The relation of cerebral ischemia, hypoxia, and hypercarbia to the Cushing response

JOHN E. McGILLCUDDY, M.D., GLENN W. KINDT, M.D., JAMES E. RAISSIS, M.D., AND CAROLE A. MILLER, M.D.

Section of Neurosurgery, Department of Surgery, University of Michigan Medical Center, Ann Arbor, Michigan

A marked increase in intracranial pressure (ICP) produces a concomitant increase in systemic blood pressure (the Cushing response). In this study a comparison is made between this response of systemic blood pressure to increased ICP and the blood pressure responses produced by ischemia, hypoxia, and hypercarbia of the primate brain. A carotid-to-carotid cross-perfusion system was used to produce a purely cerebral hypoxia and hypercarbia. Each stimulus, except hypercarbia, produced a hypertensive response that was qualitatively and quantitatively similar. These responses were characterized by a short latent period, a rapid development, and an increase in mean arterial pressure of 60% or more. The similarity of the responses suggests that these stimuli act through a final common pathway independent of the purely mechanical effects of increased ICP upon the brain.

Key Words
- Cushing response
- cerebral ischemia
- cerebral hypoxia
- intracranial pressure
- cerebral cross-perfusion

The rise in systemic arterial pressure that often follows an increase in intracranial pressure (ICP) was studied for many years before the work of Harvey Cushing.\(^4,21,24\) Cushing, however, was the first to investigate the response from the quantitative standpoint and to show its graded nature. Using subdural saline infusion to produce a generalized increase in ICP, he found that blood pressure did not change until ICP exceeded arterial pressure.\(^7\) At that point arterial pressure rose until diastolic pressure exceeded ICP. This reaction could be repeated with successive further increases in ICP. Noting that the production of this hypertensive response was related to the difference between arterial pressure and ICP, he postulated that it was induced by medullary ischemia and served to restore blood flow to the brain-stem centers. Although often associated with bradycardia and slowing of respirations, the most reliable finding in these experiments was the increase in arterial pressure.\(^8\)

Although later studies have continued to confirm Cushing's belief that this response was mediated by the sympathetic nervous system,\(^15,18,22\) there is less agreement on the mechanism of initiating the response. Initially widely accepted, Cushing's theories were cast into doubt by clinical studies\(^6,14\) that demonstrated that there was no consistent relationship between the level of ICP and changes in vital signs. Since systemic hypertension was not always evoked even at intracranial pressures approaching arterial
Cerebral factors in the Cushing response

pressure, the role of cerebral ischemia was minimized and other factors were invoked to explain the Cushing response.

Recent experimental studies have centered attention on transtentorial pressure gradients and brain-stem distortion. Local pressure on discrete areas of the floor of the fourth ventricle has also been found to produce a rapid rise in systemic blood pressure. The areas involved closely corresponded to the vasomotor area of the brain stem. As a consequence of this attention to the mechanical effects of increased ICP, there has been less interest in the influence of brain ischemia, hypoxia, and hypercarbia on the Cushing response. In a preliminary study we demonstrated that cerebral ischemia and cerebral anoxia, acting alone and without an associated increase in ICP, could produce a systemic hypertensive reaction similar to the Cushing response. The present study was undertaken to make more detailed comparison of the blood pressure responses to increased ICP, hypoxia, and hypercarbia in the primate. An attempt was made to exclude the effect of peripheral baroreceptors and chemoreceptors, and thus facilitate the investigation of the effects of purely cerebral hypoxia, ischemia, and hypercarbia. Although each of these stimuli has previously been investigated individually, comparison of all the responses in one species has not been previously reported.

Materials and Methods

Twelve adult rhesus monkeys weighing 2 to 5 kg were tranquilized with phencyclidine hydrochloride. Light surgical anesthesia was maintained with sodium pentobarbital. A tracheostomy was performed and both carotid and vertebral arteries were exposed on all animals. The vertebral arteries were ligated near their origins. In five animals the carotid bifurcations were denervated bilaterally by adventitial stripping and nerve section. The femoral artery and veins were isolated on each side. A polyethylene catheter was inserted into one artery and connected to a strain gauge for measurement of arterial pressure. The probe of a mass spectrometer,† inserted into the opposite femoral artery until the tip was in the aorta, was used to monitor arterial blood gases. The femoral veins were cannulated for intravenous infusion of saline and medications. Bilateral parietal twist drill holes were made. The dura was opened and modified plastic three-way stopcocks were inserted. One was attached to a strain gauge for continuous recording of intracranial (subdural) pressure; the other stopcock was used as a portal for subdural saline infusion.

All animals were placed on a specially modified respirator‡ and ventilated at a constant rate and volume throughout the experiment. This system was capable of delivering any desired concentration and combination of oxygen, nitrogen, and carbon dioxide. All animals were initially ventilated with 100% oxygen. Continuous monitoring of arterial pO2 and pCO2 was accomplished using the mass spectrometer. The spectrometer was calibrated frequently against arterial gases determined by the standard electrode method on blood withdrawn from the opposite femoral artery. Arterial blood gases, and arterial pressure were recorded on an eight-channel polygraph.§

The ICP was increased above arterial pressure by subdural saline infusion in a manner similar to that used by Cushing. Only 1 to 5 cc of saline were required during any experiment. Cerebral ischemia was produced by acute, reversible occlusion of the common carotid arteries with vascular clamps. Hypoxia was obtained by rapidly changing the ventilatory gas to 100% nitrogen. Six monkeys were subjected to increased ICP, ischemia, and hypoxia with appropriate recovery periods between each trial. Because the animals tended to deteriorate after several trials, es-

†Mass spectrometer, Medspect model MSBR, manufactured by Chemetron Medical Products, Division of Chemetron Corp., 6707 Whitestone Road, Baltimore, Maryland.

‡Respirator was assembled in our laboratory using a Dupaco anesthesia machine, manufactured by Dupaco, Inc., Arcadia, California, and Bird Mark 4 and Mark 7 respirators, manufactured by Bird Corp., Palm Springs, California.

§8-Channel polygraph, Beckman type R dynograph 8-channel ink chart recorder, manufactured by Beckman Instruments, Inc., 3900 River Road, Schiller Park, Illinois.

*Statham model P23Db and P37 strain gauges are manufactured by Statham Instruments, Inc., 2230 Statham Boulevard, Oxnard, California.
FIG. 1. Schematic representation of the carotid-to-carotid cross-perfusion system. The vertebral arteries are ligated. Arrows indicate the direction of the flow in the shunts. When the uncatheterized carotid arteries are occluded, the cerebral circulation of each animal was perfused with blood from the systemic circulation of the other.

Especially after systemic anoxia, the stimuli were presented in a variety of sequences. For the same reason each stimulus was discontinued soon after the peak blood-pressure response. Three monkeys were subjected to hypercarbia as well.

Cerebral cross-perfusion was instituted on three pairs of monkeys. A common carotid system was devised using polyethylene catheters such that one proximal carotid artery of each animal was connected to a distal common carotid artery of the other (Fig. 1). The remaining intact carotid artery in each animal could be simultaneously occluded with vascular clamps. Since the vertebral arteries in both animals had been ligated, opening the cross-perfusion system caused the brain of one animal to be perfused with blood from the systemic circulation of the other. The animals were heparinized before cross-perfusion.

Results

Increased Intracranial Pressure

When ICP was abruptly raised to or slightly above arterial pressure, the expected hypertensive response was uniformly seen (Fig. 2). The rise in blood pressure thus produced was rapid in onset, having a latent period of less than 10 seconds. An initial fall in pressure was seen in four of the six animals in which reproducible responses were obtained. After this brief depressor response, the blood pressure rose rapidly to reach its

---

Fig. 2. The effect of a rapid infusion of subdural saline. The blood pressure rises rapidly following a brief depressor response. Increase in blood pressure is greatest in the first 5 seconds, and increases more slowly thereafter. Fixed dilated pupils appear at the height of hypertensive response. Arterial blood gases are unchanged.
Cerebral factors in the Cushing response

peak in 25 to 30 seconds. The pressure rose most rapidly in the 5 to 10 seconds following the initial fall and then tended to increase more slowly until maximum pressure was attained. The maximum rate of increase in mean arterial pressure (MAP) averaged 6.2 mm Hg/sec. The MAP rose an average of 53 mm Hg or 64% above resting MAP. A significant slowing of the pulse rate described in the classic Cushing response, but only inconstantly seen in other studies, was not seen during the hypertensive response in these experiments. Almost simultaneously with the attainment of maximum arterial pressure, both pupils became fully dilated and fixed to light. Dilatation of one pupil often preceded the other by as much as 5 seconds but no correlation between the side of initial pupillary dilatation and the side of saline infusion was observed. This dilatation was rapidly reversed by discontinuing the saline infusion. As ICP returned toward normal, the pupillary responses also returned. Since respirations were controlled, there were no changes in arterial blood gases during this response.

Cerebral Ischemia

If the vertebral arteries had been previously ligated, the blood pressure response to acute bilateral carotid occlusion resembled the response to increased ICP (Fig. 3). The latent period was slightly longer, averaging 8 seconds with a range of 4 to 14 seconds. One of the animals showed an initial brief drop in arterial pressure after onset of ischemia. The hypertensive response, while brisk, did not show the abrupt early rise seen with increased ICP, but rather arterial pressure tended to rise at a fairly steady rate during the response. The maximum MAP attained averaged 68% above resting MAP. The maximum rate of rise of MAP was 4.1 mm Hg/sec, or about two-thirds the maximum rate induced by increased ICP. Again, fixed dilated pupils were seen at the peak of the pressor response, although pupillary changes sometimes occurred as much as 10 seconds after maximum systolic pressure was reached. Maximum systolic pressure was reached in approximately 30 seconds and both pupillary size and arterial pressure returned rapidly to normal when the carotid clamps were released.

Prior denervation of the carotid bifurcation caused no change in the response to bilateral carotid occlusion. If bilateral carotid occlusion was attempted before ligation of the vertebral arteries, only a small increase in MAP of 20% or less was produced. This response to carotid occlusion alone more closely resembled the carotid sinus reflex, and could be easily distinguished from the response to total cerebral ischemia. During the ischemic episode there was no change in pO₂ or pCO₂. In addition, there was no increase, but rather a slight fall, in ICP during cerebral ischemia.

Hypoxia and Hypercarbia

Hypoxia produced by ventilation with 100% nitrogen resulted in a rise in systemic blood pressure similar in magnitude to that caused by ischemia and increased ICP (Fig. 4). The response was quite prolonged, however, with a slow increase of blood pressure, reaching peak pressure only after an average of 45 seconds. Although the increase in blood pressure averaged 56 mm Hg or 64% above resting MAP, the maximum rate of rise of blood pressure was only 2 mm Hg/sec, or less than one-third of the maximum rate of
Fig. 4. The response to acute change in ventilatory gas to 100% nitrogen. Note the slow change in arterial pO2. Blood pressure begins to rise slowly after arterial pO2 drops to low levels. The exact time of blood pressure increase cannot be ascertained. There is no change in ICP. Bilateral pupillary dilatation occurs during the peak of the response.

rise with increased ICP. The duration of the latent period could not be established. The time required for washout and mixing of the ventilatory gases as well as that required for desaturation of the blood made determination of the latent period impossible with this technique. Despite the relatively prolonged and slow hypertensive response, the occurrence of reversible, fixed, dilated pupils at the peak of the response and the magnitude of arterial pressure change suggested a strong similarity to the responses to increased ICP and ischemia. The animals deteriorated rapidly during this trial and the pressor response was quickly followed by a dramatic fall in blood pressure associated with a slow, irregular pulse. Denervation of the carotid bifurcation had no effect upon this response, but, since this was a systemic hypoxia, the influence of other peripheral chemoreceptors could not be ruled out.

The response to hypercarbia was in some ways similar to the hypoxic response. There was a slow rise in arterial pressure with an indeterminate latent period. However, the height of the blood pressure increase was less and varied with the depth of anesthesia. It is of interest that the pressor response was elicited at relatively low (pCO2 45 to 60 mm Hg) values. There were no pupillary changes during the course of the hypercarbia experiment. It was not possible to make a quantitative comparison between the action of increased ICP and ischemia and the actions of hypoxia and hypercarbia because of the prolonged, rather than acute, nature of the latter two stimuli. Not only was there difficulty in determining the stimulus-response latency but, in addition, the critical pO2 or pCO2 required to elicit the pressor response could not be determined. Also the effects of alterations of the blood gases on peripheral chemoreceptors and on cardiac function could not be controlled.

Cerebral Cross-Perfusion

Because of the problems in comparing the responses to hypoxia and hypercarbia with those to ischemia and intracranial hyperten-
Cerebral factors in the Cushing response

sion, the common carotid-to-common carotid cross-perfusion system was instituted. This served not only to furnish an acute hypoxic or hypercarbic stimulus to the brain but also to separate the systemic and cerebral effects of these blood gas alterations. Both chronic and acute cross-circulation experiments were performed.

In the chronic experiments the shunt remained open and the remaining carotid arteries were occluded throughout the experiment. As in Fig. 5, one animal (A) was ventilated with 100% nitrogen while the other (B) was ventilated with 100% oxygen. The animals ventilated with 100% oxygen but receiving hypoxic blood in their cerebral circulation showed a distinct hypertensive response. This occurred despite perfusion of the remainder of the animal's circulation with well oxygenated blood. The animals ventilated with 100% nitrogen showed circulatory collapse, falling blood pressure, and an irregular pulse rate. This occurred despite perfusion of their cerebral circulation with well oxygenated blood. This response was seen in all pairs of monkeys tested and implies that the effect of hypoxia on the heart and systemic circulation is circulatory collapse with hypotension, while its effect on the brain is to produce a hypertensive response even in an otherwise well oxygenated animal. Carotid bifurcation denervation did not appear to affect the hypertensive response. The ICP was not increased in either animal.

Hypercarbic stimuli caused a somewhat similar response. The animal with its brain perfused with hypercarbic blood showed an increase in systemic blood pressure despite perfusion of the remainder of its body with normocarbic blood. The other animal showed no increase in blood pressure. The hypercarbic response was quite sensitive, with elevations in blood pressure in response to small increases in the pCO₂. Bilateral fixed dilated pupils, a uniform occurrence in response to perfusion of the brain with hypoxic blood, did not occur when the brain was perfused with hypercarbic blood.

In the acute cross-perfusion trials (Fig. 6) one animal was again ventilated with 100% nitrogen while the other was ventilated with 100% oxygen. The cross-perfusion catheters remained occluded and the remaining carotid arteries open until the animal ventilated with nitrogen developed a hypertensive response. The carotid arteries were then occluded simultaneously with opening of the shunts. A rapid rise in blood pressure was seen in the animal ventilated with 100% oxygen when its cerebral circulation was suddenly perfused with extremely hypoxic blood. The MAP was increased 69% above control value. The latent period from opening the shunt until the start of the pressor response averaged 7 seconds. The maximum rate of rise of MAP was 3.2 mm Hg/sec, much faster than that occurring with systemic hypoxia. Near the peak of the blood-pressure response, bilaterally fixed and dilated pupils were noted in the animal whose brain was perfused with hypoxic blood. Systemic arterial gases remained stable in this animal and no change in ICP was noted in either animal.
TABLE 1

Comparison of stimulus-response latencies and changes in mean arterial pressure*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Increased ICP (6)</th>
<th>Ischemia (6)</th>
<th>Hypoxia (4)</th>
<th>Acute Hypoxia (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>latency (secs)</td>
<td>7.8 ± 0.9</td>
<td>8.2 ± 1.5</td>
<td>ID</td>
<td>7.0 ± 0.6†</td>
</tr>
<tr>
<td>increase in MAP (mm Hg)</td>
<td>53 ± 6</td>
<td>59 ± 7</td>
<td>56 ± 12</td>
<td>61 ± 1</td>
</tr>
<tr>
<td>increase in MAP (%)</td>
<td>64.6</td>
<td>68.2</td>
<td>64.2</td>
<td>68.7‡</td>
</tr>
<tr>
<td>maximum rate of increase of MAP (mm Hg/sec)</td>
<td>6.2 ± 0.7</td>
<td>4.0 ± 1.2</td>
<td>2.1 ± 0.2</td>
<td>3.2 ± 0.3</td>
</tr>
</tbody>
</table>

*Number of animals appears in parentheses. MAP = mean arterial pressure; ICP = intracranial pressure; ID = indeterminate.
†H = 0.81 (Kruskal-Wallis test): differences not significant.
‡H = 0.5 (Kruskal-Wallis test): differences not significant.

After the cross-perfusion was opened, the animal ventilated with 100% nitrogen received a cerebral perfusate of normally oxygenated blood. The systemic blood pressure in this animal fell and circulatory collapse often followed. Differences in blood pressure between the two animals were initially slight and appeared to have no effect on the latency, the intensity, or the duration of the response. Because of the promptness of the response and the small shunts involved, production of systemic hypertension in the animal with its brain perfused with hypoxic blood was felt not to be due to bulk transfusion of blood. With this cross-perfusion technique, the critical pO2 for the initiation of this pressor response was felt to be at a point below 40 mm Hg.

**Comparison of Responses**

A comparison of the responses to the various stimuli showed some notable similarities (Table 1). The rise in MAP averaged more than 60% of resting mean pressure in response to increased ICP, cerebral ischemia, and both systemic and acute hypoxia. There was no statistically significant difference among these values by the Kruskal-Wallis test (H = 0.81). The latent period was 10 seconds or less for all of the stimuli with the exception of systemic hypoxia. Again the difference among these values was not statistically significant (H = 0.15). All of the stimuli except hypercarbia produced reversible, fixed, dilated pupils.
Cerebral factors in the Cushing response

pupils at or near the peak of the hypertensive response. Because of the variability of the responses in the animals subjected to hypercarbia, no attempt was made to quantitatively compare this stimulus to the others. Nonetheless, the usual response to systemic or cerebral hypercarbia was an increase in systemic blood pressure, as well as an increase in ICP. While the degree of elevation in systemic pressure was quite similar in all, the time course. Increased ICP caused an initial rapid rate of increase, which later declined in intensity. Ischemia and acute hypoxia on the other hand led to a relatively steady rate of rise. Systemic hypoxia and systemic hypercarbia tended to produce a slow, relatively prolonged, and steady increase in arterial pressure.

Bradycardia was not seen as a regular feature in the pressor response to any of the stimuli. When seen, bradycardia was usually a late occurrence signaling impending cardiovascular decompensation. This was most commonly seen during the responses to systemic hypoxia. The intensity of the responses varied somewhat from animal to animal, although the responses were reproducible in each animal. These differences seemed to depend on the condition of the animal and the depth of anesthesia. Animals deteriorated rapidly during induced systemic hypoxia and no more than two reproducible responses to the stimulus could be elicited from any animal. For this reason, hypoxic stimulation was nearly always done last.

Discussion

Cerebral ischemia and acute cerebral hypoxia can initiate a hypertensive reaction in the primate. Systemic hypoxia causes a similar degree of blood-pressure elevation over a more prolonged course. None of these stimuli resulted in an increase in ICP and thus mechanical stimulation of the central nervous axis cannot be implicated. That the responses persisted unchanged after denervation of the carotid bifurcation implies that the primary effect was on the brain itself, not on the peripheral receptors. Further evidence that the action of hypoxia is on the brain itself is derived from the cross-circulation experiment in which only the cerebral circulation was perfused by hypoxic blood. In these experiments the aortic chemoreceptor areas were also isolated from exposure to hypoxic blood, yet the response to this stimulus was not diminished.

Even before Cushing’s experiments it was known that acute brain ischemia produced by extracranial vessel ligation led to an increase in systemic blood pressure. Although later experiments have confirmed this, the discovery of the carotid sinus reflex diverted attention from brain ischemia to the effects of peripheral baroreceptor activation in order to explain the pressor response to extracranial occlusion. More recent studies have shown, however, that the carotid sinus reflex is involved minimally if at all in the ischemic pressor response.

The theory of the ischemic origin of the Cushing response remains attractive, especially since the initiation of this response depends not on the absolute level of ICP but on the difference between ICP and the systemic arterial pressure. It is generally accepted that increased ICP causes a decrease in cerebral blood flow (CBF). This decrease occurs only at relatively high levels of ICP, when the difference between MAP and ICP, namely, the cerebral perfusion pressure (CPP), is small. Although measured blood flow appears to change little until high levels of ICP are attained, anatomical studies by Hekmatpanah show a progressive decrease in capillary and small vessel circulation as ICP is increased; at a level of ICP sufficient to initiate a hypertensive response there is virtual absence of flow in arterioles, capillaries, and venules. Large decreases in CBF do appear to produce a systemic hypertensive response, although an absolute relationship among ICP, CPP, and CBF has not been found. The increase in arterial pressure is associated with an increase in CBF. This suggests that the blood-pressure rise acts to preserve cerebral perfusion and that its onset might be initiated by some effect of decreased perfusion such as ischemia or hypoxia. Studies showing a very narrow difference in arterial and venous oxygen content just before the onset of a Cushing response induced by increased ICP suggest cellular metabolic derangement and lend further support to an ischemic origin for the response.

There are some objections to this ischemic hypothesis. First, elevations of CSF
pressure to levels approaching arterial pressure in humans have not caused systemic hypertension, even when a significant decrease in CBF occurred. Conversely, a hypertensive response can be occasioned by relatively low levels of ICP, either by creating a pressure gradient across the tentorium or by the establishment of areas of locally increased ICP. However, the occurrence of local areas of ischemia cannot be excluded in these situations.

The role of hypoxia as the stimulator of the Cushing response is less well elucidated. Anoxia has been shown to be a powerful effector of increased sympathetic activity in the thoracic cord and extracorporeal perfusion of the isolated head with hypoxic blood does cause a rapid, large, and reversible increase in systemic blood pressure. Objections to the implication of hypoxia in the Cushing response have centered on the long latency and the slow evolution of the hypertension. These criticisms fail to consider the time required for a dead space washout and blood deoxygenation when respiratory gases are acutely changed. When a sufficiently acute cerebral hypoxic stimulus is provided, the blood-pressure response is prompt and marked.

The considerable variability in the results of prior studies of the Cushing response have led to a number of differing conclusions concerning the nature of the adequate stimulus for this response and the receptor site of action for this stimulus. Forster showed that structures rostral to the pons were not necessary for the development of a Cushing response to a generalized increase in ICP, and attention has since centered on the vasomotor areas of the pons and medulla. However, a hypertensive response can be elicited by hypothalamic stimulation, by diffusely increased CSF pressure confined to the spinal subarachnoid space, and by local pressure on the cervical and dorsal cord. Such a wide distribution of involved areas comprising different groups of neurons and axons of passage leads us to believe that simple pressure sensitivity alone of the neurons and axons does not adequately explain the initiation of the Cushing response.

Our study directs attention to the possible role of ischemia, hypoxia, and hypercarbia in the initiation of the Cushing response. Hypoxia and ischemia can produce a hypertensive response. The effect of these agents is on the central nervous system and not on the peripheral receptors. The responses to acute hypoxia and ischemia closely resemble the response to increased ICP in stimulus-response latency, in the degree of blood-pressure elevation, and in their development by a sympathetic discharge accompanied by the onset of reversible pupillary dilatation. The latent period in this study is approximately 10 seconds for all the stimuli acutely applied, except hypercarbia. This is in agreement with those latencies found for abrupt increases in ICP and for acute cerebral ischemia produced by arterial inflow occlusion. Ischemia and hypoxia cause an elevation in arterial pressure equal to or greater than the response to generalized increased ICP produced by the method of Cushing. Since neither ischemia nor hypoxia caused an increase in ICP, axial distortion or direct brain-stem pressure cannot be implicated in the production of the Cushing response by these stimuli. Our findings do not support the existence of intracranial baroreceptors.

Hypercarbia, either systemic or cerebral, also produces an increase in blood pressure. However, this elevation is noted even at relatively low levels of pCO₂, is slow in evolution, and is not associated with the development of pupillary dilatation. Although cerebral hypercarbia alone does not seem to elicit a Cushing response, it may contribute to its intensity.

The similarity of the responses suggests that ischemia and hypoxia may be adequate stimuli for the Cushing response. Increased ICP may act by producing ischemia and/or hypoxia in some critical areas of the brain. Our findings do not necessarily contradict the evidence that local distortion or pressure on the brain can cause the Cushing response. Indeed such local distortion or pressure may cause focal ischemia in areas of the brain stem. There are also suggestions that ischemia and hypoxia may facilitate the response to increased ICP. The initial rate of rise of blood pressure in this study was greatest with increased ICP and this early acute change may represent the effect of mechanical forces alone. Ischemia, with attendant hypoxia and hypercarbia, may play its role in the next few seconds of the classic Cushing response.
Acknowledgments

The authors wish to express their appreciation to George W. Williams, Ph.D., for his help with the statistical analysis of the data, and to Elwyn R. Gooding and Eugene Szabo for their technical assistance.

References

11. Evans A: Cerebral ischemia as a factor in the vasomotor response to increased intracranial pressure. Tex Med 63:84–90, 1967
31. Naunyn VB, Schreiber J: Aus der medizinischen Klinik in Königsberg I Pr Über...
Gehirndrucke. Arch Exp Path Pharmakol 14: 1–112, 1881
34. Spencer W, Horsley V: On the changes produced in the circulation and respiration by increase of the intracranial pressure or tension. Philos Trans 182B:201–254, 1892

This paper was presented at the Annual Meeting of the American Association of Neurological Surgeons at St. Louis, Missouri, April 20–25, 1974, and in part at the Second International Symposium on Intracranial Pressure at Lund, Sweden, June 17–19, 1974.

This work was supported in part by the Michigan Heart Association and by the Begole-Brownell Neurosurgical Fund.

Address reprint requests to: John E. McGillicuddy, M.D., Section of Neurosurgery, University of Michigan Medical Center, Ann Arbor, Michigan 48109.