THE "MILIEU INTERIEUR" – A MODEL OF BRAIN PHYSIOLOGY AND PATHOPHYSIOLOGY

JOHN G. WADE

ABSTRACT

The "milieu interieur" or "internal environment" of the brain is determined by the glial cells, the cerebrospinal fluid, the blood-brain barrier, the cerebral blood flow, the central regulation of respiration, and the intracranial pressure. Anaesthetic agents and anoxia-ischaemic insult can disrupt this important but vulnerable neuronal environment. Head injury is used as an example of a common insult to the neuronal environment and the principles of management are discussed, using a model of brain physiology and pathophysiology which can be modified to include other clinical situations.

THE ANAESTHETIC MANAGEMENT of the brain requires a sound knowledge of cerebral physiology, pharmacology, and pathophysiology. The continuing evolution of our knowledge in these areas is often confusing to the practising anaesthetist who must deal with a variety of complex clinical problems. The aims of this review are: (1) to present a working model of the brain; (2) to integrate our present knowledge of physiology, pharmacology, and pathophysiology into a model flexible enough to allow for new knowledge; and (3) to apply such a model to the anaesthetic management of the brain, using head injury as the initial model but with the capability of expanding to anaesthesia for carotid endarterectomy, intracranial tumors and aneurysms, to perinatal cerebral problems and to acute care problems such as cardiac arrest and near drowning.

Head injury currently represents approximately one-third of all admissions to emergency units. It is the second leading cause of death in the United States and primarily affects the 20–40 age group. About 60 per cent of head injury deaths occur before the patient reaches hospital. It is said that 38 per cent who die talk at some time following the injury. As many as 11.5 per cent may be fully co-operative and apparently completely lucid before lapsing into a fatal coma minutes or, more usual, several hours after the accident. Many of these patients die from post-injury avoidable factors. The three major causes of death in head injury are cerebral hypoxia, cerebral oedema and intracranial haematoma.[1]

John G. Wade, M.D., F.R.C.P.(C), Department of Anaesthesia, Faculty of Medicine, University of Manitoba, Health Sciences Centre – General, 700 William Avenue, Winnipeg, Manitoba, R3E 0Z3.

PHYSIOLOGY

The neurons are among the most important but vulnerable cells in the body. To function normally their environment must be normal. The physiology of the brain may be thought of as the study of the process controlling the neuronal environment – the "milieu interieur" or "internal environment" of the brain. This environment must have adequate oxygen and substrate, a normal acid-base balance, a normal ionic concentration and a normal pressure. Determinants of this "internal environment" are:

(1) *The glial cells*

Glial cells may be viewed as the scavenger cells of the brain. Their ionic pumping mechanisms have the ability to clear the environment of substances liberated during neuronal activity.[2]

(2) *Cerebrospinal fluid*

Cerebrospinal fluid (CSF) is actively secreted by the choroid plexus (whose cells morphologically resemble those of the renal tubule), flows through the ventricular system, and is resorbed in the arachnoid villae.[2,3] The CSF freely crosses the ependyma and is in direct communication with the extracellular fluid of the brain. It percolates between brain cells, cleansing the interstitial space. The CSF has been called the lymphatic system of the brain or the "urine of the brain".

(3) *Blood-brain barrier*

The blood-brain barrier is anatomically located at the capillary endothelium of the cerebral vessels.[3] Cerebral capillaries are unique because they have extremely tight junctions between the endothelial cells. "Tight junctions" protect the

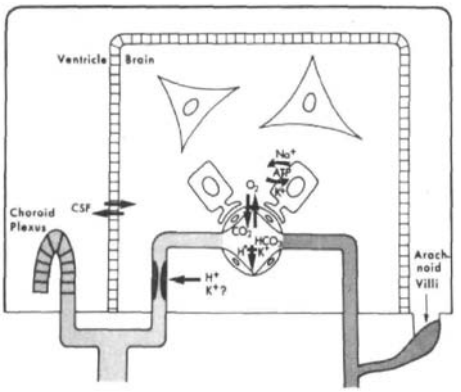

FIGURE 1 A model of the brain illustrating neurons, glial cells, CSF circulation, blood-brain barrier, and the cerebral circulation.

brain from unwanted substances in the blood such as large molecules, ions and drugs. However, substances necessary for the nutrition of the brain, such as oxygen and glucose, cross quite freely. In addition, the blood-brain barrier conserves substances necessary to cerebral function, such as neurotransmitters.

(4) *Cerebral blood flow*

Blood flow is necessary to provide the oxygen and substrate required for the energy production of the brain (ATP) and to carry away metabolic by-products such as carbon dioxide. Cerebral blood flow is closely linked with metabolic activity by a mechanism thought to be related to the increased carbon dioxide and hydrogen ion concentration produced by active neurons and glial cells.

The brain autoregulates; that is, between mean cerebral perfusion pressures of 6.65–20.0 kPa (50–150 torr) cerebral blood flow remains constant. Below a mean perfusion pressure of 6.65 kPa (50 torr) cerebral blood flow decreases in proportion to pressure, decreasing the delivery of oxygen and substrate to the brain. High cerebral perfusion pressure (CPP), greater than 20 kPa (150 torr), "breaks through" autoregulation, increases capillary hydrostatic pressure, and disrupts the blood-brain barrier, causing it to leak.[4]

The main factor controlling cerebral blood flow is thought to be the hydrogen ion concentration of extracellular fluid of the brain, which acts directly on the cerebrovascular smooth muscle. An increase in hydrogen ion concentration, or acidosis, dilates the vessels and increases cerebral blood flow while a decrease in hydrogen ion concentration, or alkalosis, constricts the vessels and decreases cerebral blood flow. Thus, cerebral blood flow is an important determinant of the acid-base balance of the brain. For example, an increase in neuronal activity increases carbon dioxide production, causing an intracerebral acidosis. The increased H^+ concentration directly dilates cerebrovascular smooth muscle, increasing cerebral perfusion, washing out carbon dioxide and returning the acid-base balance toward normal.

(5) *Regulation of respiration*

The major drive to ventilation arises from the central chemoreceptor located on the ventrolateral aspect of the medulla. The chemoreceptor responds to the hydrogen ion concentration of the neuronal environment. Acidosis stimulates while alkalosis depresses ventilation. Respiratory regulation provides a buffer against intracerebral acid-base changes. An intracerebral acidosis accompanying increased neuronal activity stimulates respiration, thus lowering Pa_{CO_2} and returning the intracerebral hydrogen ion concentration toward normal.[2]

(6) *Intracranial pressure*

Intracranial pressure is determined by the contents of the skull which includes the volume of brain tissue, the volume of blood, and the volume of the cerebrospinal fluid. In normal circumstances an increase of volume in one compartment can be compensated by a decrease in volume by another compartment, giving the brain a certain compliance.[2-9,16]

PHARMACOLOGY OF THE ANAESTHETIC AGENTS AND DRUGS

Both volatile and fixed anaesthetic agents decrease the metabolic activity of the brain. However, the volatile agents directly dilate and increase cerebral blood flow while the fixed agents are direct cerebral vasoconstrictors and reduce cerebral blood flow.[4]

Anaesthetic agents and drugs have secondary effects:

(1) All are respiratory depressants and will increase the arterial P_{CO_2} when patients are allowed to breathe spontaneously.

(2) Anaesthetic agents and drugs often produce cardiovascular depression and will lower the cerebral perfusion pressure.

(3) Any change in cerebral blood flow will change cerebral blood volume, influencing intracranial pressure and cerebral perfusion pressure.

"Protection of the Brain"

It has been known for many years that hypothermia decreases the metabolic activity of the brain and can protect against periods of cerebral ischaemia. Recently barbiturates have been shown to protect against regional ischaemia in animal experiments.[10,11] Cerebral metabolic activity ($CMRO_2$) is the sum of two broad areas of function of brain cells. The first is the neuronal or functional activity of the brain, such as occurs with thinking, seeing and hearing. The second is comprised of those processes necessary for cell viability, such as ion pumping and protein synthesis. Anaesthetic agents reduce the metabolic activity by reducing or abolishing the functional or neuronal activity of the brain but have no effect on the metabolic processes related to cell viability. On the other hand, hypothermia reduces the metabolic processes related to both neuronal activity and to cell viability. The barbiturates may act to protect the brain by other mechanisms such as decreasing intracranial pressure, reducing capillary hydrostatic pressure, constricting vessels and abolishing intracerebral steals, scavenging free radicals or stabilizing cell membranes.[11]

Pathophysiology of Head Injury

Injuries vary in severity from minimal or temporary disturbances of consciousness to a comatose state. In studying the pathophysiology of head injuries, it is convenient to build upon our model of the physiological mechanisms protecting the internal environment of the brain:

(1) *Glial cells*

Glial cells form the architecture of the brain which, in concussion, may be "scrambled", causing abnormal neurotransmission. If the insult is severe enough to impair delivery of oxygen and substrate to the glial cells, their normal ionic pumping and scavenging function is impaired, causing an accumulation of ions and other substances within the interstitial fluid of the brain, while sodium and water enter the cells causing "cytogenic cerebral oedema".[3]

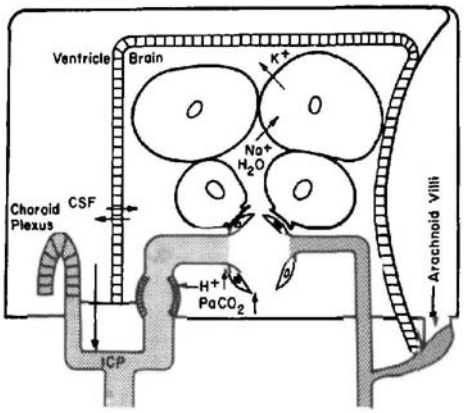

FIGURE 2 Pathophysiologic model of the brain following head injury and/or anoxic-ischaemic insult. A large haematoma is present, obstructing CSF circulation. The brain cells are swollen (cytogenic oedema) and the blood-brain barrier is disrupted (vasogenic oedema). The intracerebral acidosis dilates cerebral vessels, abolishing autoregulation and stimulating respiration. Intracranial pressure is elevated.

(2) *Cerebrospinal fluid*

Bleeding into the CSF and/or obstruction of the venous drainage of the brain may impair the homeostatic mechanisms of the CSF circulation and lead to an increased CSF volume and intracranial hypertension.[5]

(3) *Blood-brain barrier*

The blood-brain barrier may be disrupted by the direct tissue trauma or by increases in capillary hydrostatic pressure sufficient to break the tight endothelial junctions. This capillary leak allows protein, ions, and water to enter the internal environment, causing an increased volume of extra-cellular fluid. It is called "vasogenic cerebral oedema".[3]

(4) *Cerebral blood flow*

Either direct trauma to cerebral vessels or decreased cerebral perfusion pressure from intracranial hypertension and/or systemic hypotension (perhaps compounded by arterial hypoxia) will cause cerebral hypoxia, intracerebral acidosis, and loss of autoregulation of cerebral blood flow. The brain becomes extremely vulnerable to changes of systemic blood pressure; arterial hypotension provides inadequate cerebral perfusion, exaggerates intracerebral acidosis and further impairs cellular metabolism, resulting in "cytogenic oedema". Systemic hypertension is conducted by the dilated vessels to the capillary

where the blood brain barrier is disrupted. This "vasogenic oedema" is part of a vicious circle which leads to further impairment of tissue perfusion and to increased intracranial pressure.[4–6,9,16]

(5) *Regulation of respiration*

Head injury may interfere directly with the respiratory centres and their afferent and efferent connections to produce inadequate respiration or apnoea. A more frequent manifestation of inadequate cerebral perfusion and accompanying intracerebral acidosis is a stimulation of the central chemoreceptor and hyperventilation.[2]

(6) *Intracranial pressure*

Trauma can produce cerebral haemorrhage and intracranial haematoma. Cerebrospinal fluid volume can increase. Vasomotor paralysis can increase blood volume. Cytogenic and vasogenic oedema can increase interstitial volume, intracellular volume, and total brain volume. All these factors can increase intracranial pressure and cause either herniation of the brain or further reduction of cerebral perfusion pressure and cerebral hypoxia.

An increase in arterial blood pressure in response to intracranial hypertension was described by Cushing. This may be a compensatory mechanism but, by increasing capillary hydrostatic pressure, may cause further vasogenic oedema.[5,6]

Regional Cerebral Ischaemia

Regional cerebral ischaemia and the accompanying acidosis and vasomotor paralysis uncouples the normal link of perfusion to metabolism. Oxygen supply exceeds the metabolic demand of the tissues, causing the venous blood to be bright red, the "luxury perfusion syndrome". The regionally ischaemic brain is vulnerable to vasodilation or vasoconstriction of the normal brain, which can occur with anaesthesia or changes in Pa_{CO_2}. Vasodilation of the normal vessels will drain blood from the maximally dilated ischaemic brain, producing an "intracerebral steal". Vasoconstriction in the normal brain will direct blood to the ischaemic brain – the "Robin Hood syndrome".

Management of Head Injury

The principles of management includes:[6]

(1) Rapid stabilization and accurate diagnosis.

(2) Prompt surgical treatment with appropriate anaesthetic management.

(3) Prevention of hypoxia and hypercarbia, including protection of the airway and lung.

(4) Normalization of cerebral perfusion pressure by manipulation of systemic arterial pressure, venous pressure and intracranial pressure.

(5) Prompt recognition and management of associated medical complications.

Stabilization and Diagnosis

Head-injured patients require the stabilization and resuscitation common to all patients with multiple trauma. Because they have lost their protective reflexes, the airway must be protected, if necessary by a tracheal tube. Many would advocate a large dose of dexamethasone (50–100 mg intravenously) as soon as possible.[5,6]

Those patients with a history of loss of consciousness or minimal to moderate disturbances of consciousness, but without focal neurologic deficit, require close observation. More serious head injuries demand early diagnosis by immediate computerized tomography scan or cerebral angiography.[5,6]

Such patients present to the anaesthetist the dual problem of a "full stomach" and brain injury. Intubation of the trachea, controlled hyperventilation and blood pressure control are essential. A thiopentone nitrous oxide-oxygen relaxant technique is suggested. Mannitol may be used to complement hyperventilation to control intracranial pressure. Monitors, especially an intra-arterial line, should be instituted as soon as possible.

Anaesthetic Management For Surgical Intervention

The principles of anaesthetic management include protection of the airway, adequate oxygenation, hyperventilation, and control of cerebral perfusion pressure by management of intracranial pressure and systemic blood pressure.

Patient Assessment

The patient can be assessed by monitoring and/or recording the direct arterial blood pressure, the electrocardiogram, the body temperature, the urine output, the arterial blood gases, and the intracranial pressure.

Technique

The volatile anaesthetic agents will increase intracranial pressure by their cerebral vasodilating action. They also may reduce arterial blood pressure and lower cerebral perfusion pressure. They may be used with caution as a means to control systemic blood pressure (but only after hyperventilation).

The most common anaesthetic technique is probably one of nitrous oxide-oxygen and relaxant, with hyperventilation (Pa_{CO_2} at 4 kPa (30 torr)), supplemented with thiopentone or a volatile agent to control the pressor response to surgical or anaesthetic stimulation. Intracranial pressure can be managed by hyperventilation, osmotic diuretics (mannitol 1.0–1.5 $g \cdot kg^{-1}$) steroids, appropriate control of blood pressure, and the use of barbiturates.

Postoperative Management

The patient should be transferred to an acute care area. Protection of the airway and control of intracranial pressure and blood pressure should be continued until the patient is stable. Sound judgement is necessary to decide when to discontinue aggressive monitoring and therapy, to allow the patient to assume physiological responsibility and the neorosurgeon the opportunity to resume close neurological assessment. The place of long-term barbiturate therapy in head-injury patients is not clear, but some centres are now using such therapy to control intracranial pressure.[5,6]

Summary

A model of the brain damaged by head injury has been presented as an example of a method of understanding the principles of pathophysiological and anaesthetic management of the stressed brain. The model may be expanded to include the anaesthetic management of the brain in patients with brain tumors,[9,16] intracranial aneurysms,[9,16] cerebrovascular occlusive disease,[12] perinatal hypoxia,[13,14] and acute problems such as cardiac arrest[10] and near drowning.[15]

References

1. Frost, E.A.M. Head injuries – changing times. (Editorial) Survey of Anesthesiology. *22*: 109 (1978).
2. Davson, H. Physiology of the cerebral spinal fluid. Baltimore: J. A. Churchill (1967).
3. Katzman, R. & Pappius, H. Brain electrolytes and fluid metabolism. Baltimore: Wilkins & Wilkins (1973).
4. Lassen, N.A. & Christensen, M.S. Physiology of cerebral blood flow. Brit. J. Anaesth. *48*: 719 (1976).
5. Shapiro, H.M. Intracranial hypertension: therapeutic and anesthetic considerations. (Review Article) Anesthesiology *43*: 445 (1975).
6. March, M.L., Marshall, L.F. & Shapiro, H.M. Neurosurgical intensive care. Anesthesiology *48*: 149 (1977).
7. Geevarghese, K.P. Basic considerations: anesthesiological care of patients undergoing neurological surgery and neurological procedures. Int. Anesthesiol. Clin. *15*: 1 (1977).
8. McDowell, D. Neurological anesthesia and intensive care. Int. Anesthesiol. Clin. *16*: 16 (1978).
9. Shapiro, H. Physiology and pharmacologic principles of neuroanesthesia. ASA Refresher Course Lectures (1977).
10. Safar, P., Bleyart, A., Nemoto, E.M., Moossy, J. & Snyder, J.V. Resuscitation after global brain ischemia-anoxia. Crit. Care Med. *6*: 215 (1978).
11. Ping, F.C. & Jenkins, L.C. Protection of brain from hypoxia. Canad. Anaesth. Soc. J. *25*: 468 (1978).
12. Wade, J.G. Carotid endarterectomy. ASA Refresher Course Lectures (1978).
13. Johnson, G.N., Palahniuk, R.J., Tweed, W.A., Jones, M.V. & Wade, J.G. Regional cerebral blood flow changes during severe fetal asphyxia produced by slow partial umbilical cord compression. Am. Journal Obstet. Gynaecol. *135*: 48 (1979).
14. Volpe, J.J. Cerebral blood flow in the newborn infant: relation to hypoxic-ischemic brain injury and periventricular hemorrhage. (Editorial) Journal of Pediatrics *94*: 170 (1979).
15. Conn, A.W., Edmonds, J.F. & Barker, G.A. Near drowning in cold fresh water: current treatment regime. Canad. Anaesth. Soc. J. *25*: 259 (1978).
16. Popp, A.J., Bourke, R.S., Nelson, L.R. & Kimelberg, H.K. Seminars in neurological surgery: neural trauma. New York: Raven Press (1979).

Résumé

Le milieu intérieur du cerveau est déterminé par les cellules gliales, le liquide céphalo-rachidien, la barrière hémato-encéphalique, le débit sanguin cérébral, le contrôle central de la respiration et la pression intra-crânienne. Les agents anesthésiques et l'agression anoxique et ischémique peuvent perturber cet environnement neuronal qui malgré son importance est très vulnérable. Le traumatisme crânien est utilisé comme exemple d'un type fréquent d'agression subie par l'environnement neuronal et les principes de management en sont discutés en employant un modèle de physiologie cérébrale et de physiopathologie qui peut être modifié de façon à pouvoir faire face à d'autres situations cliniques.