sinus was made by obliteration of the diploic veins with scraping of the skull along the sinus from both sides, which provides a ready source for sampling mixed venous blood exclusively representative of the brain tissue. \(^4\) By these means, sagittal sinus flow was isolated and drained into the superior vena cava via a cannula. With this technique, 43 per cent of the total brain weight as determined at autopsy is drained by the isolated sagittal sinus. \(^5\)

As a control or non-diluted state, the Ht was adjusted to about 40% (Ht 40) by infusion of red blood cell suspension or plasma before the commencement of hemodilution. The relationship between the MAP and CBF was determined by the stepwise exsanguination of arterial blood (1 mg/kg-min). Each step lasted for at least five minutes before measurement in order to obtain a steady state of circulation, which was estimated by no changes in arterial pressure and CBF. These procedures were repeated until the MAP reached 40 torr. Then, rapid infusion of warmed Ringer’s solution (6.54 ± 0.59 ml/kg-min) and further exsanguination of blood were undertaken to obtain 20 or 5% of Ht values (Ht 20 or Ht 5). The same procedures for the measurement of the CBF at each MAP value were repeated under these hemodiluted conditions. At the termination of the estimation, stepwise re-infusion of shed blood was carried out, and the MAP-CBF relationship was re-estimated at the recovered state. If a similar relationship between the MAP and CBF was not re-established at the recovery as compared to control, the data were discarded.

The CMRO\(_2\) was calculated from the CBF and oxygen contents of arterial and sagittal sinus blood with the MAP at 100 and 40 torr. Oxygen contents were measured by a Lex-\(\text{O}_2\)-Con\(^\text{®}\) (Lexington Instruments, Waltham, Mass.).

The EEG (fronto-parietal lead), electrocardiogram (ECG), arterial pressure (AP), CBF and Fe\(_{\text{E}}\)CO\(_2\) were all recorded continuously on a polygraph (Nihon-Kohden RM-6000).

Rectal temperature was monitored by a thermister. A blanket was used for the maintenance of rectal temperature at 37.5–38.0°C.

Standard statistical methods, including paired or nonpaired t tests, and the chi-square test for paired observations were used, and significance was defined as \(p \leq 0.05\).

Results

First, we tested the relationship between Ht values and the CBF at a MAP of 100 torr by changing the Ht levels in a wide range (3 to 50%) (normotensive hemodilution) (fig. 1). There was an inverse relationship between Ht and CBF values. A regression line was demonstrated between Ht and CBF values as follows (fig. 1): \(\text{CBF (ml/100g·min)} = -98.9 \log \text{Ht} (%) + 195.5\)

Figure 2 shows a summary of the CBF values at MAPs of 100, 80, 60 and 40 torr during the control (Ht 40), profound (Ht 20) and extreme (Ht 5) hemodilution. At Ht 40, the CBF did not change significantly within the MAP range of 60 to 100 torr, though there was a tendency to decrease as the MAP was lowered.
At a MAP of 40 torr, the CBF decreased significantly ($p < 0.05$). In the profound hemodilution (Ht 20), the CBF increased to about 1.7 times that of the control at a MAP of 100 torr ($p < 0.01$). As the MAP declined to 60 torr, the CBF decreased significantly ($p < 0.05$) as compared to that at a MAP of 100 torr in this profoundly hemodiluted state. Thus, the autoregulation of CBF was thought to be already disturbed within this range of the MAP at Ht 20.

During extreme hemodilution (Ht 5), the CBF increased to about three times that of control at a MAP of 100 torr ($p < 0.001$). It decreased significantly at MAPs of 80 ($p < 0.05$), 60 ($p < 0.01$) and 40 ($p < 0.001$) torr in comparison with that at a MAP of 100 torr.

When the MAP was maintained at 100 torr, the changes in the EEG patterns could be barely demonstrated even during extreme hemodilution (Ht 5) (table 1). However, the EEG changes, reflected as slowing of the EEG frequency, became more pronounced during 40 torr of MAP at the Ht value of 5% (table 1). Table 1 shows the changes in the EEG frequency and amplitude as a function of the MAP at each Ht value. When the MAP ranged from 100 to 60 torr, the frequency of the EEG did not show any significant change at each Ht value, but revealed a significant slowing during 40 torr of MAP. Further, the EEG amplitude tended to increase as MAP decreased to 40 torr at both Ht 40 and 20 (not significant), while it decreased prominently at Ht 5 under 40 torr of MAP (table 1). Thus, the EEG slowed progressively with reduction in Ht at a MAP of 40 but not at pressures above this level.

The CMRo2 measured at 100 and 40 torr at each Ht level is shown in table 2, with arterial oxygen content (Cao2), sagittal venous oxygen content (Csvo2) and oxygen transport to brain (O2T). The CMRo2 showed a significant reduction in the hemodiluted states even at a MAP of 100 torr (during isotonic hemodilution). In contrast, there were no significant differences in CMRo2 values between MAPs of 40 and 100 torr in the control as well as in the hemodiluted states. The data in table 2 indicate that the CMRo2 is maintained at MAP)}
of 40 by a considerable increase in oxygen extraction as shown by the reduction in the $Csvo_2$.

**Discussion**

The present study has demonstrated that the range of CBF autoregulation becomes narrower as Ht values are reduced. With hemodilution, a progressive increase in CBF has been observed. In this case, it can be caused not only by vasodilatation but also by a blood viscosity reduction.

In the presence of extreme hemodilution, the cerebrovascular bed must be submaximally dilated and less responsive to changes in blood gases and pressure (incomplete disturbance of the CBF autoregulation). This might account for the differences in the MAP-CBF relationship at each Ht value (fig. 2). It has been postulated that the pH of the extracellular fluid of arteriolar smooth muscle is the ultimate mechanism controlling the cerebrovascular caliber. According to this hypothesis, cerebral hypoxia caused by hemodilution might reduce the pH of the arteriolar extracellular fluid to produce vasodilatation. This, in turn, might lead to a partial failure of the CBF responsiveness to the changes in MAP as seen in the present study. Besides pH (hydrogen ion), however, the number of candidates for mediating metabolic flow regulation is proposed. At present, adenosine and potassium ion appear to be the most promising other candidates. Adenosine is a strong dilator of pial vessels when applied in the peripheral vascular space. Brain adenosine concentration increases under conditions of hypoxia, ischemia, or increased metabolic activity of the brain. Similarly, it has been demonstrated that potassium dilates pial arterioles.

The results demonstrated in table 2 reveal that the $CMRo_2$ is very susceptible to changes in Ht values, whereas it is not significantly changed by decreases in the MAP down to 40 torr. On the other hand, the cortical function reflected on the EEG showed no noticeable alterations as a result of profound and extreme hemodilutions when the MAP was maintained at 60-100 torr (table 1), while the EEG slowed in frequency at 40 torr of MAP. The mechanism of this discrepancy between the brain function and the $CMRo_2$ remains to be clarified. A possible explanation may be that the regional distribution of blood flow inside the brain tissue becomes uneven as a result of the decrease in the MAP to 40 torr even when the $CMRo_2$ remains unchanged, and this might affect the brain function. Thus, the $CMRo_2$ value did not seem to correlate well with the brain function as detected by electrical activity in hemodiluted states. Deterioration of cerebral activities in terms of the EEG as a result of the decrease in the MAP seemed to correlate more with the rate of the CBF reduction (table 1) than with the $CMRo_2$ values. For instance, EEG frequencies were not significantly different at each Ht value as long as the MAP was maintained at 60-100 torr. This may indicate that the cerebral function can be kept at almost normal levels during normotensive hemodilution at down to 5% of Ht values when MAP is maintained adequately.

Recently Fan et al have carried out isovolemic hemodilution of up to Ht values of 13% with plasma in dogs in order to measure the responses of alterations in regional hemodynamics and oxygen transport rate. They have demonstrated that oxygen transport to the myocardium does not change significantly at the expense of the increase in coronary blood flow up to an Ht value of 13%, while that to the brain decreases significantly even with an increase in the CBF as the Ht value is reduced to 22%. The MAP, however, was not controlled in their experiment, and systemic arterial pressure was decreased when the Ht value was lower than 20%. The time factor must be also considered in this regard.

The present experiment has further shown that the $CMRo_2$ is decreased even by normotensive hemodilution without noticeable changes in the EEG when the Ht value is reduced to 20% (table 2). The significant decrease in the $CMRo_2$, without any change in the brain function in terms of EEG might be characteristic in normotensive hemodilution (anemic hypoxia). In contrast, the $CMRo_2$ is reported to be barely affected by a moderate degree of anemia, and hypoxic or ischemic hypoxia even when the brain function is greatly disturbed. Michenfelder and Theye observed no significant change in $CMRo_2$ during hemodilution with plasma expander (dog plasma or low-molecular-weight dextran) down to approximately 15% of Ht value. Discrepancy between their data on $CMRo_2$ and these in the present study might be due to the differences in the solutions infused and/or anesthetics used. In a whole animal, Schwartz et al have also suggested that oxygen consumption represents a physiological marker of impending death in the face of progressively diminishing oxygen delivery caused by hypovolemia, anemia, and hypoxia. A more prolonged exposure to hemodilution, however, might have some effect on the EEG in the present experiment. In fact, our previous study has shown that reversible slowing of the EEG frequency is noted as a result of extreme normotensive hemodilution (Ht 3-5%) for more than one hour. The present experiment further suggests that an adequate cerebral perfusion is indispensable for the maintenance of the brain function rather than the values of oxygen content in blood or $CMRo_2$.

In summary, the present study showed that the range of autoregulation of the CBF became narrower as hemodilution became more profound. Furthermore, the change in the brain function in terms of EEG seemed to be more correlated with that of the CBF in response to the fall of the MAP than with the $CMRo_2$ value during hemodilution.

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