Cerebral Hemodynamics of Experimental Cerebral Embolization

By Eugene D. Robin, M.D., Fred Fowler, M.D., Robert D. Whaley, M.D., and Charles H. Crump, M.D.

Cerebral embolization in anesthetized dogs produces a fall in cerebral blood flow but no significant increase in cerebrovascular resistance. The mechanism of the decreased flow is usually a decrease in mean arterial blood pressure. Section of the sympathetic-vagus trunks produces no consistent increase in cerebral blood flow or fall in cerebrovascular resistance.

The cerebral hemodynamics of cerebrovascular disease are not well understood. One limitation to their physiologic evaluation is the marked variability of human cerebrovascular disease. Important variations include the nature of the acute episode (i.e., thrombosis, embolus, hemorrhage with or without cerebral infarction); the amount of underlying cerebrovascular disease; the presence and degree of complicating diseases, such as congestive heart failure, and the length of time between the occurrence of an acute cerebrovascular accident and the time of study.

Some of these variations can be obviated by the study of experimentally produced vascular accidents in an appropriate laboratory animal. This study deals with the changes in cerebral blood flow, cerebrovascular resistance and cerebral oxygen consumption in dogs occurring as a result of experimentally produced cerebral emboli.

Methods

Mongrel dogs weighing approximately 15 Kg. were used. Each dog was anesthetized by the intravenous injection of pentobarbital (30 mg./Kg.). During the course of each experiment, additional doses of pentobarbital were administered as required to suppress the outer canthus reflex but to maintain the inner canthus reflex intact.

Determinations of cerebral blood flow were performed by the integrated Scheinberg-Stead modification of the Kety-Schmidt nitrous oxide technic.1,2 This technic is based on the Fick principle and requires a source of mixed cerebral venous blood. In the dog, the jugular venous drainage contains significant amounts of blood from the face and scalp region3 and is not suitable for cerebral blood flow determinations. In order to obtain mixed cerebral venous blood, a midline burr hole was made and the superior longitudinal sinus identified. A small incision was made in the sinus and it was intubated with a no. 14 polyvinyl catheter. The catheter was passed posteriorly in the direction of the confluence of sinuses. After appropriate positioning of the catheter, it was sutured to the dura. The catheter served as a ready source of mixed cerebral venous blood. The dura was re-sutured over the catheter and the wound packed with Gelfoam. Between determinations the dead space of the catheter was kept filled with sodium heparin solution.

Arterial blood was obtained by means of an indwelling no. 14 polyvinyl catheter placed in a femoral artery. The dural sinus catheter and the femoral arterial catheter were trimmed to exactly the same length so that the dead spaces of the two were equal.

A blank sample for nitrous oxide analysis was obtained from the dural sinus catheter. Fifteen per cent nitrous oxide in air was administered for a 10 min. period, while blood was sampled at the rate of 1 ml./min. simultaneously from the longitudinal sinus and femoral artery. After this
10 min. period, an equilibrium sample of mixed cerebral venous blood was obtained. Cerebral blood flow was calculated as follows:

\[
\text{Cerebral blood flow (ml. blood/100 Gm. brain/min.)} = \frac{N_2O \text{ concentration in equilibrium sample} \times 10}{(N_2O \text{ conc. integrated arterial} - N_2O \text{ conc. integrated venous sample})}
\]

The integrated technic of Scheinberg was used rather than the original multiple point technic since the number of samples required for analysis is smaller with the former. It was deemed impractical to attempt to do 3 complete studies in each dog using the multiple point technic. However, the use of the integrated technic did not permit any estimate of the degree of contamination of cerebral blood with blood from extra cerebral sources. Nor was any correction made for the effect of catheter dead space in the calculations. This may partially explain the fact that the control value for cerebral blood flow measured 54 ml./100 Gm. brain/min., a value which seems surprisingly high. However, since these studies are based on relative, rather than absolute values, the interpretations drawn from the data seem valid.

There was a possibility that the time required for equilibrium might be prolonged by the production of cerebral emboli. Therefore, in 3 dogs, the production of cerebral emboli, simultaneous 10 min. arterial and cerebral venous samples were analyzed for nitrous oxide concentration. These concentrations were essentially equal (less than 0.5 vol. per cent difference).

The partition coefficient for nitrous oxide between blood and brain was assumed to be the same in dogs as in humans, where its value is approximately 1. This assumption seems valid, since the partition coefficient for myocardium is identical in the two species. Nitrous oxide was determined in a Van Slyke apparatus by a modification of the method of Orcutt and Waters.

Arterial blood pressure was continually monitored by means of an indwelling femoral needle using a Sanborn electromanometer and a Sanborn Poly-viso recorder.

Cerebrovascular resistance was calculated as the ratio of mean arterial pressure to cerebral blood flow. In accordance with the Kety-Schmidt technic, its value was expressed in arbitrary units whose dimensions were the millimeters of Mercury necessary to force 1 ml. blood through 100 Gm. brain/min.

The arterial and cerebral venous bloods for oxygen analysis were collected over a 1 min. period after the equilibrium samples had been drawn, while nitrous oxide was still being administered to the animal.

Oxygen contents were determined in a Van Slyke apparatus by the method of Van Slyke and Nell. Cerebral oxygen consumption was calculated as the product of the cerebral blood flow and the arteriovenous oxygen difference. Its units were expressed as ml. of O$_2$/100 Gm. brain/min.

Cerebral embolization was produced by the intraarterial injection of polyvinyl latex, a thick gelatinous material which solidifies upon injection into the blood stream. It has been shown by Whistnant, Millikan, Wakin and Sayre that it is a useful substance for the experimental production of cerebral emboli. The following procedure was followed:

One common carotid artery was exposed at its bifurcation. A small incision was made in its wall and a no. 14 polyvinyl catheter was passed through the common carotid into the internal carotid artery. At a suitable time, approximately 1 ml. of polyvinyl latex was rapidly injected into the catheter while the external carotid and proximal internal carotids were temporarily occluded. Three milliliters of physiologic saline was then injected into the catheter for the purpose of flushing the latex into the cerebral vasculature.

Studies were made in 18 dogs before and after cerebral embolization. Following anesthesia, catheters were placed in the superior longitudinal sinus, a femoral artery and an internal carotid artery. The cervical portions of the sympathetic-vagus trunk on each side were exposed, identified and a ligature placed around each. Following these manipulations, 30 min. were allowed to permit the development of a steady state. After this period, control determinations of cerebral blood flow, arterial pressure, cerebral oxygen consumption, and cerebrovascular resistance were performed. After the control determinations, cerebral embolization was accomplished as described. Observations were repeated 30 min. after embolization.

In 13 of the dogs the sympathetic-vagus trunks were sectioned bilaterally. Thirty minutes after this section, a third series of observations was made. For control purposes, the sympathetic-vagus trunks were exposed but not sectioned in.
CEREBRAL HEMODYNAMICS FOLLOWING EMBOLIZATION

TABLE 1.—Reproducibility of Duplicate Determinations

<table>
<thead>
<tr>
<th></th>
<th>Cerebral blood flow (ml./100 Gm. brain/min.)</th>
<th>Mean arterial blood pressure (mm. Hg)</th>
<th>Cerebral oxygen consumption (ml. O2/100 Gm. brain/min.)</th>
<th>Cerebrovascular resistance (mm. Hg/ml. blood/100 Gm. brain/min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
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<tr>
<td>1</td>
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<td>59</td>
<td>57</td>
<td>142</td>
<td>154</td>
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<td>57</td>
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<td>3.6</td>
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<tr>
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<td>45.4</td>
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<td>149</td>
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<tr>
<td></td>
<td></td>
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<td>3.5</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Standard deviation ±4.9 ±19.3 ±1.6 ±0.56

5 dogs. In these dogs, repeat observations were obtained 30 min. after embolization.

In 5 other dogs, 2 control series of observations 30 min. apart were made for the purpose of determining the reproducibility of the results.

RESULTS

Since this technic for the measurement of cerebral hemodynamics has not previously been applied to the dog, data concerning reproducibility are shown in table 1. Duplicate determinations of cerebral blood flow showed a standard deviation of ±4.9 ml./100 Gm. brain/min. Duplicate determinations of cerebrovascular resistance showed a standard deviation of ±0.56 mm. Hg/ml. blood/100 Gm. brain/min. Duplicate determinations of mean blood pressure showed a standard deviation of 19.3 mm. Hg.

Duplicate determinations of cerebral oxygen consumption agreed less well. The reproducibility of duplicate determinations of cerebral oxygen consumption was low, as shown by a standard deviation of ±1.6 ml. O2/100 Gm. brain/min. The poor agreement between separate determinations may be related to the problem of maintaining a constant level of anesthesia. It has been shown by Ilmwich 8 that barbiturate administration results in a depression of cerebral oxygen consumption. The criterion employed for constancy of anesthesia was abolition of the outer canthus with maintenance of the inner canthus reflex. This criterion is presumably a gross one. There may be fairly wide variations in cerebral oxygen consumption related to changes in the depth of anesthesia without changes in the canthus reflexes.

Data concerning changes in cerebral blood flow, mean arterial pressure, cerebral oxygen consumption and cerebrovascular resistance are shown in table 2. The mean value for cerebral blood flow during the control period was 54 ml./100 Gm./min. There was a significant fall in cerebral blood flow to 43 ml. 30 min. after cerebral embolization. There was no return to control levels of cerebral blood flow in the 13 dogs treated with sympathetic-vagus section. There was a significant fall in blood pressure following embolus (142 to 113 mm. Hg). Sympathetic-vagus section produced no return in blood pressure toward normal. There was no significant change in cerebrovascular resistance following cerebral embolization (2.9 to 2.7). Sympathetic-vagus section likewise produced no change in cerebrovascular resistance. The fall in cerebral oxygen consumption following cerebral embolization was not statistically significant nor was the increase in cerebral oxygen consumption following sympathetic-vagus section significant. In view of the wide variations in cerebral oxygen consumption found in duplicate control determinations, these data must be interpreted cautiously.

Data concerning changes in cerebral hemodynamics in the dogs whose sympathetic-vagus trunks were exposed but not sectioned...
are also shown in table 2. Sixty minutes after embolization 2 of the 5 dogs (dogs 14 and 17) showed a persistent reduction of cerebral blood flow and one dog (dog 16) showed a significant reduction of cerebral blood flow with a spontaneous return to control levels. Two dogs (dogs 15 and 18) had no significant change in cerebral blood flow despite embolization.

Statistical analysis of the relationship between cerebral blood flow and mean arterial pressure showed a correlation coefficient of 0.54 with a p value of less than 0.001. Thus, there was a small, but highly significant relationship between these variables.

Preliminary gross studies indicate focal cerebral infarction in the distribution of the middle cerebral artery in the majority of the dogs. There was no correlation between the extent of cerebral infarction and the changes in cerebral blood flow. A more detailed report of the anatomic changes occurring as a result of experimental cerebral embolization will be reported in another communication.

**Discussion**

These data establish that experimental cerebral embolization produces a significant reduction of cerebral blood flow. Moreover this effect is a decrease in over-all flow, since the nitrous oxide technic measures only flow to perfused cerebral tissue and areas of the brain whose vasculature is occluded are excluded from total measured flow. This fact explains the seeming paradox of an unchanged cerebrovascular resistance in the face of mechanical blockage of part of the cerebral vasculature. These blocked areas presumably are excluded from the areas measured by the nitrous oxide technic. These data also establish that the mechanism for the decrease in cerebral blood flow is a de-
Cerebral Hemodynamics Following Embolization

A fall in mean arterial pressure is the most consistent consequence of cerebral embolus. It was found in 16 of the 18 dogs studied. An example of this fall in mean arterial blood pressure is shown in figure 1. The fall in mean pressure results from a decrease in both systolic and diastolic pressures. It becomes manifest approximately 90 sec. after the embolization and usually persists in some measure for approximately 60 min. The mechanism of this decrease in blood pressure is not known. Theoretically, it could result from a decrease in cardiac output, a decrease in systemic resistance, or both. It seems probable that it results from reflex systemic vasodilation, but a fall in cardiac output as its cause has not been excluded.

Factors important in cerebrovascular resistance include metabolites, such as carbon dioxide and H+ acting locally on the cerebral vasculature, extrinsic vasodilator and vasoconstrictor impulses arising from the sympathetic and parasympathetic nervous systems respectively; vasoconstrictor fibers accompanying the vagus nerve as part of a cranio-cervical sympathetic system; obstructive vascular lesions, such as atherosclerosis; and the intrinsic ability of cerebral vessels to constrict independent of impulses arising from the nervous system (Bayliss reflex).

It is generally accepted that in the normal animal the control of the cerebral vasculature is mediated chiefly by local metabolites and that nervous impulses play an insignificant role. However, it has been suggested that in the acute cerebrovascular episode impulses arising in the sympathetic nervous system become functionally important and are responsible for widespread cerebrovascular spasm and a generalized reduction of cerebral blood flow. A large and controversial literature has accumulated regarding the importance of vasospasm during acute cerebrovascular disease.

Studies of cerebral hemodynamics during acute cerebrovascular accidents have shown conflicting results. Harmel, Halkenschiel,
Austin, Crumpton and Kety,12 Naffziger and Adams,13 and Scheinberg14 have shown no increase of cerebral blood flow or decrease in vascular resistance following stellate block. Shenkin, Cabrises and Van Den Noordt12 and Linden10 have shown an increase in cerebral blood flow and a decrease in cerebrovascular resistance following block when the vascular resistance was abnormally high before block was attempted. The present study showed no increase in vascular resistance following the production of cerebral emboli, nor does sympathetic-vagus section improve cerebral hemodynamics.

The results reported here must be applied with great caution to human vascular disease. These studies were performed on dogs whose cerebral vasculature may differ physiologically from the cerebral vasculature of humans. The changes in hemodynamics produced by polyvinyl latex emboli on normal vessels may be quite different from the changes produced by emboli consisting of blood clots on previously abnormal vessels. The method used to measure cerebral blood flow only measures flow per 100 Gm. of perfused cerebral tissue. It is possible to have an increase in flow in small critical areas without an over-all increase in blood flow as measured by this technic.

On the other hand, the failure to demonstrate significant increases in cerebrovascular resistance in the majority of dogs is impressive. In this respect it is important to consider the data obtained from the dogs whose sympathetic-vagus trunks were exposed but not sectioned. In these 5 control dogs, 2 showed no significant change in cerebral blood flow throughout the period of study, 2 showed a fall in cerebral blood flow which persisted, and 1 demonstrated a spontaneous return to normal cerebral hemodynamics, despite the fact that no therapy was given.

The changes in cerebral hemodynamics as a result of cerebral embolization show a consistent pattern on a statistical basis, but individual dogs may vary from this pattern. At least 3 patterns of change occur. Figure 2, taken from the data on dog 9, shows the
most common pattern. Cerebral blood flow dropped from 44 to 22 ml./100 Gm./min. as a result of a decrease in mean arterial pressure from 154 to 42 mm. Hg. Cerebrovascular resistance remained unchanged.

The data of dog 16 (fig. 3) illustrates that in an occasional dog increased cerebrovascular resistance does appear to be an important mechanism for the changes in cerebral hemodynamics. In this dog cerebral blood flow decreased from 38 to 20 ml./100 Gm./min. at a time when mean arterial pressure actually was elevated. Cerebrovascular resistance increased from 2.9 to 5.5 units. In dog 2 (fig. 4) cerebral embolization occurred without any significant change in cerebral blood flow, mean arterial pressure or cerebrovascular resistance. These patterns obviously have their counterparts in human cerebrovascular disease.

**SUMMARY**

Cerebral blood flow, mean arterial pressure, cerebrovascular resistance and cerebral oxygen consumption have been measured in a group of dogs before and after embolization. Cerebral embolization produces a fall in cerebral blood flow. There is no significant increase in cerebrovascular resistance. The decreased flow can usually be attributed to a decrease in mean arterial blood pressure. Section of the sympathetic-vagus trunks produces no consistent increase in cerebral blood flow or fall in cerebrovascular resistance. These studies do not support the thesis that cerebrovascular spasm plays any important role in the altered cerebral hemodynamics of experimental cerebral embolization in the dog.

**SUMARIO IN INTERLINGUA**

Le fluxo de sanguine cerebral, le pression medie arterial, le resistitutia cerebrovascular, e le consumption cerebral de oxygo es eva mesurate in un gruppo de canes ante e post le production experimental de embolismo cerebral. Le embolismo produce un reduction del fluxo de sanguine cerebral. Il non accurre un augmento significative del resistitutia cerebrovascular. Le reduction del fluxo de sanguine cerebral es usualmente explicable complemente per le reduce valores medie del pression de sanguine arterial. Le section del trunco sympathtico-vago non produce uniformemente un augmento del fluxo de sanguine cerebral o un reduction del resistitutia cerebro-vascular. Iste studios non supporta le thes que spasmio cerebro-vascular ha un rolo importante in le alterate hemodynamica cerebral de embolismo cerebral experimental in canes.

**ACKNOWLEDGMENT**

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