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Brain protection - The clinical reality

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One of the most feared complications of anesthesia and surgery is the occurrence of cerebral ischemia and neuronal injury. Although the incidence of stroke during surgery is quite low, during certain procedures the risk of stroke can be high. For example, the incidence of neurologic complications during cardiac surgery has been reported to be approximately 2-6%[1]. The majority of these complications occur during the intraoperative period[2]. The risk of perioperative stroke in patients undergoing carotid endarterectomy ranges from a high of about 15% to the more recently reported risk of 2.1%[3]. Neurosurgical procedures, particularly aneurysm and AVM surgery, entail a significant risk of ischemia. Given the large number of patients who undergo these procedures, the "at risk" population is substantial. This has fostered a considerable amount of interest in not only evaluating measures designed to prevent cerebral ischemia but also in identifying anesthetic agents that might decrease the brain's vulnerability to ischemia.

In the present discussion, the pathophysiology of cerebral ischemia is presented briefly. This is then followed by summary of the available information regarding the cerebral protective efficacy of anesthetic agents. Finally, the influence of physiologic parameters on ischemic brain injury and the management of the injured brain is discussed.

PATHOPHYSIOLOGY

The brain is metabolically very active and its oxygen consumption is about 3.5 - 4.0 ml/100 gm/min. Electrical activity of neurons (transient depolarization and repolarization with their attendant ionic shifts) consumes about 50% of the total energy production of neurons. Thus, energy consumption can be reduced significantly by agents that can render the EEG isoelectric (e.g., barbiturates). The remaining 50% is used to maintain basal cellular homeostasis. Although this portion of the total energy consumption is not amenable to reduction by anesthetic agents, hypothermia can reduce it substantially.

The normal CBF in humans is about 50 ml/100 gm/min. The response of the brain to ischemia has been well characterized[4]. With a moderate reduction of CBF, slowing of the EEG is observed. When CBF reaches about 20 ml/100 gm/min, EEG isoelectricity occurs. At a flow of about 15 ml/100 gm/min, evoked responses can no longer be obtained. Although neurons do not immediately die at this flow rate, death will eventually occur if flow is not restored. Below a flow of 10 ml/100 gm/min, ATP levels decline rapidly (within 5 minutes) and the neuron is unable to maintain ionic homeostasis. At this point, the neuron undergoes depolarization (anoxic depolarization) and neuronal terminals release massive quantities of neurotransmitters[5]. These neurotransmitters (such as glutamate) activate post-synaptic receptors which results in the neuron being flooded with calcium[6]. By activating several biochemical cascades in a haphazard manner, calcium ultimately leads to neuronal death.

Cerebral ischemia is broadly classified into two categories: global ischemia and focal ischemia. Global ischemia is characterized by a complete cessation of CBF (e.g., cardiac arrest). In this situation, neuronal depolarization occurs within 5 minutes. Selectively vulnerable neurons within the hippocampus and cerebral cortex are the first to die. The window of opportunity for the restoration of flow is very small because death of neurons is rapid. Focal ischemia is characterized by a region of dense ischemia (the so called "core") that is surrounded by a larger variable zone that is less ischemic (the penumbra). Within the core, flow reduction is severe enough to result in relatively rapid neuronal death. Flow reduction in the penumbra is sufficient to render the

EEG isoelectric but not severe enough to kill neurons rapidly. If, however, the flow is not restored, death and infarction will also occur in the penumbra albeit at a much slower rate. Because of this slow rate of neuronal death, the window of opportunity for therapeutic intervention that is designed to salvage neurons is considerably longer in the setting of focal ischemia. Most episodes of ischemia in the operating room are focal in nature.

INFLUENCE OF ANESTHETICS ON THE ISCHEMIC BRAIN

A) Barbiturates

The approach to the problem of cerebral ischemia was initially focused on reducing the brain's requirement for energy. The rationale was that by reducing ATP requirements, the brain would be able to tolerate ischemia for a longer time. Such a supply - demand concept had already been proven to be relevant in the case of cardiac ischemia. Therefore, the agents investigated first were those that could render the EEG isoelectric (such agents would be capable of reducing ATP requirements by 50%).

Barbiturates can produce isoelectricity of the EEG and they have been studied extensively. In the setting of global ischemia, barbiturates in EEG burst suppression doses do not reduce ischemia injury[7]. This is not particularly surprising because the EEG is rendered isoelectric rapidly after the occurrence of global ischemia. In this situation, barbiturates would not be expected to provide much benefit. Barbiturates have been found to be efficacious in the treatment of focal ischemia. A number of investigators have shown that barbiturates can reduce the extent of cerebral injury produced by occlusion of the middle cerebral artery[8]. In humans, thiopental loading has been demonstrated to reduce post-cardiopulmonary bypass neurologic deficits. As a result, barbiturates have been considered to be the "gold standard" cerebral protectants among anesthetics. The protective efficacy ascribed to the barbiturates has recently been questioned on the basis that reduction in injury produced by barbiturate anesthesia might have been a function of anesthesia induced hypothermia rather than barbiturates per se[9]. Although more recent studies, in which brain temperature was rigidly controlled, have confirmed the protective efficacy of barbiturates[8], it should be noted that the magnitude of the protective efficacy is modest. In addition, doses that produce burst suppression of the EEG may not be necessary to achieve protection; Warner and colleagues have shown that a dose of barbiturate that is approximately a third of the dose required to achieve EEG suppression can yield a reduction in injury that is of similar magnitude to that achieved with much larger doses[10].

The decision to administer barbiturates for the purposes of cerebral protection should be made after due consideration of the hemodynamic effects of barbiturates, the potential need for prolonged post-operative mechanical ventilation of a patient in whom emergence from anesthesia is significantly delayed, and the relatively modest degree of protection that will be achieved.

B) Volatile anesthetics

Like barbiturates, the volatile agents isoflurane, sevoflurane and desflurane can EEG burst-suppression in high doses (≈ 2 MAC). Their effects on ischemic neuronal injury has therefore received considerable attention. Isoflurane has been shown to be neuroprotective in models of hemispheric[11], focal[12] and near complete ischemia[13]. Similarly, the available data suggest that both sevoflurane[14,15] and desflurane[16] can reduce ischemic cerebral injury. There does not appear to be a substantial difference among the volatile agents with regard to neuroprotective efficacy.

In most of the studies cited above, injury was evaluated a few days after the ischemic insult. Data from Du and colleagues indicate that post-ischemic neuronal injury is a dynamic process in which neurons continue to die for a long time after the initial ischemic insult[17]. These investigators suggested that therapeutic strategies that are neuroprotective after short recovery periods may not produce long lasting neuroprotection because of the continual loss of neurons in the post ischemic period. Volatile anesthetics do produce neuroprotection after short recovery periods. However, Kawaguchi et al recently demonstrated that isoflurane's neuroprotective efficacy was not sustained when the recovery period was extended to two weeks[18]. This suggests that volatile anesthetics delay but do not prevent neuronal death. It should be noted that, by delaying neuronal death, volatile agents might increase the duration of the therapeutic window for the administration of other agents that have neuroprotective efficacy.

More recent work by Werner, Engelhard and colleagues has shown that, under some circumstances, sustained neuroprotection with volatile agents can be achieved. In a model of hemispheric ischemia combined with hypotension, sevoflurane[19] produced neuroprotection that was apparent even four weeks after ischemia. In this study, it should be emphasized that the anesthetized animals did not manifest any injury at all; in fact, not a single neuron was found to be injured. By contrast, a modest amount of injury was observed in the control animals. These data suggest that volatile agents can produce long term neuroprotection *provided that the severity of injury is very mild*. Once a moderate amount of neuronal injury does occur, infarct expansion will preclude long term neuroprotection.

C) Propofol

Propofol shares a number of properties with barbiturates. In particular, propofol can also produce burst suppression of the EEG, thereby reducing CMRO2 by 50%. In a model of focal ischemia, propofol significantly reduced the extent of cerebral infarction[20]. In fact, the ability of propofol to reduce injury is similar to that achieved with pentobarbital[21]. More recent data from Gelb's group suggest that propofol neuroprotection, like that of isoflurane, is not sustained beyond a period of one week[22]. By contrast, sustained neuroprotection with propofol can be achieved provided that the severity of injury is very mild[23]; in this regard, the neuroprotective efficacy of propofol is similar to that of volatile agents.

D) Etomidate

On paper, etomidate appears to be the ideal neuroprotective agent. It can reduce CMRO2 by up to 50% by producing EEG burst suppression. Furthermore, unlike the barbiturates, etomidate is cleared rapidly and it does not cause myocardial depression or hypotension. Initial studies in the setting of global ischemia demonstrated that etomidate can reduce ischemic injury[24]. However, this reduction in injury was relatively small and it was confined to a single structure (the hippocampus). Subsequent studies in models of focal ischemia revealed, surprisingly, that etomidate actually increased the volume of brain infarction[25]. This injury enhancing effect of etomidate has been attributed to its ability to reduce nitric oxide levels in ischemic brain tissue (either by inhibiting nitric oxide synthase or by directly scavenging nitric oxide). Since nitric oxide is thought to be important in the maintenance of blood flow during ischemia, it is conceivable that etomidate might increase the severity of ischemia. The available data therefore do not support the use of etomidate as a neuroprotective agent.

Summary

Collectively, the available data indicate that barbiturates can protect the brain and that doses required to achieve this protection may well be less than those that produce EEG burst-suppression. This has considerable clinical relevance because neuroprotection might be achieved with doses that do not render the patient unconscious for a prolonged period of time. Similarly, protection may also be achieved with clinically relevant concentrations of volatile anesthetics (≈ 1 MAC) and with propofol. The relative equivalence of protection that might be achieved with agents that have a different effect on CMRO2 suggests that the ability of anesthetic agents to reduce ischemic neuronal injury may have less to do with CMRO2 reduction per se but with modulation of pathophysiologic cascades that are initiated by ischemia.

CEREBRAL ISCHEMIA - INFLUENCE OF PHYSIOLOGIC PARAMETERS

Physiologic parameters, such as MAP, $PaCO_2$, blood glucose and body temperature, have a significant influence on the outcome after cerebral ischemia. In this section, information regarding the effect of these parameters on the ischemic brain is summarized. Where possible, specific management recommendations have been suggested.

A) Body temperature

The effect of deep and moderate hypothermia on the brain's tolerance is well known. For example, while the normothermic brain undergoes injury after 5 min of ischemia, the brain made hypothermic to a temperature of 16° C can tolerate ischemia for up to 30 minutes (and longer in certain situations). Similarly, CPB is usually conducted at a temperature of 28° C in part to reduce the potential of ischemic brain injury. Therefore, induction of deep and moderate hypothermia for cardiac surgery has been well established.

What has only recently been appreciated is that temperature reduction of only a few degrees (≈ 33 - 34° C) can also reduce the brain's vulnerability to ischemic injury. In animal models of global cerebral ischemia, intraischemic mild hypothermia (temperature of 33° C) has been shown to dramatically reduce neuronal injury[26,27]. In addition, the application of mild hypothermia after the ischemic insult has also been shown to reduce injury provided the temperature is reduced within 30 minutes of the insult and duration of the hypothermia is extended to several hours. Similarly, intra and post-ischemic mild hypothermia can reduce cerebral injury after focal ischemia[28]. This protective effect of hypothermia is greater in situations in which flow is restored after ischemia and is less evident in situations where ischemia is permanent (e.g., permanent occlusion of a cerebral vessel that is not recanalized)[29,30].

In light of this dramatic protective effect of mild hypothermia, its use in the operating room setting has been advocated. Proponents of its use argue that hypothermia is readily achieved and it is not accompanied by significant myocardial depression or arrhythmias. In addition, the patient can be readily rewarmed in the operating room after the risk of ischemia has subsided. The efficacy of mild hypothermia in reducing cerebral injury in humans who have sustained subarachnoid hemorrhage and who present in the operating room for aneurysm clipping has been evaluated

in a randomized clinical trial (IHAST-2). Induction of mild hypothermia *did not* reduce the incidence of new neurologic abnormalities in the post-operative period[31]. These data do not support the use of intraoperative hypothermia for aneurysm clipping. It should be noted, however, that only patients with grades I-III SAH or unruptured aneurysms were included in the IHAST trial. Furthermore, the number of patients in whom a temporary clip was applied for a prolonged period was too small to draw meaningful conclusions about the efficacy of mild hypothermia in this setting. There is a body of opinion, therefore, that in patients with grade IV and V SAH and in whom prolonged temporary clip application is anticipated, induction of mild hypothermia may be of some, largely unproven, benefit.

The application of mild hypothermia after the head injury reduced ICP[32] and improved neurologic outcome[33,34] in pilot trials. Of note is the finding that complications attributable to hypothermia were not observed. A subsequent multi-center trial of hypothermia in head injured patients, however, failed to confirm the findings of the pilot studies[35]. The induction of mild hypothermia did not improve long term neurologic outcome. Note should be made, however, of the post-hoc finding that the outcome in patients younger than 45 years of age who were hypothermic on presentation was worse if these patients were re-warmed; these data suggest that such patients should not be warmed.

The data with regard to the application of mild hypothermia in survivors of cardiac arrest is more positive. Two recent trials have demonstrated that induction of hypothermia (32-34 °C) after successful resuscitation from cardiac arrest resulted in a significantly better neurologic outcome 6 months after the arrest[36,37]. These studies demonstrate the clinical efficacy of hypothermia for purposes of reducing ischemic cerebral injury and provide strong support for use of intraoperative hypothermia for those patients who are considered to be a high risk.

By contrast, increases in brain temperature during and after ischemia aggravate injury[38]. An increase of as little as 1° C can dramatically increase injury. Ischemia that normally results in scattered neuronal necrosis produces cerebral infarction when body temperature is elevated. It therefore seems prudent to avoid hyperthermia in patients who have suffered an ischemic insult or those who are risk of cerebral ischemia. In the operating room, hyperthermia is seldom a problem (witness our efforts to prevent hypothermia). One situation in which body temperature is often allowed to increase is during rewarming after hypothermic CPB. In that situation, hyperthermia (core body temperature in excess of 38° C) is not uncommon. The suggestion that increases in temperature in excess of 37-38° C be avoided has some merit given the recent information regarding the deleterious effect of hyperthermia.

B) Cerebral perfusion pressure

Cerebral blood flow is normally autoregulated over a CPP range of 60 to 150 mmHg. In hypertensive patients, the lower limit of autoregulation is shifted to the right. In most normotensive otherwise healthy patients, maintenance of CBF can be assured with a CPP in excess of 60 mmHg. The question is whether this CPP is adequate to maintain perfusion in a brain that has undergone ischemic injury. Within and immediately surrounding brain tissue that is injured, autoregulation is either attenuated or abolished. Cerebral perfusion in brain regions is pressure passive and is dependent upon the CPP. The ideal CPP in such patients has not been adequately studied; firm guidelines have not been established and blood pressure management must be individualized. In head injured patients however, a higher than normal CPP is required to maintain normal CBF. Chan and colleagues have shown that CPP of about 70 mmHg is adequate is head injured patients[39]. A CPP of 70 mmHg is therefore a reasonable goal in patients who are at risk of cerebral ischemia. Patients who have sustained an ischemic cerebral injury may benefit from an augmentation of cerebral blood flow by induced hypertension[40]. Induced hypertension, with an increase of mean arterial pressure 20% above baseline pressure, can lead to a clinical improvement in a substantial proportion of patients with acute stroke in whom thrombolysis is not feasible[41]. Induced hypertension can be tolerated in such patients for several hours[42]. Resulted in a clinical improvement In such patients, the potential risk for hemorrhagic conversion of the stroke exists. Hence, blood pressure should be increased slowly; an increase of about 10-15% above the patient's baseline pressure is a reasonable goal.

By contrast, hypotension has been shown to be quite deleterious to the injured (ischemic or traumatic) brain. Hypotension can increase cerebral infarct volumes significantly and should be avoided in patients who have suffered a stroke. Similarly, hypotension has been demonstrated to be one of the most important contributors to a poor outcome in patients who have sustained head injury. Maintenance of an adequate MAP and CPP is therefore critical. Elevation of MAP by alpha agonists such as phenylephrine is appropriate (with the assumption that the patient's intravascular volume is normal). There is a concern that these vasoconstrictors might produce cerebral vasoconstriction, thereby obviating the beneficial effect of an increased MAP. However, alpha agonists do not reduce CBF[43].

C) Blood glucose

In the normal brain that is adequately perfused, glucose is metabolized aerobically. The end products of aerobic glu-

cose metabolism are water, CO_2 and ATP. When the brain is rendered ischemic, oxygen is no longer available and aerobic metabolism of glucose is inhibited. Glucose is then metabolized anaerobically via the glycolysis pathway. The end products of this pathway are lactic acid and ATP. The lactic acid produced contributes to the acidosis that occurs in many ischemic tissues.

Because the brain does not have glucose stores, the extent of lactic acidosis is limited. However, during hyperglycemia, the supply of glucose to the brain is increased. Indeed, with hyperglycemia, neuronal stores of glucose may be increased. In this situation, the amount of lactic acid produced is considerable and the cerebral pH decreases. This acidosis contributes significantly to neuronal necrosis[44]. In models of global ischemia, hyperglycemia enhances cerebral injury[45]. Acute hyperglycemia or diabetic hyperglycemia is associated with increased cerebral infarction in studies of focal ischemia; treatment of hyperglycemia with the administration of insulin mitigated this increased injury[46]. Hyperglycemia enhances cerebral injury and worsens outcome in patients with stroke[47]. In long term outcome studies, hyperglycemia (diabetic and non-diabetic) has been shown to be an independent predictor of poor outcome[48]. In the NIH sponsored rt-PA stroke trial, hyperglycemia was associated with significantly lower odds for desirable clinical outcomes and a highcer incidence of intracranial hemorrhage[49]. It should be noted, however, the benefit of control of the blood glucose values in patients with ischemic cerebral injury has not yet been demonstrated in a randomized, prospective clinical trial. Nonetheless, the preponderance of evidence indicates that treatment of hyperglycemia in such patients should be considered and implemented.

By contrast, hypoglycemia is also associated with cerebral injury. With a gradual reduction in blood glucose values of about 40 mg/dl, a shift in EEG frequences from alpha and beta toward delta and theta occurs[50]. Below a blood glucose level of 20 mg/dl, suppression of the EEG (flat) is observed. Persistence of this level of hypoglycemia results in seizure activity and neuronal injury, particularly to the hippocampus.

The adverse impact of hypoglycemia on the brain has tempered an aggressive approach to the control of hyperglycemia in patients at risk of cerebral ischemia. In a large study of ICU patients in whom blood glucose concentrations were "tightly" controlled between 80 and 110 mg/dl, the incidence of hypoglycemia was 5%; this did not lead to increased morbidity[51]. A more recent investigation in which the target glucose levels were between 100 and 140 mg/dl, the incidence of hypoglycemia (less than 60 mg/dl) was 0.2%[52]. These data are consistent with the premise that hyperglycemia can be safely treated with an insulin-glucose infusion. Should blood glucose control be implemented, it is essential that blood glucose levels be monitored frequently and that the dose of insulin adjusted to prevent hypoglycemia. If frequent glucose level monitoring is not feasible, then aggressive control of hyperglycemia cannot be advocated.

Based on this discussion, it is this author's current practice to control blood glucose levels with an insulin-glucose-potassium infusion. The targets for glucose levels are relatively liberal: between 100 and 180 mg/dl. These "liberal" levels are justified on the basis of the lack of proof of the efficacy of tight control of glucose levels in patients with CNS injury and on the very real risk of hypoglycemic injury. This threshold, although arbitrary, is similar to what has been proposed by Wass and Lanier[53].

D) $PaCO_2$

Maipulation of arterial carbon dioxide tension is a potent means by which to effect cerebral blood flow and cerebral blood volume. Hypocapnia can reduce CBF, CBV and ICP. Hence, hyperventilation is often employed in patients with expanding mass lesions and intracranial hypertension and in the operating room to produce brain relaxation. The advantages of short term, temporary use of hyperventilation are readily apparent.

A significant concern about hypocapnia in patients with ischemic or traumatic CNS injury is whether blood flow reduction can enhance injury. Prophylactic hyperventilation has not been shwon to be of any benefit in patients with stroke. In fact, laboratory data have shown that hypocapnia can significantly decrease CBF in the ischemic brain; the net result is an increase in the amount of brain tissue in which the flow reduction is severe (and within what is considered to be ischemia)[54]. In the setting of head injury, the application of prophylactic hyperventilation is associated with a worse outcome 3 and 6 months after injury. In such patients, the regions of the brain that are ischemic increase dramatically with hypocapnia. Based on these data, the Brain Trauma Foundation has recommended that prophylactic hyperventilation be avoided during the early stages after head injury[55].

Hyperventilation is not entirely innocuous and it should be treated like other therapeutic interventions. It should be applied with an understanding of its complications. In the setting of head injury and cerebral ischemia, it has the potential to enhance injury. If applied, hyperventilation should be withdrawn when the intended goal has been achieved or is no longer necessary.

E) Seizure prophylaxis

Seizures commonly occur in patients with intracranial pathology. Seizure activity is associated with increased neu-

ronal activity, increased cerebral blood flow and cerebral blood volumes (consequently increased ICP) and cerebral acidosis. Untreated seizures can actually produce neuronal necrosis even with normal cerebral perfusion. Prevention of and rapid treatment of seizures is therefore an important goal. Seizures can be rapidly treated with benzodiazepines, barbiturates, etomidate and propofol. For more long lasting antiepileptic activity, phenytoin and pentobarbital are often used.

Summary

Based on the above discussion, our approach to "brain protection" is outlined below:

- The anesthetized brain is less vulnerable to ischemic injury than the awake brain. Although human data regarding the relative merits of individual anesthetics are lacking, the available information is consistent with the premise that volatile anesthetics do provide some, albeit transient, protection.
- Barbiturates, although long considered to be the gold standard, are not used routinely. In situations in which the risk of ischemic injury is high (i.e., aneurysm and AVM surgery), barbiturates are administered. This practice is largely empirical. Barbiturates are not administered during carotid endarterectomy. If, upon carotid cross-clamping, EEG changes suggestive of severe ischemia are present, then a shunt is inserted.
- Patients undergoing aneurysm and AVM surgery are routinely made hypothermic to a core body temperature of 33-34° C. This practice will be re-evaluated given the negative results of the recently completed IHAST trial. CEA patients are not made hypothermic because the risk of myocardial ischemia in these patients upon rewarming is significant. Hyperthermia should be avoided.
- Cerebral perfusion pressure is maintained in the "normal range" for the individual patient. In CEA patients, the MAP (in the absence of a shunt) may be increased by upto 10%.
- In diabetic patients, insulin is administered if glucose values exceed 250 mg/dl. Close monitoring of blood glucose is strongly advised to ensure that *hypoglycemia* does not develop.

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