

Hemodilution and Fluid Management in Neurosurgery

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Early in his career, the senior author (RCH) became interested in the experimental study of cerebral vasospasm, which continues to be one of the most important causes of morbidity from subarachnoid hemorrhage (SAH).^{21–23,45} The initial approach was to find a single pharmacological agent, the so-called “silver bullet,” to prevent and reverse vasospasm. Arterial smooth muscle relaxants were the first class of tempting agents that were studied. These agents turned out to be “fool’s gold” and were generally ineffective in treating vasospasm.^{19,20,55,58} While treatments were being developed in experimental models, clinical observations were reported that hypertension may improve neurological deficits resulting from cerebrovascular insufficiency.⁹ This led to the demonstration that vasospasm-induced cerebral ischemia could be treated successfully with iatrogenic hypertension.^{13,34} The benefits of intravascular volume expansion combined with hypertension were reported soon afterwards.²⁷ These foundations, along with the additional strides made in the understanding of rheology, cerebral oxygen transport, and cerebral blood flow (CBF) augmentation, led to the formalization of the concept of hyperdynamic therapy. Gaining broad acceptance by the late 1980s, the combination of hypervolemia, hypertension, and hemodilution, colloquially known as “triple-H therapy,” is now considered essential in the treatment for cerebral vasospasm.

We have observed that the hypervolemic and hypertensive arms of the hyperdynamic therapy receive the most attention from clinicians. It seems that the hemodilution aspect of the treatment is often overlooked or taken for granted because some degree of hemodilution occurs with an increase in intravascular volume. However, the benefits of hemodilution are well grounded in the laboratory, beginning with the pioneering work of Wood et al.^{59–61} The senior author concentrated on the effects of hemodilution on cerebral ischemia for longer than 15 years in his laboratory. In this report, we shall discuss the evolution of this work and its translation into clinical practice. We shall also review the current status of hemodilution in clinical practice and describe the implications of this work for fluid therapy in general for neurosurgical patients.

RATIONALE FOR HEMODILUTION IN CEREBRAL ISCHEMIA

The Hagen-Poiseuille equation indicates that flow is inversely proportional to viscosity (*Fig. 26.1*). Blood viscosity is a complex variable determined by several factors, including erythrocyte aggregation and flexibility, platelet aggregation, plasma viscosity, and hematocrit. Of these factors, hematocrit is by far the most important determinant of blood viscosity.^{15,52} In ischemic brain, the regional blood vessels are dilated maximally, and blood viscosity becomes a major determinant of blood flow. The low blood flow inherent to the ischemic region results in a dramatic rise in viscosity, favoring microaggregation and thrombus formation. Thus, the hematocrit becomes an even more important factor in these low-flow states.¹⁵

It follows that hemodilution is an effective way to increase perfusion to the ischemic brain, and a large amount of evidence supports this hypothesis. Although hemodilution increases perfusion in the ischemic brain, it also reduces the oxygen-carrying capacity of blood. In ischemic brain, the autoregulation of blood flow is lost, and rheological factors, such as viscosity, hence, hematocrit, become a most important determinant of regional blood flow.

HEMODILUTION WITH A HEMOGLOBIN SUBSTITUTE

Our initial work focused on the hypothesis that the optimal hemodilutional agent would achieve the rheological advantages of reduced viscosity and at the same time enhance or at least maintain the oxygen-carrying capacity of blood. Perfluorocarbons (PFCs) are inert organic compounds derived from the substitution of fluorine for hydrogen. These compounds have a high affinity for oxygen and carbon dioxide, and interest grew in their potential for the gas transport function of red blood cells.¹² PFCs are frequently referred to as substitutes for blood, a technically incorrect concept. They are intended to supplement the oxygen-carrying capacity of red blood cells, hence, are considered more correctly as oxygen carriers or red blood cell substitutes. These compounds must be prepared in a microemulsion to prevent liquid embolism during intravenous administration. The first commercial PFC tested and approved for red cell supplementation was Fluosol-DA, a mixture of perfluoro-

HAGEN-POISEUILLE EQUATION

$$Q = \frac{\pi PR^4}{8L\eta}$$

Q: Blood Flow **L:** Vessel Length

P: Pressure Gradient **η :** Viscosity

R: Vessel Radius

FIGURE 26.1. Hagen-Poiseuille equation.

decaline and perfluorotripropylamine emulsified at 20% with Pluronic surfactant.⁴⁴

Its oxygen-carrying property made Fluosol an appealing agent to treat cerebral ischemia. Preliminary work in a feline model of middle cerebral artery (MCA) occlusion indicated PFCs reduced the area of cerebral infarction in animals killed within 6 hours of ischemia.⁴² The protective effects of Fluosol were thought to be caused by a combination of hemodilution and its oxygen-carrying capacity. The small particle size and the ability to remain in the intravascular compartment were thought to decrease blood viscosity and improve microcirculation.

We performed additional work on Fluosol on a chronic stroke model in which animals were killed after 1 week. In one set of experiments, Fluosol was compared with the volume expander Dextran 40 to separate the hemodilutional from the oxygen-carrying properties.²⁹ The MCA was occluded for 4 hours, and the mortality was 66%. No differences were detected between the two agents in terms of animal survival or extent of infarctions. Another set of experiments reduced the MCA occlusion time to 2 hours after infusion of Fluosol.³⁰ The results were no different, with massive mortality and no improvement in the size of the stroke. In fact, the Fluosol-treated animals seemed to have a larger infarction volume than control animals. Both of these chronic ischemia models produced negative results for Fluosol, suggesting that this agent did not prevent delayed ischemic edema and secondary cerebral injury. The early studies suggesting the benefits of Fluosol simply did not take into account the role of the cerebral edema that develops from a

massive infarction and the decreased blood flow to this edematous tissue.

ISOVOLEMIC VERSUS HYPERVOLEMIC HEMODILUTION

After abandoning the idea of using a hemoglobin substitute, we turned to colloids as the next potential candidates for hemodilution. The choice of colloids as opposed to crystalloids was empirical and based partly on what solutions were being used clinically in the early 1980s for hyperdynamic therapy of vasospasm.² We became aware of the studies of Wood et al.^{59,60} reporting equal efficacy of isovolemic hemodilution when compared with hypervolemic hemodilution. The idea of isovolemic hemodilution was attractive because of the potentially adverse effects of hypervolemia, such as elevated intracranial pressure (ICP) in experimental models. A direct relationship between cardiac output and CBF was found after hemodilutional intravascular volume expansion. The increased cardiac output and CBF were attributed to the reduced blood viscosity resulting from hemodilution. Further support for the importance of hemodilution came in a study in which animals with strokes were infused with whole blood. The resultant nondilutional hypervolemia did not increase the regional CBF to the ischemic areas despite significant increases in cardiac output.^{59,60}

Isovolemia was attractive because we envisioned hemodilution to be useful for all age groups. Although young and otherwise healthy patients with SAH could generally tolerate a hypervolemic state, the older stroke patients with cardiopulmonary comorbidities might not tolerate hypervol-

emia. Furthermore, the maintenance of a hypervolemic state is more labor intensive and requires frequent intravascular infusions.

CHOICE OF AN ISCHEMIC MODEL

Although our primary clinical interest was in cerebral aneurysms and, therefore, subarachnoid hemorrhage and vasospasm, we thought that experimental models of vasospasm were too unpredictable and unreliable to properly study an isolated form of therapy. This is particularly true because, although angiographic vasospasm could be predictably achieved with several of the models we had at the time, hemodilution was not directed at angiographic vasospasm *per se*, but, rather, at the ischemic consequences, which could only be studied by looking at the effect of the therapy in the severity of brain infarction and in neurological outcome. Existing models of vasospasm rarely resulted in a predictable focal brain infarction and, unless the animals died, it was only rare and then only with primate models that a focal deficit could be achieved by inducing experimental subarachnoid hemorrhage.^{8,10,26} Therefore, we settled on a simple model of ischemia by MCA occlusion.^{24,36,53,54} It became quickly apparent that we had to use a large animal to be able to perform all of the intended physiological measurements, to measure CBF, and to keep the animal alive for eventual histological study of infarction and measurement of clinical outcome. Within these parameters, a canine model seemed ideal for these experiments. This model was used widely and provided adequate opportunity to study histologically the effects of hemodilution on ischemic brain.^{5,6,40} As we began our pilot studies, we encountered tremendous variability in blood volume measurements from animal to animal and even within one animal at different times. Unfortunately, we had to kill more dogs than we want to remember before we found an obscure reference in the literature to the effect that the canine spleen had a tremendous capacity to accumulate large volumes of blood that were released into the circulation at times of stress.³ This made all of our previous volume measurements in normal dogs worthless; we overcame this obstacle by performing splenectomies in the dogs 1 week before the experiments. Once this modification was made, we obtained relatively reliable volume measurements.

The effects of isovolemic hemodilution on regional CBF and the size of infarction were studied after inducing focal ischemia. Seventy-six mongrel dogs were used for this study. Seven animals were excluded from the study because of technical errors or trauma to the brain during craniotomy. The remaining 69 animals were randomized into two groups of hemodilution (treatment groups) and a control group. In the hemodilution group, 28 animals were subjected to 6 hours of arterial occlusion (proximal MCA and distal internal carotid artery) and 7 animals had a sham operation (arterial manipulation without occlusion). In the control group, 26

animals received 6 hours of arterial occlusion and 8 animals were sham-operated. Thirty minutes into occlusion or sham surgery, isovolemic hemodilution was performed by repeated withdrawal of 50 ml of blood and infusion of 35 ml of 10% low molecular weight dextran until the hematocrit reached 30 to 32%. Dextran was used for volume replacement because it is readily available, inexpensive, safe, has a similar molecular weight to physiological albumin, it can effectively expand the blood volume 1.5 times the amount infused, and it can maintain an isovolemic state in a splenectomized dogs for at least 1 week. In deciding the value for hematocrit, 30% was thought to be ideal based on physiological experiments that indicated that, indeed, this was the optimal range to deliver oxygen to tissues.⁵⁰ Obviously, with increasing hematocrit, there is higher oxygen content, but the increased viscosity may compromise flow at the level of capillaries. On the other hand, lowering the hematocrit may decrease the oxygen-carrying capacity of blood, which may override the advantage of increased flow to the tissue; a hematocrit of approximately 30% achieves an ideal balance between these two conflicting effects.^{35,39}

The hemodilution groups were further subdivided into acute and chronic groups. The acute group underwent blood flow measurements using the radiolabeled microsphere technique. Microspheres are approximately 15 μm in diameter and carry a radioactive label to the brain. They are injected directly into the left atrium and they do not pass beyond the capillaries of the brain. The amount of radioactive microspheres that gets "fixed" in the brain reflects the amount of blood flow at the time of injection. Four different radionuclides were used for measuring the blood flow at four different times. The CBF was measured at baseline (microspheres labeled with tin-113), 30 minutes after occlusion of intracranial arteries (using ruthenium-103), 2 hours after hemodilution (niobium-95), and lastly 30 minutes after reperfusion (scandium-46). After 8 hours, animals were killed, the radioactivity was measured using a gamma counter in the brain tissue samples, and the local blood flow was calculated using a standard method. We used tetrazolium salts (TTC), a histochemical indicator of mitochondrial respiratory enzyme viability, to estimate the size of infarction in the acute group. In our earlier studies, we found TTC to be a reliable marker of cerebral infarction under the conditions studied currently.³⁷ TTC is taken up by functioning mitochondria, and it is thought that the tissue that does not take up this dye will become infarcted (*Fig. 26.2*). Although this method provided an indirect estimation of infarct size, we had dedicated the second half of our experiment to use the "gold standard," histological preparations, to confirm and compare the infarct size between the groups. After four blood flow measurements with microspheres, animals go into pulmonary hypertension and, as a result, cardiac failure. These animals do not survive long enough for final histological studies, for which we

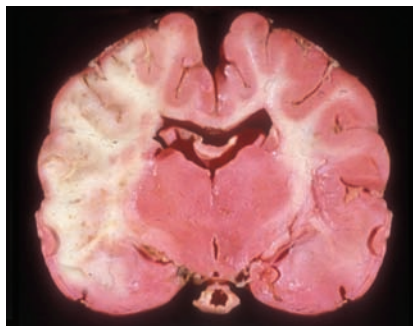


FIGURE 26.2. Cross-section of brain showing infarct area (lack of TTC staining) in the distribution of left MCA

wanted to keep the dogs alive for at least 1 week. In addition, these animals were considered to be radioactively contaminated and could not be housed thereafter. For these reasons, we had to divide the experiment into an acute group with measurements of CBF and a chronic group for histological studies.

At the end of 1 week, the chronic group was injected with fluorescein and killed. The areas stained with fluorescein that corresponded to the areas of infarct, which were confirmed by histopathological examination, were measured and quantified (Fig. 26.3).

In the first part, we studied the effects of isovolemic hemodilution on hemodynamics, hemorheology, and ICP.⁵³ The hemorheological parameters studied were viscosity, hematocrit, and plasma fibrinogen, and all three had a statistically significant reduction after hemodilution. The mean viscosity and the hematocrit fell to 61% and 69% of its original baseline value, respectively, at 2 hours after hemodilution. An average hematocrit value of 32.9% was still maintained at the end of 1 week in the chronic group. The

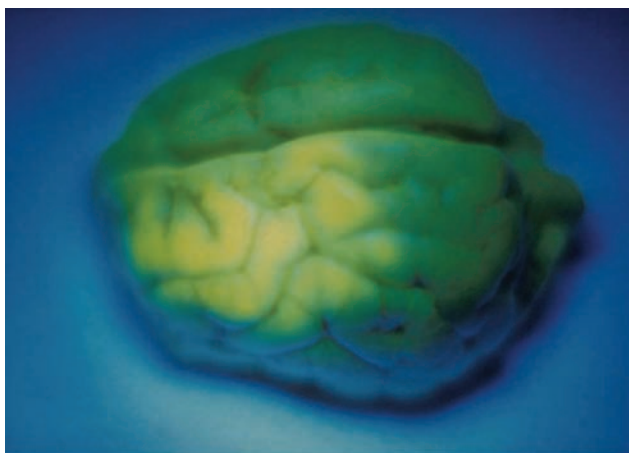


FIGURE 26.3. Canine brain stained with fluorescein. Areas that "light up" after staining correspond to infarct as demonstrated histologically.

mean plasma fibrinogen level dropped from 0.26 ± 0.03 gm% to 0.18 ± 0.02 gm% with hemodilution. There was also excellent correlation between hematocrit and viscosity ($r = 0.81$) (Fig. 26.4).

Even though the mean arterial pressure dropped slightly from baseline after hemodilution, there was no significant change in central venous pressure, wedge pressure, or pulmonary pressure. Cardiac index decreased slightly in both hemodiluted and control groups, which may be attributed to anesthesia. ICP increased significantly after arterial occlusion in both hemodiluted and control groups but there was a trend toward lower ICP in the hemodiluted group.

The CBF was measured at baseline, 30 minutes after arterial occlusion, 2 hours after hemodilution, and 30 minutes after reperfusion. In the hemodiluted and the control groups, the CBF decreased, especially in the MCA territory. After hemodilution, the decrease in the CBF was substantially improved, in contrast to the control group; however, the CBF worsened as time progressed (Fig. 26.5). Reperfusion tended to restore the CBF toward baseline in the hemodiluted animals, whereas this was only partially restored in the control animals. The mean infarct volume (lack of staining with TTC) was significantly less in the hemodiluted groups compared with control groups ($P < 0.005$) when examined at 8 hours after arterial occlusion (Table 26.1).

Animals in the chronic group treated with hemodilution fared better neurologically than those in the control groups. These animals had a significant improvement in their neurological exam and returned to normal after 3 days, whereas the control animals never returned to their baseline. Both histopathological examination and fluorescein stain showed a significantly higher volume of infarcted tissue in the control group than the hemodiluted group ($P < 0.005$) (Table 26.1). Finally, there was a significant correlation between the infarct volume ($P < 0.001$) and hematocrit, and between infarct volume and viscosity ($P < 0.001$).

COLLOIDS VERSUS CRYSTALLOIDS FOR HEMODILUTION

When resuscitation of all critically ill patients is considered, it seems that the choice of fluid used for resuscitation has no effect on mortality.⁴³ Crystalloids extravasate into the interstitial space, resulting in edema formation. For example, 1 L of infused lactated Ringer's solution expands the plasma volume by only 250 ml. Therefore, it would seem that the infusion of large amounts of crystalloid would result in an edematous patient with a depleted intravascular space. Other concerns regarding crystalloids include impaired gas exchange from pulmonary edema and metabolic acidosis from excessive normal saline administration. Nevertheless, it seems that, in patients with systemic trauma, shock, and burns, crystalloids are as effective as colloids.^{4,43,56} It should be kept in mind, however, that, generally, these patients have

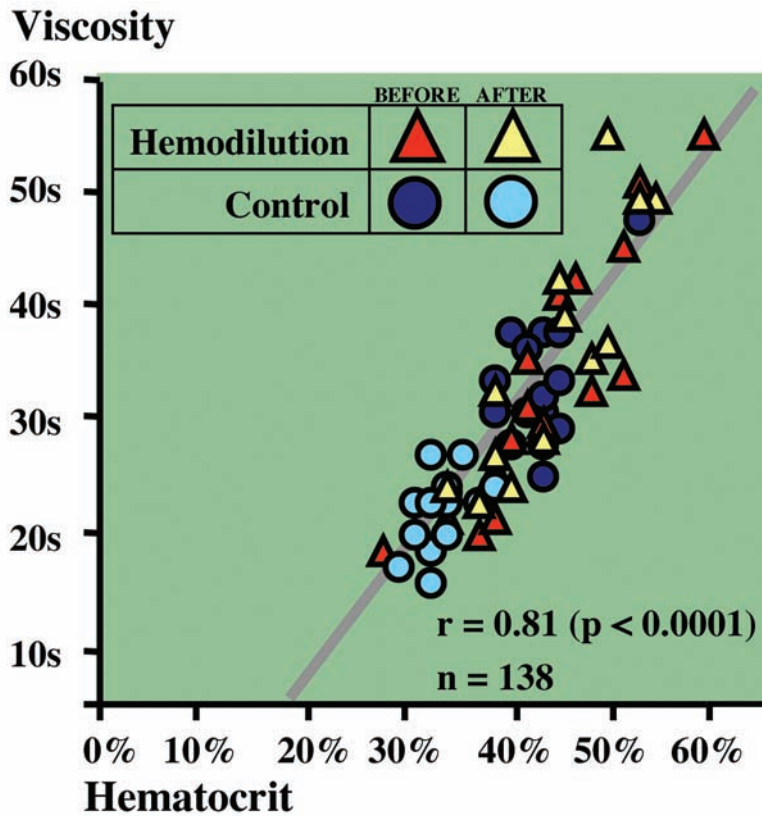


FIGURE 26.4. Graph showing positive correlation ($r = 0.81$) between viscosity and hematocrit of blood.

normal brains; the situation may be different, as we have shown, in patients with injured or ischemic brain.

In contrast, to crystalloids, colloids are much more efficient plasma volume expanders. Typically, smaller volumes of colloid are required to produce similar resuscitation end points as crystalloids. There are four types of colloid—albumin, dextrans, gelatins, and starches. The model colloid is albumin, which is responsible for the vast majority of plasma oncotic pressure. Its main advantages are that it does not cause coagulopathies and has a half-life of 16 hours, resulting in sustained intravascular volume repletion. Its disadvantages include its short supply, its significant expense, and the rare possibility of anaphylaxis. One myth surrounding albumin is the risk of viral transmission. There have been no reports of viral transmission through albumin infusion since its inception longer than 60 years ago. Albumin is essentially a byproduct of plasma electrophoresis. Between the improved screening process for donors and its pasteurization, the risk of disease transmission with albumin infusion seems to be theoretical. Hypersensitivity reactions also are rare with an incidence between 0.011% and 1.5%.^{11,38}

Dextrans and gelatins are rarely used for resuscitation because of their limited half-life and their anticoagulant effects. Starches, such as hetastarch, increase plasma volume for a prolonged period with small effects on coagulation.

They are inexpensive and have a long shelf life. After considering all of the above, we decided to use dextran as the colloid agent in our hemodilution studies.

We compared the hemodilutional properties of crystalloids with colloids in a canine model of cerebral ischemia. Isovolemic hemodilution with a hematocrit of 30% to 32% was reached by either the infusion of lactated Ringer's solution or dextran in two respective groups of animals that underwent temporary occlusion of the internal carotid and middle cerebral arteries. Although systemic parameters, such as mean arterial, central venous, pulmonary arterial, and pulmonary wedge pressures remained the same in both groups, the neurological status of the crystalloid group was consistently worse than the colloid group. Furthermore, the median infarct volume of the crystalloid group was almost seven times greater than that of the colloid group⁵⁴ (Fig. 26.6). These results demonstrated that hemodilution with crystalloids was detrimental in the setting of temporary focal cerebral ischemia, whereas hemodilution with colloids was beneficial. The likely explanation for these results was the decrease in oncotic pressure from crystalloid administration, leading to the formation of brain edema in the area of ischemic injury. In fact, this was confirmed by specific gravity measurements that demonstrated a marked increase in water content in the region of ischemia in the animals

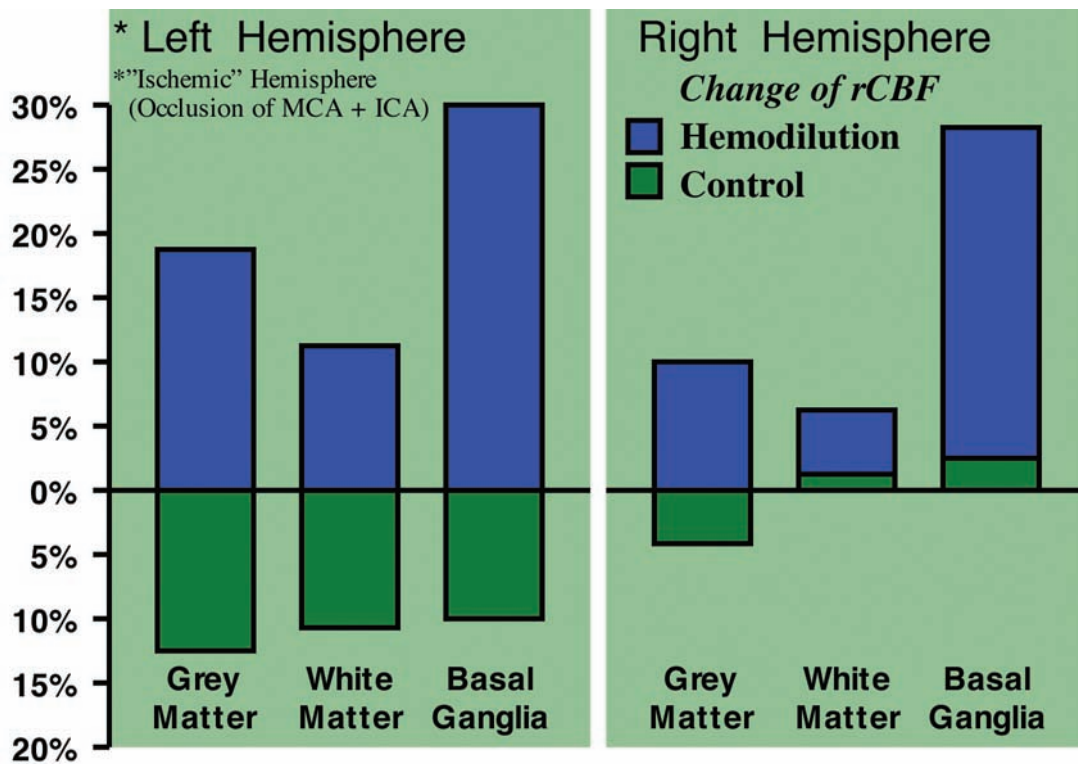


FIGURE 26.5. Histograms showing the percent change in regional CBF the MCA territory in the control and hemodiluted group of animals.

hemodiluted with crystalloids as compared with nonhemodiluted controls²⁴ (Fig. 26.7). A very important consequence of this is the observation in our acute experiments that hemodilution with crystalloids significantly increased the ICP in the group of animals subjected to arterial occlusion²⁴ (Fig. 26.8).

TABLE 26.1. Infarction volume in each animal group^a
Infarction Volume (%)

| Chronic Group | Fluorescein Stain | Histopathology |
|------------------------|-------------------|----------------|
| Control (n=12) | 9.84 ± 3.29 | 10.92 ± 5.44 |
| Hemodilution (n=13) | 1.26 ± 0.23 | 1.20 ± 0.42 |
| Control sham (n=5) | 0.31 ± 0.27 | 0.15 ± 0.11 |
| Hemodilutin sham (n=3) | 0.22 ± 0.26 | 0.25 ± 0.25 |

| Acute Group | T.T. C. Stain |
|-------------------------|---------------|
| Control (n=14) | 7.36 ± 1.32 |
| Hemodilution (n=13) | 1.09 ± 0.28 |
| Control sham (n=3) | 0 ± 0 |
| Hemodilution sham (n=4) | 0.13 ± 0.13 |

^aValues are percentages of left hemisphere volume expressed as means ± SEM.

This observed increase in edema in the ischemic regions, represented by decreased specific gravity, with consequent increase in ICP is attributable, in our opinion, to the marked decrease in measured oncotic pressure brought about by hemodilution with crystalloids.²⁴ In contrast, hemodilution with colloids maintained normal oncotic pressure and did not result in edema or increase in ICP in the ischemic animals.⁵⁴ It is interesting that although, in normal brain, hemodilution with crystalloids slightly increased regional CBF, we observed a decrease in flow in the areas of maximal ischemia (the basal ganglia) in the MCA territory in the animals hemodiluted with crystalloids as opposed to the significant increase in blood flow observed in the animals hemodiluted with colloids.²⁴

AN IMPROVED EXPERIMENTAL ISCHEMIC MODEL

Canine models of stroke are useful not only because of the amount of infarct tissue they provide but also because they offer the possibility to test different therapeutic modalities that would otherwise be impractical on smaller animals. We had used a canine model of stroke routinely in the past but had difficulty in producing uniformly sized strokes. These differences among animals may arise from variable collateral

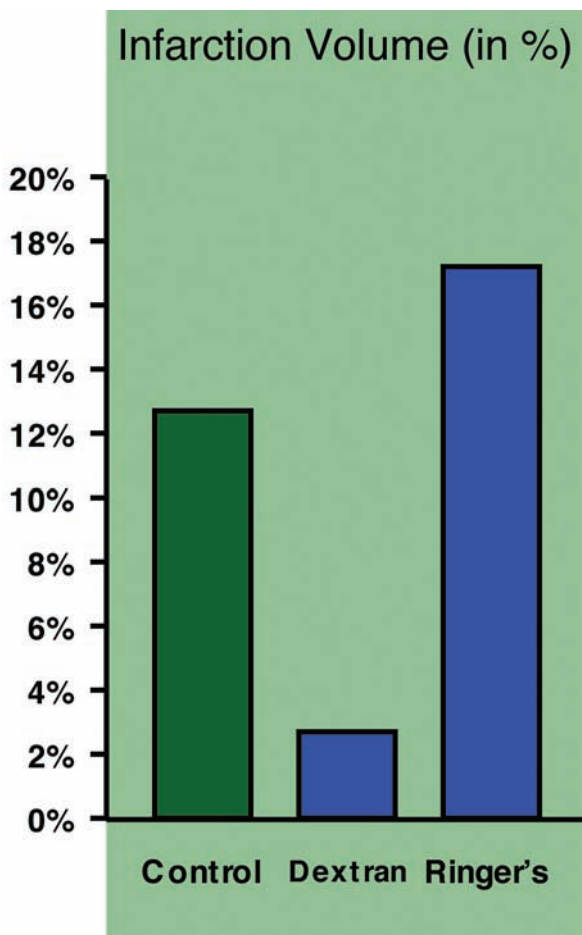


FIGURE 26.6. Comparison of infarction volume in the crystalloid, colloid, and control group of animals. True size of infarct was the smallest in the colloid-treated animals.

circulation, thus, leading to difficulty with statistical comparisons between groups. We had to use a large number of animals in our studies to overcome this variability in the size of infarct. Our aim was to develop a reliable canine model that would produce a moderate size infarct because small infarcts in dogs have no consequence and large infarcts are incompatible with life. We postulated and later showed that somatosensory evoked potential (SSEP) amplitude just after occlusion of arteries could be used to predict which animals would have a moderate sized infarct. We found that animals that showed a significant deterioration of SSEPs after temporary occlusion of the MCA would predictably develop huge infarcts; therefore, when they occurred, the clip was removed and the animals were excluded and used for other experiments. Animals that retained good SSEPs after MCA occlusion went on to have occlusion of the azygous anterior cerebral artery (ACA); if the SSEPs remained intact, we found that these animals would develop either no infarct or a very small one; therefore, these animals were also rejected.

This left us with the animals that had minimal or no change of SSEPs on MCA occlusion and then developed a significant change with additional occlusion of the azygous ACA (Fig. 26.9). These were the animals used for further studies of ischemia because they predictably developed a moderately sized infarct compatible with survival.⁴¹

OPTIMAL DEGREE OF HEMODILUTION

Now that it was proven that hemodilution improves CBF in ischemic brain, the question arises of what is the optimal degree of hemodilution. As stated before, the most important determinant of blood viscosity is the hematocrit. In fact, there is an inverse relation between the hematocrit and CBF.¹⁶ With hemodilution, the CBF increases, but lowering the hematocrit further could compromise the oxygen-carrying capacity of the blood and, thus, be detrimental. The balance between these two factors becomes critical, especially when autoregulation is lost in infarcted tissue. Here, the vessels are maximally dilated and the rheological factors of blood may play a major role in determining the oxygen delivery to the brain.

To address these questions, we studied five groups of dogs with hematocrits of 25%, 30%, 35%, 40%, and control (45%). Isovolemic hemodilution was achieved 1 hour after occlusion of MCA and azygous ACA in the experimental animals and, on day 6, the infarction volume was determined using fluorescein stain. The desired hematocrit was achieved by multiple withdrawals of blood and dextran infusions. Results showed that the mean infarct volume was the lowest in animals with a hematocrit of 30% (Fig 26.10). There was a significant reduction in infarct size compared with the control ($P = 0.02$) and to the other groups ($P < 0.05$). In conclusion, we found a hematocrit of 30% to be optimal in protecting the brain from the consequences of experimental ischemia.³⁶

OPTIMAL TIMING FOR HEMODILUTION

The next issue to be answered was the ideal time when the hemodilution therapy can be instituted so that it can be protective after the onset of ischemia. This has direct clinical importance, especially when patients present with a lag period after the onset of ischemia and the “window of opportunity” becomes important when certain therapeutic or protective measures may be used to recover as much ischemic brain as possible.

After occluding the MCA and the azygous ACA, we randomized the dogs into four groups: hemodilution after occlusion, hemodilution 3 hours after occlusion, hemodilution at 6 hours, and no hemodilution (control). Isovolemic hemodilution was achieved to a 30% hematocrit and the size of infarct volume was measured after 6 days. There was a significant reduction in the size of infarction in the groups with hemodilution immediately and 3 hours after occlusion as

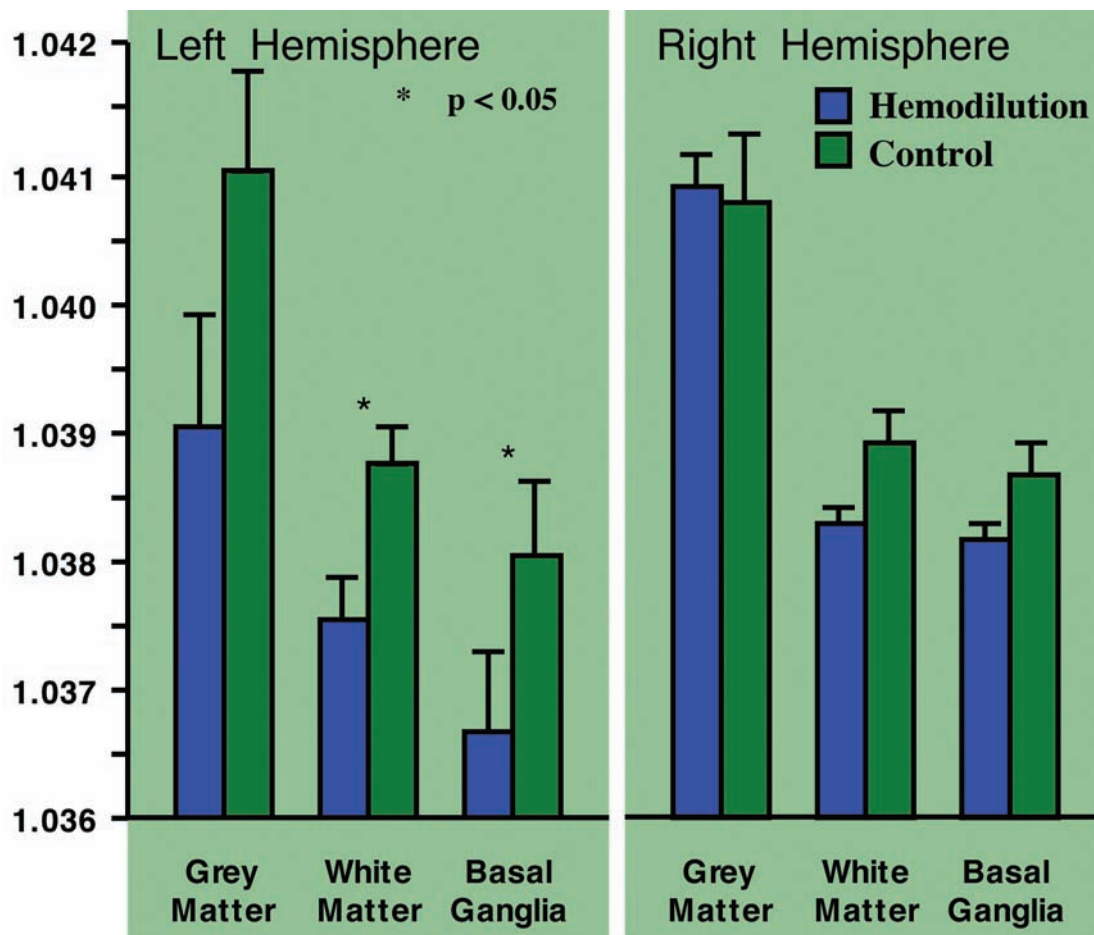


FIGURE 26.7. Histogram comparing the specific gravity of the brain tissue in the MCA territory at different sites in hemodiluted and control (nonhemodiluted) group of animals.

compared with control ($P < 0.0001$) (Fig. 26.11). The neurological function was significantly better in the animals treated immediately and 3 hours after the occlusion compared with the other two groups. Animals treated after 6 hours had a trend toward a larger infarct size and had a significantly higher incidence of hemorrhagic infarction.

This study suggests that hemodilution can be protective when instituted as late as 3 hours after arterial occlusion; however, after 6 hours, hemodilution is not helpful and may be unsafe.⁶² Not surprisingly, this “window of opportunity” for hemodilution is similar to that generally found in experimental and clinical studies of reperfusion.

MECHANISM OF THE EFFECT OF HEMODILUTION

Preliminary work in hemodilution clearly showed an increase in CBF.¹⁸ This naturally raised the question of how hemodilution caused an augmentation of CBF. It was unclear whether the increased blood flow was a direct rheological effect related to decreased blood viscosity or whether it was an indirect

vasodilatory effect of reduced oxygen-carrying capacity. It seemed that the former hypothesis was more logical because of the maximal vasodilatation already present in the ischemic brain from inherently increased oxygen demands in this territory.^{32,33} Therefore, an additional decrease in oxygen transport from hemodilution should not cause further vasodilatation.

The hypothesis was tested in a rabbit model of cerebral ischemia. Hypoxia was first induced in *normal* animals by either hemodilution (anemic hypoxia) or reduction of the inspired oxygen concentration (hypoxic hypoxia). The CBF response was exactly the same between the anemic hypoxia group and the hypoxic hypoxia group. Both types of hypoxia, in these animals with normal brain, caused a linear increase in CBF as the arterial oxygen content decreased.

The experiment was then repeated in animals with cerebral ischemia. The results clearly showed that there was a significant increase in CBF with graded hemodilution (anemic hypoxia). In contrast, graded hypoxic hypoxia did not increase CBF in the ischemic brain, although it did so in normal brain. We concluded that the improvement in CBF in

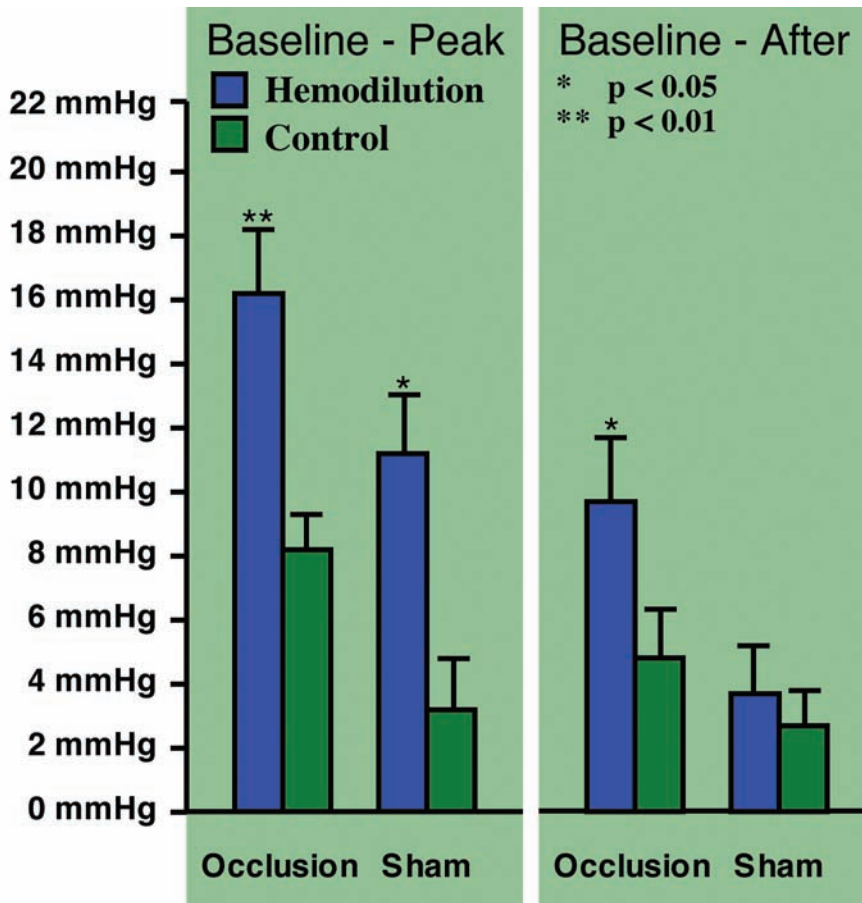


FIGURE 26.8. ICP after hemodilution with crystalloids in ischemic animals.

the ischemic brain was mainly caused by a rheological response to decreased blood viscosity as opposed to a vasodilatory response to decrease arterial oxygen content.³¹ This confirmed that in hypoxic brain, despite maximal reactive vasodilation, improvement in CBF can still be achieved by rheological manipulations, such as a decrease in viscosity. These findings also implied that in ischemic brain, viscosity is likely to be a major determinant of regional blood flow.

CLINICAL EXPERIENCE WITH HEMODILUTION

Supported by the large body of experimental evidence that hemodilution improves blood flow to ischemic brain, several trials were designed in the 1980s to establish clinical benefit. The first randomized, controlled trial was based at a single center in Sweden and measured the benefit of isovolemic hemodilution during the first 48 hours after an ischemic stroke. The treatment arm of the study involved venesection and infusion of dextran to reduce the mean hematocrit from 43 to 37%. In this study, the treated patients had improved early neurological recovery and less functional impairment compared with the control group. However, hemodilution did not affect mortality.⁴⁸

The positive results from this study led to a larger, multicenter trial in which the Scandinavian Stroke Study Group followed the initial protocol described above.^{46,47} However, this study failed to demonstrate any clinical benefit in patients treated with hemodilution. Similar negative results were obtained from a multicenter Italian trial, which followed a similar protocol of phlebotomy and infusion of dextran 40.²⁵

A trial from North America investigated the benefits of hypervolemic hemodilution based on the experimental evidence that increased cardiac output enhances blood flow to ischemic brain. This study, which used pentastarch as a volume expander, found a modest benefit in patients treated within 12 hours of stroke onset, patients with 15% reduction in hematocrit, and those with a 10% increase in cardiac output. However, 4 deaths occurred in the treatment group of 45 patients. These deaths were attributed to severe cerebral edema from massive strokes.⁵¹

The issue of hemodilution resurfaced in a double-blinded study from Austria in the late 1990s. In this study, patients were randomized within 6 hours of stroke onset and treated patients received hydroxyethyl starch to achieve mild hypervolemic hemodilution. Although treatment was initiated within 6 hours, a maximum reduction of hematocrit of 10% was not achieved

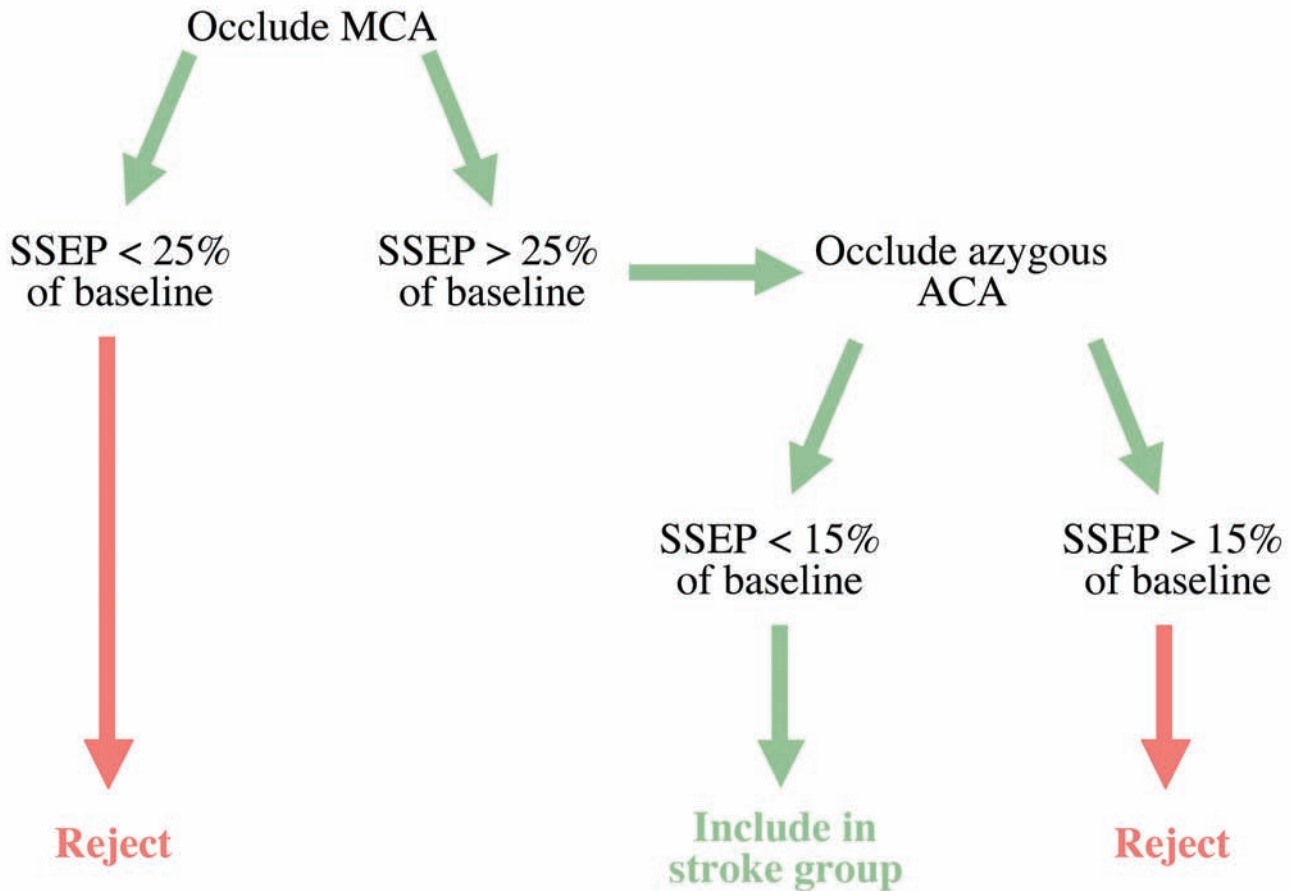


FIGURE 26.9. Stroke paradigm used to select animals with uniform, moderately sized strokes. Animals were subjected to MCA occlusion. If the SSEP amplitude remains above 25%, the animals were subjected to further occlusion of azygous ACA. If the SSEP amplitude drops to less than 15% of baseline, the animals were included in the stroke group.

until the fifth day of treatment. This study failed to show any significant benefit for the treated patients and added to the clinical weight against hemodilution as a treatment for ischemic stroke.¹

The results of these clinical trials raise the question of why hemodilution, a concept well grounded in theory and in the laboratory, has failed to show clinical efficacy. Several factors may be responsible for the discordant clinical findings. Hemodilution therapy was initiated relatively late in these studies. The Scandinavian and Italian trials used entry times of 48 and 12 hours, respectively. The proportion of patients in who underwent hemodilution within 6 hours of neurological symptoms was only 6% in the Scandinavian trial and 55% in the Italian study. The Austrian study attempted to balance experimental and practical considerations by randomizing all patients within 6 hours. However, based on the experimental evidence, even this time window may be too big for hemodilution to be effective. Furthermore, the gradual hemodilution regimen over several days in the

Austrian trial may have been too mild to achieve a positive result.

The protocol of phlebotomy before adequate volume replacement in the Scandinavian and Italian studies could have led to an initial period of potentially dangerous hypovolemia. Therefore, the intended benefit of improved rheology from hemodilution may have been prevented by an initial phase of negative rheological effects. Finally, the degree of hemodilution achieved in these studies may have been inadequate. The mean hematocrit after treatment in both studies was 37%, far from the optimal degree of hemodilution that we demonstrated in our experimental work.

IMPLICATIONS FOR FLUID MANAGEMENT IN CLINICAL NEUROSURGERY

Our experimental work has established that hemodilution is beneficial in protecting ischemic brain when instituted very early (less than 6 hours) after the insult. We also

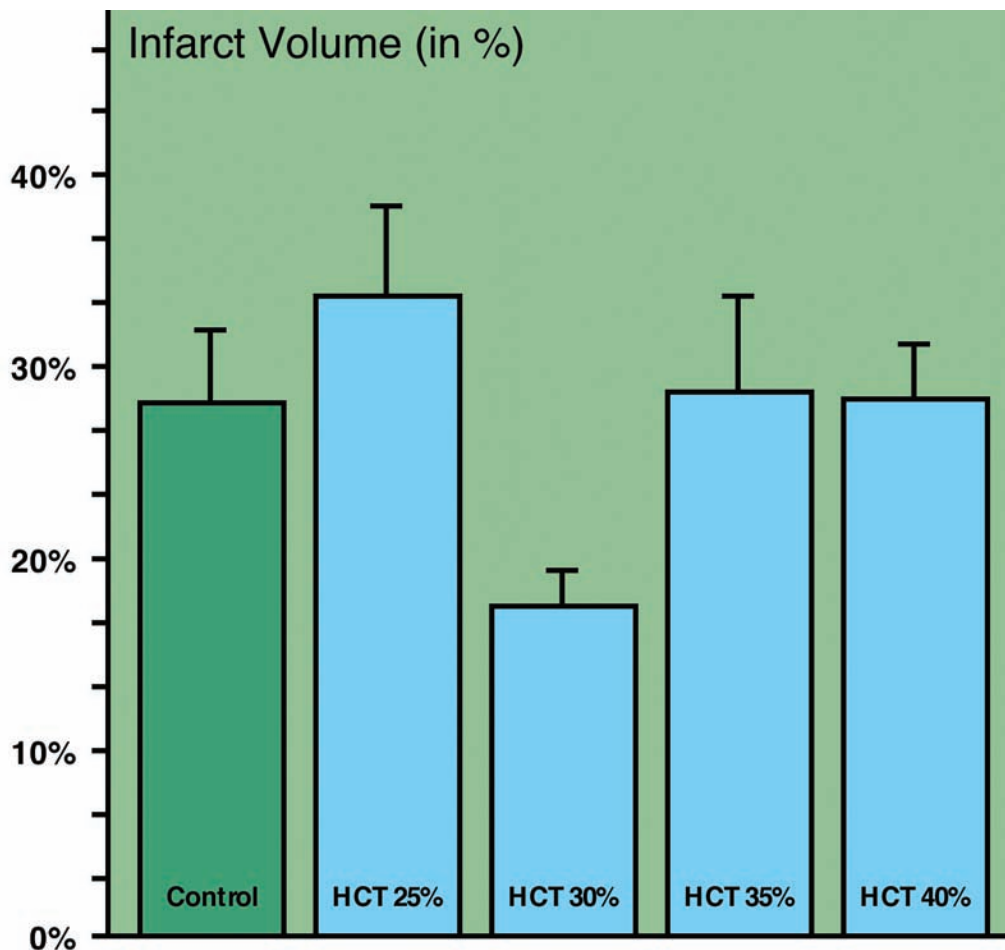


FIGURE 26.10. Graph showing the volume of infarct size at various degrees of hemodilution. Hematocrit of 30% was optimal hemodilution at which the size of infarct was significantly smaller than in the control animals (ischemic but nonhemodiluted). HCT, hematocrit.

established that hemodilution increases regional CBF in ischemic brain through a decrease in viscosity rather than through the decrease in oxygen capacity that results from hemodilution. We have observed that a hematocrit of 30% is the limit of effective hemodilution, below which, augmentation of CBF no longer compensates for the reduction in oxygen-carrying capacity. We, along with others, have investigated various agents used to achieve hemodilution. Despite all of these experimental advancements, there is little clinical evidence to support the use of hemodilution in the setting of cerebral ischemia.^{14,28} The number of variables in the clinical setting is enormous and cannot be controlled as strictly as in the laboratory. The use of hyperdynamic therapy (hypervolemic hemodilution in conjunction with hypertension) is supported in the specific setting of vasospasm,⁷ but the effect of hemodilution itself has not been isolated in clinical practice.

Perhaps, most importantly, our work lays an experimental foundation for fluid therapy in patients with cerebral

ischemia. Although hypervolemic hemodilution is well-tolerated by the normal brain, it is potentially injurious to ischemic brain and can result in cardiac overload and pulmonary edema in patients with compromised cardiovascular function. Colloids such as albumin exert their inherent oncotic pressure, and tend to stay in the intravascular space until the blood-brain barrier is completely disrupted (which, of course, is the case with profound ischemia and infarction). In contrast, crystalloids tend to “leak” into ischemic brain, even in early stages where the blood-brain barrier is not yet completely disrupted. We confirmed this important presumption with specific gravity measurements that demonstrated a marked increase in water content in ischemic brain of animals hemodiluted with crystalloids compared with that of animals infused with colloids. This increase in water content in ischemic brain (edema) resulted in a significant increase in ICP in the animals hemodiluted with crystalloids as opposed to control animals and animals hemodiluted with colloids.

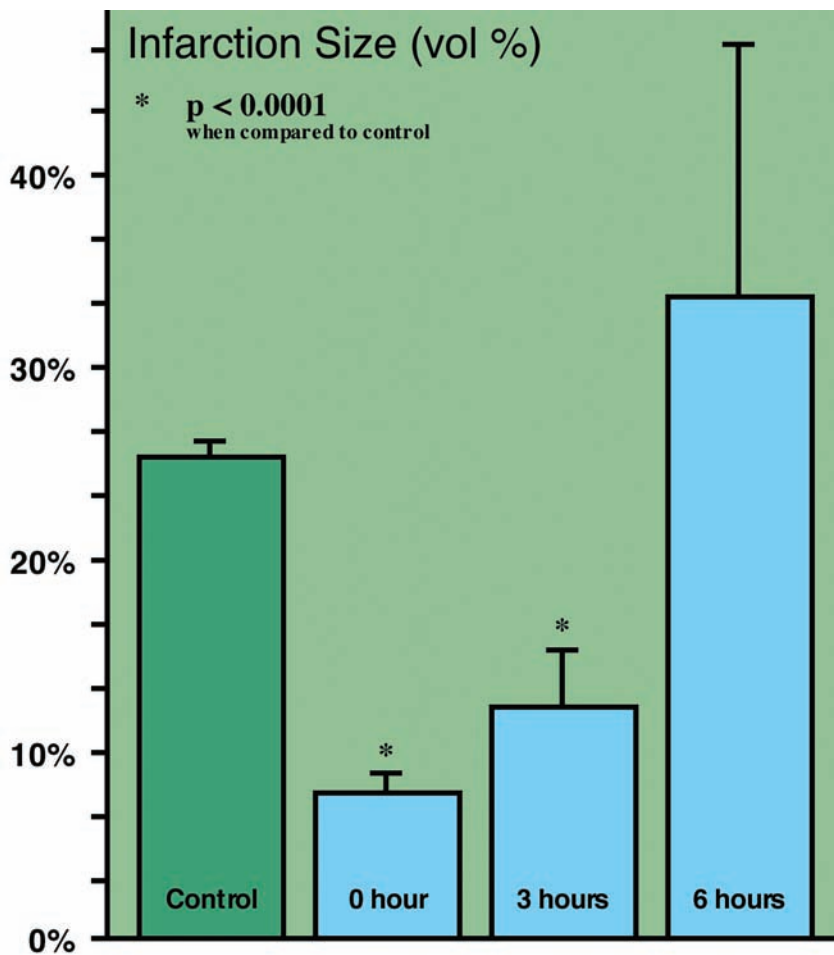


FIGURE 26.11. Graph shows the size of infarct volume at different times when hemodilution was instituted. There was a significant reduction ($P < 0.0001$) in the size of infarct in the 0 hour and 3 hour group compared with the control and 6-hour group.

The likely explanation for this difference probably lies in our observation that the animals hemodiluted with colloids maintained normal oncotic pressure, whereas a marked decrease in oncotic pressure was observed in the animals hemodiluted with crystalloids.

The concepts of “healthy brain” and “injured brain” are extremely important with regard to fluid management of patients with neurosurgical problems. Although it seems clear that colloids are superior to crystalloids with respect to brain edema, there is still controversy because of inappropriate extrapolations from fluid management of patients with systemic problems, such as shock and trauma, but usually with uninjured brains. Failure to separate these concepts of “healthy” and “injured” brain has potentially severe consequences for patient management.

Fluid administration is one of the most basic principles in resuscitation and is a routine part of most hospitalized patients. Although the trauma literature includes many poor studies, meta-analyses suggest that the choice of resuscitation fluid has little effect on mortality in the setting of *hemor-*

rhagic shock.⁴³ Colloids have also been associated with higher mortality in trauma patients.⁵⁶ Despite analyses that are more recent that favor albumin, the most optimistic evaluation of these studies is that there is a trend toward decreased mortality when crystalloids are used to resuscitate surgical and trauma patients.^{4,57} Therefore, crystalloids remain the fluid of choice for the resuscitation of most trauma patients. However, none of the major trauma studies categorize patients with head injury. There is an assumption that the patients in these studies have healthy, uninjured brains. If so, then crystalloids should carry no neurological morbidity because the blood-brain barrier is completely intact. However, we have observed a trend of increased crystalloid use in the management of the “injured brain” (i.e., neurotrauma, stroke). We think that this detrimental practice is becoming more prevalent because crystalloids are used widely in fluid resuscitation and because fluid resuscitation is a routine part of hospital practice. The results of experimental and clinical work on cerebral ischemia seem to have been overshadowed by the more prevalent trauma work.

The practical considerations of all this debate lie with the cost and availability of colloid, particularly albumin. Because of inappropriate extrapolation from the trauma literature, we have suffered pressures from hospital committees to restrict or discontinue the use of albumin as part of the hyperdynamic therapy for vasospasm.^{17,49} These types of restrictions are not based on scientific evidence, and even the fiscal justifications are not well grounded. Although the initial expense of colloid use may be high, the reduced hospital stay and improved neurological outcomes result in far greater long-term reduction of medical expenses.⁴⁹

CONCLUSIONS

Our work has shown that isovolemic hemodilution with a colloid, namely low molecular weight dextran, markedly reduces the size of an infarct that results from a 6-hour period of MCA occlusion in dogs. Importantly, it does so without a resultant increase in ICP or in cardiac output, both of which are well-known side effects of hypervolemic hemodilution. Hemodilution with crystalloids, on the other hand, is detrimental in the setting of ischemia and results in larger infarctions than in animals hemodiluted with colloids or in control animals. The detrimental effects of crystalloids seem to be related to worsening of brain edema and consequent increase in ICP. The optimal hematocrit to protect ischemic brain is between 30% and 32%. To be effective, hemodilution must be completed within 6 hours of ischemia onset and may be detrimental if initiated beyond this small window of opportunity. The mechanism whereby hemodilution increases CBF in ischemic brain seems to be related to its rheological effect of decreasing blood viscosity rather than to a compensatory effect against reduced oxygen-carrying capacity.

There are clear implications of this work to the general fluid management of neurosurgical patients. Neurosurgical patients with nonischemic brains (i.e., spine, epilepsy, functional, and peripheral nerve patients) should tolerate large infusions of crystalloids if they have good cardiovascular function. However, in the setting of brain injury, cerebral ischemia, or increased ICP, large infusions of crystalloids are dangerous because of their tendency to increase cerebral edema, raise ICP, and consequently exacerbate cerebral ischemia. Colloid infusions seem to be not only safe in this setting but actually beneficial, particularly in ischemic conditions such as vasospasm, acute stroke, and iatrogenic or planned arterial occlusion.

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