

## Review Article

# Cerebral Circulatory Response to Acute Brain Disease:

## Implications for Anesthetic Practice

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Acute brain injury produces not only abolition of neuronal function but also tissue acidosis, edema, and a state of vasomotor paralysis. This altered vasomotion first affects autoregulation to blood pressure changes and later all cerebral vasomotor control, resulting in paradoxical flow changes with alteration of  $P_{CO_2}$ . In the initial state, these changes are reversible, and often there is absolute hyperemia. More profound, irreversible brain damage is characterized by very low perfusion. Nevertheless, provided no mechanical obstruction to blood flow exists, as from edema, blood flow in both situations is in excess of metabolic need. This stereotyped derangement is seen with brain tumors, acute cerebrovascular accidents, hypoxia, and severe trauma to the head, and following neurosurgical intervention. The clinical management of all these conditions must, therefore, follow a similar pattern, which consists of the maintenance of normal levels of perfusion pressure, the avoidance of cerebrovasodilatation from hypercapnia and general anesthetics, and the induction of respiratory alkalosis to offset cerebral acidosis.

ALTHOUGH there have been numerous investigations of the cerebral circulation in the 25 years since Kety and Schmidt developed the first satisfactory method for measurement of cerebral blood flow (CBF) in man, knowledge of the response of this vascular bed to acute pathologic processes has become avail-

able only in the past few years.<sup>1</sup> Previous lack of knowledge stemmed largely from the limitations of the Kety-Schmidt technique and its modifications. This technique, with its requirements of a relatively long period (10–15 min) of stable conditions, a special respiratory circuit, and elaborate procedures for the determination of tracer concentrations in both arterial and cerebral venous blood, has proved formidable in studying many acute conditions. In addition, the method yields only average flow values over the several areas of the brain and is consequently insensitive to focal changes in cerebral circulation. Thus, the large regional deviations in flow typical of many acute brain disorders may produce no apparent alteration of CBF as determined by the Kety-Schmidt method.<sup>2</sup>

Studies of cerebral circulatory physiology have received considerable impetus from the development of new instrumentation and techniques. The perfection of a procedure which is capable of measuring regional cerebral blood flow (rCBF) simultaneously in as many as 35 areas has been particularly important. This method, based on the same mathematical principle as the Kety-Schmidt technique, has been described in detail elsewhere.<sup>3,4</sup> In brief, it involves the rapid injection of  $^{133}\text{Xe}$  or  $^{85}\text{Kr}$  in 5 ml of saline solution into the internal carotid artery through an indwelling plastic catheter. Regional blood flow is calculated from the clearance of the isotope from the brain, as recorded over a period of two to ten minutes with multiple collimated scintillation detectors over the ipsilateral hemisphere. Typical rCBF results obtained with the  $^{133}\text{Xe}$ -injection method in a patient with normal cerebral circulation are shown in figure 1.

These technological developments have shifted attention from the normal to abnormal

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cerebral circulation, and much knowledge which bears directly on the anesthetic management of patients with acute intracranial disease has been obtained. Furthermore, there is now considerable knowledge about the effects of anesthetics and techniques on the cerebral circulation. The purpose of this communication is to review these recently-developed pathophysiologic concepts and point out their relevance to anesthetic practice. Other aspects of neuroanesthesia have been reviewed extensively in the past year<sup>5</sup> and will not be repeated here.

### Normal Cerebrovascular Control

The physiology of the normal cerebrovascular bed has been the subject of several comprehensive reviews; therefore, only the salient facts bearing on this discussion will be summarized.<sup>6,7,8</sup> It has long been known that during normocapnia the circulation of the normal brain is controlled to maintain cerebral venous  $P_{O_2}$  ( $P_{VO_2}$ ) constant at about 45 torr, despite widely varying conditions of cerebral function, hence metabolism. The factor ordinarily linking perfusion and metabolism is thought to be  $CO_2$ , the end-product of cerebral metabolism. Small acute changes in  $P_{aCO_2}$  produce large alterations of CBF; a one-torr increase in  $P_{aCO_2}$  augments CBF about 1 ml/100 g/min over the  $P_{CO_2}$  range usually encountered in anesthetic practice (20–60 torr).<sup>9,10</sup> Carbon dioxide rapidly diffuses across the blood-brain barrier; its action on cerebral arterioles is now thought to be mediated via an effect on the pH of cerebral extracellular fluid, which acts as the main factor controlling CBF.<sup>11</sup> Nonvolatile acids and bases cross the blood-brain barrier at a slow rate, and CBF is altered only minimally by acute systemic metabolic acidosis or alkalosis, provided  $P_{CO_2}$  remains constant.<sup>7,12</sup> Large alterations in extracellular fluid pH and CBF occur if  $P_{aCO_2}$  is altered.

Cerebral perfusion and  $P_{VO_2}$  are virtually normal in chronic acid-base disturbances associated with altered  $P_{aCO_2}$  levels.<sup>13,14,15</sup> That cerebral extracellular pH is also within the physiologic range in such states supports the hypothesis that the  $[H^+]$  of this fluid is predominant in the control of cerebral perfusion. Although the exact location of the pH-

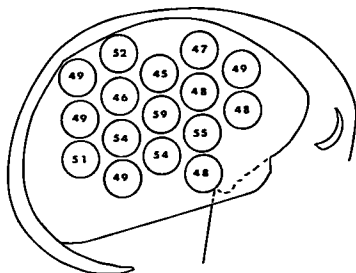


FIG. 1. rCBF values (in ml/100 g/min) obtained in a patient with normal cerebral circulation. Mean flow is 50 ml/100 g/min. The rCBF values are superimposed on a tracing made from a lateral radiograph of the patient's skull.

sensitive site is still problematical, present evidence suggests that it is on the arteriolar walls.<sup>16</sup>

A normal cerebrovascular bed also compensates for wide variations in perfusion pressure: cerebrovascular resistance is regulated to maintain a constant blood flow when perfusion pressure is varied from 60 to 150 torr in normal man.<sup>7</sup> This adjustment takes place in response to changes in arterial, venous, or intracranial pressure that influence A-V pressure gradients.<sup>17</sup> The mechanisms responsible for the constancy of cerebral perfusion in the presence of varying perfusion pressure are not yet understood but have been commonly attributed to myogenic reflexes (myogenic theory) or to a negative feedback from cerebral  $CO_2$  production through an effect on extracellular pH (metabolic theory).<sup>18</sup>

Patients with chronic elevations in blood pressure deserve special mention, as their autoregulatory mechanisms are set at higher levels: it is well known that they will not tolerate reduction of arterial pressure to the same low level as normals without exhibiting signs of cerebral ischemia. Nevertheless, the relative reduction tolerated is not different from the normal.<sup>7,19</sup>

### Vascular Response of Diseased Brain

Cerebral circulatory control is unaltered by chronic brain diseases such as senile dementia, which are associated with diffuse derangement of function and a reduced metabolic

rate.<sup>7</sup> In such chronic brain syndromes there are parallel reductions of perfusion and metabolism, thus maintaining normal levels of cerebral oxygenation. These patients possess normal cerebrovascular reactivity to  $\text{CO}_2$  (having the same percentage change in flow per torr alteration of  $\text{P}_{\text{CO}_2}$  and also exhibit the physiologic autoregulatory response to changes in perfusion pressure.<sup>7, 20</sup>

While cerebrovascular control is normal in chronic diffuse brain disorders, such is not the case in the presence of acute brain damage characterized by tissue acidosis and edema. The extreme sensitivity of neuronal tissue to low oxygen tension and trauma has long been known. However, that acute brain injury is typified by acidosis and cerebrovasoparalysis has become apparent only recently.<sup>21-25</sup> Anaerobic metabolism is increased in hypoxic brain tissue in an attempt to compensate for the diminished aerobic production of ATP, and tissue acidosis results from the locally-increased lactate concentration. This local increased  $[\text{H}^+]$  acts on the cerebral arterioles to produce marked dilatation, which may extend into the surrounding normal tissue. Since oxygen consumption of such acutely deranged neuronal tissue is very low, perfusion is generally in excess of metabolic demands; this has been termed "luxury perfusion."<sup>2</sup> Thus, while non-respiratory derangements of blood acid-base balance do not strongly influence CBF, there is good evidence that metabolic acidosis of cerebral tissue causes a profound disturbance of cerebrovascular function which renders the normal relationship between blood flow and metabolism inoperative.

Although not recognized as constituting a general phenomenon, the inappropriately high perfusion after cerebral injury was observed as early as 1954.<sup>26</sup> A temporary compromise of brain oxygenation by the elevation of intracranial pressure sufficient to reduce perfusion pressure or the inhalation of hypoxic gas mixtures produces local lactacidosis and a hyperemic state which persists for several hours.<sup>23, 27</sup> Likewise, focal hyperemia with arterIALIZED cerebral venous blood has been observed directly in areas surrounding brain tumors; regional CBF measurements in patients with brain tumors also indicates that the peri-neo-

plastic areas are overperfused.<sup>28, 29</sup> Presumably, the expanding tumor distorting normal tissue impairs oxygenation, and produces local lactacidosis which spreads to regions where blood supply is not compromised. Finally, regional cerebral hyperemia has been demonstrated with the rCBF technique in patients with acute cerebral thrombosis.<sup>3, 30, 31</sup> A typical hyperemic focus bordering an ischemic area in a patient with angiographic evidence of middle-cerebral-artery occlusion is shown in figure 2.

Cerebral tissue damage, in addition to producing vasodilatation and relative hyperemia, also markedly reduces or abolishes the normal vasomotor responses to changes in perfusion pressure and  $\text{P}_{\text{CO}_2}$ . The maintenance of a constant level of blood flow in the presence of changes in perfusion pressure appears to be the most sensitive indicator of cerebrovascular integrity; this response may be abolished when both CBF and the response to  $\text{CO}_2$  are still normal.<sup>32, 33, 34</sup> Loss of cerebral autoregulatory function renders the tissue particularly sensitive to arterial hypotension, since blood flow then varies passively with perfusion pressure.<sup>34, 35</sup>

The vasoparalytic brain is also adversely influenced by arterial hypertension.<sup>36</sup> Acute edema and herniation of the brain have been produced in cats by arterial hypertension after a craniectomy in which only the usual efforts were made to avoid trauma to the brain. In contrast, no swelling of the brain occurred with hypertension after a craniectomy had been performed with meticulous care to avoid touching the brain. Schutta and his co-workers hypothesized that the trauma of the "routine" craniectomy produced vasoparalysis; the formation of edema was ascribed to the transmission of increased hydrostatic pressure through dilated arterioles to cerebral capillaries and venules. More quantitative studies of the effects of arterial hypertension on the traumatized brain are needed.

As noted above, the normal hypercapnic increase in CBF is abolished by cerebral hypoxia.<sup>3, 30, 31</sup> Indeed, decreased perfusion during hypercapnia has been observed by a number of investigators after cerebral ischemia in both man and experimental animals, although mean arterial blood pressure often



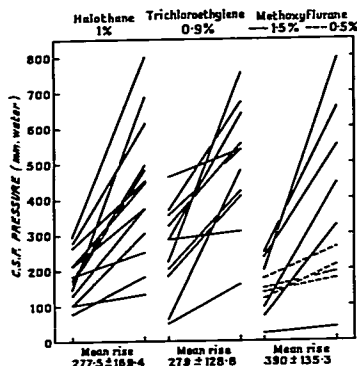


FIG. 3. Response of intracranial pressure to inhalation of halothane, trichloroethylene, or methoxyflurane for 10 minutes prior to craniotomy. Initial and final values are shown.  $P_{aCO_2}$  was maintained between 30 and 45 torr. From Jennett and co-workers.<sup>47</sup>

Inhalation anesthetics reduce cerebral metabolism, but the effects are not proportional to depth of anesthesia. Furthermore, cerebral oxygen consumption is rarely reduced more than 25 per cent.<sup>41</sup> Although anesthesia has been reported to prolong the survival of hypoxic mice, deep anesthesia would not appear to offer much protection of the brain against hypoxia induced by circulatory occlusion.<sup>46</sup> These effects contrast with the actions of barbiturates, which produce a marked dose-related reduction of metabolism.<sup>10</sup>

There have been no studies of the actions of general anesthetics on the abnormal cerebral circulation. However, the vasodilator effects of most inhalational anesthetics on normal cerebral arterioles could be predicted to contribute to an "intracerebral steal" of perfusion from abnormal to normal areas. This effect would be intensified by anesthetic-induced respiratory depression and hypercarbia. Furthermore, any beneficial effects of the hypocapnic constriction of normal vessels on the perfusion of ischemic areas would be opposed by anesthetics which dilate cerebral arterioles.

The effects of some general anesthetics on systemic arterial blood pressure can also be deleterious to the patient with focal brain dis-

ease: arterial hypotension would be expected to reduce perfusion of areas in which autoregulation has been impaired. Likewise, arterial hypertension during anesthesia may exacerbate cerebral edema formation, as noted above.

The effects of general anesthesia in the patient with increased intracranial pressure deserve special consideration. Although a moderate acute increase of intracranial pressure is normally minimized by the displacement of cerebrospinal fluid from the cranial vault, this compensatory mechanism may fail in the patient with chronically increased intracranial pressure, and cerebral vasodilatation may increase intracranial pressure markedly. Jennett and his associates measured the effects of halothane, methoxyflurane and trichloroethylene on the intracranial pressures of neurosurgical patients.<sup>47</sup> Although these agents produced slight intracranial hypertension in patients with normal CSF pathways, marked pressure elevations occurred in patients with chronic space-occupying lesions. Their data are summarized in figure 3. Since arterial pressure usually was lowered by these anesthetics, cerebral perfusion pressure was also much reduced. Reductions in perfusion pressure of the magnitude they observed would be expected to produce further vasoparalysis. The authors were careful to maintain normocapnia in their patients, and attributed the intracranial hypertension to the vasodilator action of the anesthetics. That deleterious effects could be only partially offset by hypocapnia led these investigators to advise against the use of volatile anesthetics in patients with chronic intracranial hypertension. Attention is also called to the danger of a rapid increase in intracranial pressure in patients inhaling nitrous oxide after pneumoencephalography.<sup>48</sup>

## Clinical Implications

### INTRAOPERATIVE CARE

The preceding discussion has emphasized the stereotyped pathophysiologic response of the cerebral circulation to acute brain disease, as well as the effects of general anesthesia on this vascular bed. This background provides a rational basis for the anesthetic man-

agement of patients with cerebral tissue acidosis and disordered cerebral vasomotion, a group including patients with histories of cerebral hypoxia or ischemia, head trauma, intracerebral bleeding or intracranial masses. All will have areas of tissue acidosis and edema. In addition, the vascular impairment from the underlying disorder will be intensified in patients having intracranial operations, since even the most gentle manipulation impairs cerebral vasomotion.<sup>49</sup>

Anesthetic management of these patients should be conducted in accordance with the principles which apply to the care of any patient. Ancillary measures such as the use of osmotic agents to reduce brain bulk may be indicated.<sup>5</sup> In addition, certain special considerations are necessary to minimize cerebral vasodilatation, since this has been repeatedly demonstrated to reduce the perfusion of vasoparalytic areas and to increase intracranial pressure. Thought should be given, therefore, to the use of a general anesthetic which does not have a cerebral vasodilator action. Nitrous oxide, possibly with narcotic or neuroleptanalgesic supplementation, seems especially appropriate for these patients, providing adequate arterial oxygenation can be maintained.<sup>47</sup> If other inhalation agents are required, their inhaled concentration should be minimal. Likewise, hypercarbia should be avoided, since CO<sub>2</sub> is the most powerful dilator of the normal cerebral arterioles and increases blood flow as well as local tissue [H<sup>+</sup>]. Artificial ventilation sufficient to reduce PaCO<sub>2</sub> to about 25 torr has long been used in neurosurgery; it should be employed wherever possible to counteract tissue acidosis and because of the evidence that the constriction of normal arterioles increases the perfusion of ischemic brain tissue. Although this degree of hypocarbia will reduce the flow through normal brain to about 60 per cent of normal, present evidence indicates that this reduction would not produce a significant compromise of cerebral oxygenation.<sup>10</sup>

Arterial blood pressure should also be maintained at normal levels in these patients, since the deranged cerebral circulation is unable to compensate for a lowering of pressure. Perfusion of some areas may be markedly reduced by only moderate hypotension. Deliberate

hypotension would appear hazardous with acute cerebral injury, and should be reserved for those instances in which it is vital for adequate surgical treatment, and the period of hypotension should be as brief as possible. Furthermore, if deliberate hypotension is employed, simultaneous use of hypothermia should be considered in order to reduce cerebral oxygen consumption, thus affording some protection against inadequate perfusion.<sup>5</sup> Bearing in mind the adverse effect of arterial hypertension on cerebral edema formation, anesthesia for patients with acute cerebral disease should be conducted in a manner which minimizes the likelihood of blood-pressure elevation. If nitrous oxide is the basic anesthetic agent, adequate narcotic or other non-inhalational supplementation should be used to prevent a hypertensive response from stimuli such as tracheal intubation or operation.

The anesthetic principles involved in the management of patients with definite impairment of cerebrovasomotor control also apply to the care of patients undergoing extracranial carotid surgery for relief of obstruction or stenosis. Although various investigators have advocated deep anesthesia, hypercarbia, or arterial hypertension to improve cerebral oxygenation during periods of vascular occlusion, it is now clear that these measures would tend to exacerbate any cerebrovascular damage occurring secondary to ischemia.<sup>50</sup> Furthermore, although jugular venous hemoglobin saturation is increased by these measures, this variable has not been a useful index of focal cerebral oxygenation in such patients.<sup>51</sup> It appears reasonable, therefore, to plan anesthetic management so as to avoid cerebral vasodilatation and marked alteration of arterial blood pressure. Furthermore, moderate hypothermia may reduce the sequelae from temporary ischemia. The use of local anesthesia has definite advantages, since this technique minimizes many untoward effects of general anesthesia on the brain, permitting the surgeon to communicate with the patient and thereby to assess the adequacy of cerebral oxygenation.

#### INTENSIVE CARE

It is also important to resort to specialized, intensive care in the post- or nonoperative

management of patients with acute brain disorders. This is necessary to minimize cerebral acidosis from hypoxemia, hypercarbia, and arterial hypotension. Management clearly must include those measures necessary to achieve systemic circulatory stability, adequate arterial oxygenation and moderate hypocarbia. Although many patients with acute cerebral injury have low CSF pH, which stimulates respiration and lowers  $P_{aCO_2}$ , controlled respiration may be necessary to reduce the work of breathing and to lower  $P_{aCO_2}$  further in an attempt to correct intracerebral acidosis.<sup>52, 53, 55</sup>

Hyperthermia must be prevented in order to avoid increased cerebral oxygen consumption and further compromise of brain oxygenation. Although theoretically indicated, moderate hypothermia is not yet widely used. Dexamethazone therapy is often used to relieve cerebral edema.<sup>54</sup> Light sedation with psychotropic drugs such as promazine may be indicated to prevent arousal, which is thought to elevate intracranial pressure by stimulating cerebral metabolism and increasing brain perfusion.<sup>55</sup>

Several authors have stressed the value of continuous recording of ventricular pressure through an indwelling plastic catheter in patients in whom hazardous intracranial hypertension might develop.<sup>56, 57</sup> This hazard seems particularly great following severe head injury; an intraventricular pressure greater than 60 torr carries a grave prognosis.<sup>56</sup> Vigorous hyperventilation is used in a number of centers to ameliorate such intracranial hypertension. If this is not successful, ventricular drainage is performed.

The favorable impression gained from the use of prolonged hyperventilation in the management of severe brain injury has led several authors to advocate its almost routine use in the management of acute brain disease secondary to cardiac arrest, asphyxiation, trauma to the head, and neurosurgery.<sup>53, 58</sup> Prolonged hypocapnia has even been suggested as a therapy for apoplexy, although its efficacy in this condition is more problematical since there are often significant pre-existing senile changes.

Experimental evidence in favor of long-term hypocapnic therapy for acute brain disease is provided by the data which Soloway

and his associates accumulated in a study of a small series of dogs.<sup>59</sup> After experimental occlusion of the middle cerebral and internal carotid arteries, these investigators found much less severe infarction in animals maintained at  $P_{aCO_2}$  25 torr for two hours than in those whose  $P_{aCO_2}$  were kept at 38 torr for an equal period. Recently their findings have been confirmed in cats by Battistini and his co-workers, who also noted that the level of perfusion pressure is important in minimizing infarction.<sup>60</sup>

Despite these experimental data and the clinical impression of favorable results from the long-term hyperventilation of a large number of patients with severe head injuries, the efficacy of this therapy remains unproven. Controlled clinical investigations have yet to be performed. Furthermore, the usefulness of rCBF and CSF acid-base studies in the evaluation of this expensive and involved therapeutic regimen has not yet been fully exploited. Thus, although long-term respiratory alkalosis is theoretically indicated to counteract crucial cerebral acidosis and has been shown to reduce intracranial pressure in severe brain injury, the overall value in reducing the high morbidity and mortality of acute cerebral disease has yet to be demonstrated. Nevertheless, prolonged hypocapnia shows promise of becoming a basic element of neuroanesthetic care.

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