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HEAD INJURY AND BRAIN ISCHAEMIA – IMPLICATIONS FOR THERAPY

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Brain ischaemia is a frequent and important sequel to brain injury. Areas of ischaemic brain damage are an almost invariable finding at postmortem in patients who have sustained severe head injury—that is, injury associated with coma (Graham, Adams and Doyle, 1978). Sequential computerized tomography of the head in disabled survivors of severe head injury frequently reveals sizeable cerebral infarcts (Miller et al., 1980). Traumatic brain laceration results also in ischaemia in the territory of divided vessels. Herniation of the medial temporal lobe of the brain through the tentorial hiatus and downward axial shift of the brain stem produce stretching and distortion of the brain arterial supply with ischaemia and infarction in the brain stem and occipital lobes (Miller and Adams, 1984). Brain ischaemia may therefore be the single most important mechanism in the production of secondary brain dysfunction and damage after severe head injury.

The prevention and management of brain ischaemia form the foundation of modern intensive monitoring and management of head injury. Advances in our understanding of the pathophysiology of brain ischaemia at any stage after head injury may aid the management of a major medical problem which continues to exact a terrible toll on society. The first step is to appreciate that brain ischaemia may arise at any stage after head injury (table I), but that the causative mechanisms at the various stages and their treatment, may be quite different.

EARLY PHASE BRAIN ISCHAEMIA (SECONDS TO MINUTES AFTER IMPACT)

Well-documented eye-witness accounts of head injury by experienced observers are relatively rare and drawn mostly from the sports arena. Most information on the immediate aftermath of brain injury comes from experimental animals and must be interpreted with appropriate caution. The physiological response to head injury consists of an increase in arterial pressure, accompanied by a lesser increase in intracranial pressure, and by temporary apnoea and flattening of the EEG (Sullivan et al., 1976). After approximately 1 min, systemic arterial pressure and intracranial pressure return towards normal values, spontaneous respiration resumes and EEG activity returns after a temporary phase of slow wave activity. With more severe levels of trauma, spontaneous respiration is not resumed for longer periods and death may supervene before spontaneous respiration has re-commenced. Levine and Becker (1979) have drawn attention to the length of time that post-traumatic apnoea may persist and yet be compatible with survival from injury, but by the time many severely head-injured patients reach hospital, they have already sustained significant hypoxic in addition to traumatic brain damage.

Wei and his colleagues (1980, 1981) suggested that the increase in systemic arterial pressure which follows the impact may trigger the arachidonic acid cascade and stimulate formation of prostacyclin and thromboxane A_2, with the by-production of singlet oxygen and other free radicals. These compounds produce vasodilatation, endothelial damage, intravascular sludging, haemostasis and impaired metabolism in the muscular wall of cerebral blood vessels. This results in loss of vascular reactivity to subsequent changes in transmural pressure and arterial blood-gas values.

There appears to be a relationship between the physiological response to injury and release of endogenous opioids in bringing about the restoration of arterial pressure that follows the immediate

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hypertensive response. Hayes and his associates (1983) have demonstrated that administration of the opioid antagonist naloxone can prevent the normalization of arterial pressure and produce persistent arterial hypertension after experimental concussional brain injury in cats.

TABLE I. *Principal causes of ischaemic-hypoxic brain damage in patients with severe head injury*

Systemic	Intracranial
Arterial hypoxaemia	Increased intracranial pressure
Arterial hypotension	Brain shift and distortion
Haematocrit less than 30%	Cerebral vasospasm

Other immediate concomitants of severe head injury include subarachnoid and petechial intraparenchymal haemorrhages. Subarachnoid haemorrhage may cause spasm of cerebral arteries and immediate intracranial hypertension (Steiner, Lofgren and Zwetnow, 1975; Miller and Corales, 1981). The presence of petechial haemorrhages within the brain substance presumably indicates that small vessels have been stretched to the point of tearing, with release of the contents, followed by sufficient spasm of the proximal vessel to prevent accumulation of a sizeable haemorrhage. Stresses on the vascular system of lesser severity must be distributed more widely in the brain. Where vascular stretching has occurred, it may be followed by vasospasm. Ischaemia in the territory of the vessels so affected is likely, compounded by any increase in intracranial pressure, because this is also the extravascular pressure in the cranial space, and the difference between arterial and intercranial pressure therefore represents the intracranial arterial transmural pressure.

INTERMEDIATE PHASE BRAIN ISCHAEMIA (MINUTES TO HOURS AFTER IMPACT)

The most important causative factors in the genesis of ischaemic hypoxic brain damage at this phase are arterial hypotension and hypoxaemia, increased intracranial pressure, brain shift and herniation, and cerebral vasospasm.

A reduction in mean arterial pressure in the first minutes or hours after head injury virtually always results from haemorrhagic hypotension as a consequence of blood loss from systemic injuries sustained at the same time as the head injury (Miller et al., 1978, 1981; Miller and Becker, 1982). Only in young children is blood loss from a scalp wound or intracranial haematoma likely to deplete total blood volume to the point where hypotension ensues. This form of arterial hypotension must be contrasted with toxic or drug-induced arterial hypotension that may occur at a later phase. The important difference between these mechanisms is that haemorrhagic hypotension is associated with a pronounced sympathetic discharge (see below). Early arterial hypotension is associated with a significant increase in mortality (table II). In head injury, impaired autoregulation is found in the vicinity of brain contusion on the brain surface. Lewelt, Jenkins and Miller (1980) observed impairment of autoregulatory function deep in the brain, after concussional head injury in experimental animals, in areas of the brain in which there was no visible pathological damage. Loss of autoregulation may therefore be a widespread phenomenon in the brain after blunt head injury.

Cerebral ischaemia induced by arterial hypotension represents incomplete cerebral ischaemia. Some portions of the brain are perfused slowly with blood, while in other parts there is no circulation. When the circulation has ceased entirely, the extent of reperfusion is crucial in determining the extent of

TABLE II. *Arterial hypotension (systolic pressure < 90 mm Hg) in patients with severe head injury: incidence on arrival in the neurosurgical unit and influence on outcome. †Medical College of Virginia; ‡University of Edinburgh*

Series	No. of cases	Overall mortality	No. with hypotension	Group mortality
U.S. 1976–80†	225	34%	34 (16%)	65%
U.K. 1981‡	93	45%	15 (16%)	87%

subsequent brain damage. After complete circulatory arrest when the vascular bed has been flushed by clear solutions, restitution of circulation to the brain usually results in a uniform and hyperaemic reperfusion. In the experimental studies of Lewelt, Jenkins and Miller (1980) reperfusion of the brain was attempted after arterial pressure had been decreased to less than 30 mm Hg. In control, uninjured, animals, restoration of the arterial pressure resulted in resumption of normal or greater than normal values of cerebral blood flow and subsequent alterations in arterial pressure produced a pressure-passive change in blood flow, signifying failure of autoregulation. However, in none of the animals that had been subjected to concussive head injury was adequate cerebral blood flow restored, even at normal values of arterial pressure. The combination of concussive trauma and arterial hypotension appeared to interfere with subsequent reperfusion of the brain. This situation may have parallels in human head injury where the intracranial pressure has increased so close to the level of arterial pressure that effective cerebral circulation has ceased. In the small number of such patients studied, arteriography or measurements of cerebral blood flow performed after intracranial pressure has been reduced by drainage of ventricular CSF and cerebral perfusion pressure has been restored, have failed to demonstrate a resumption of cerebral blood flow (Miller and Adams, 1972).

Arterial hypoxaemia

In the minutes and hours that follow a severe head injury, there are multiple causes of hypoxaemia, including prolongation of the apnoea that follows the injury, atelectasis, aspiration of vomited material and concomitant injuries to the lung and chest wall. In addition, brain damage may produce highly abnormal breathing patterns (North and Jennett, 1974). When arterial hypoxaemia becomes sufficiently severe to cause desaturation of haemoglobin, cerebral vasodilatation occurs (McDowall, 1966). This process may result in tripling of cerebral blood flow, with an increase in cerebral blood volume and a consequent increase in intracranial pressure. In injured brain, however, there may be attenuation of the vasodilator response to hypoxaemia, and to changes in arterial P_{CO_2}. This has been observed in patients (with head injury) in whom multiregional blood flow measurements have been made and in experimental animals subjected to controlled-intensity concussional injuries (Enevoldsen and Jensen, 1978; Lewelt, Jenkins and Miller, 1982). Loss of responsiveness to changes in blood-gases occurs at a greater degree of injury and insult than loss of autoregulation and complete absence of the response to change in P_{O_2} and P_{CO_2} is usually seen only as a pre-terminal event (Obrist et al., 1979; Overgaard and Tweed, 1979). However, impairment of the response may explain why the patient with severe head injury tends to suffer a more severe and lasting neurological deficit after an episode of hypoxaemia than does a normal patient. Early arterial hypoxaemia in head injured patients is clearly associated with an increase in morbidity and mortality (Price and Murray, 1972; Miller et al., 1981).

TABLE III. *Increased intracranial pressure in severe head injury: incidence and influence on outcome*

Intracranial pressure	No. of patients	Mortality
Not significantly increased (0–20 mm Hg)	95 (47%)	19%
Moderately increased (21–40 mm Hg)	67 (33%)	28%
Severely increased (41–80 mm Hg)	39 (20%)	79%
Total	201 (100%)	34%

Increased intracranial pressure

Intracranial hypertension is common after head injury and is associated with increased mortality. (table III). The most common causes for increased intracranial pressure soon after head injury are intracranial haematoma, congestive brain swelling and traumatic subarachnoid haemorrhage. Miller and his colleagues (1977) noted increased intracranial pressure in all but two of 62 patients with post-traumatic intracranial haematoma before surgical decompression and in more than half of all severely head injured patients even after decompression had been carried out (Miller et al., 1981). Since intracerebral venous pressure is maintained at a value just above the mean intracranial pressure, cerebral perfusion pressure (the difference between intracerebral arterial and venous pressures) is well approximated by the difference between systemic arterial pressure and intracranial pressure (Miller, Stanek and Langfitt, 1972; Johnston and Rowan, 1974). In the absence of a compensatory increase in arterial pressure, an increase in intracranial pressure

therefore implies a reduction in cerebral perfusion pressure, in addition to one in transmural pressure.

When perfusion pressure is reduced by progressively increasing ICP, cerebral blood flow can be maintained relatively constant by the same process of autoregulation until perfusion pressure decreases to 40 mm Hg. If perfusion pressure decreases below this value there is a dramatic reduction in cerebral blood flow. If autoregulation is impaired, cerebral blood flow varies passively with perfusion pressure, whether this is changed by primary alterations of arterial or of intracranial pressure.

The degree to which CBF changes with variation in perfusion pressure is a function of the residual cerebrovascular resistance. In a hyperaemic circulation with a low level of resistance, there is pronounced alteration in blood flow with relatively small changes in perfusion pressure (Miller, Stanek and Langfitt, 1973). However, when resting resistance is high, as in intravascular stasis or perivascular oedema, resting cerebral blood flow is already reduced and the passive changes in flow induced by changes in perfusion pressure are relatively small. Miller and Reilly and their colleagues studied the effects of changes in arterial pressure on cerebral blood flow in animals that had been subjected to cryogenic brain injury and increased intracranial pressure. In areas of brain oedema adjacent to the lesion, there was attentuation of the cerebral vasodilator response to carbon dioxide, but increased arterial pressure did not result in significant increase in regional CBF (Miller et al., 1976; Reilly, Farrar and Miller, 1977). In another series of experiments, Leech and Miller (1974) showed that, when intracranial pressure is already increased, progressive increase of arterial pressure causes an increase in brain elastance. This increase in the "stiffness" of the brain implies that any subsequent addition of volume to the craniospinal axis (blood, CSF or mass lesion volume) results in a great increase in ICP (Langfitt, 1969; Miller, 1975; Sullivan, Miller and Searles, 1980).

Because of this, the deliberate induction of increases in cerebral perfusion pressure in head injured subjects by increasing arterial pressure and attempting to control ICP may be both ineffective in restoring cerebral blood flow, because of the increasing level of vascular resistance that is encountered, and dangerous because of an increased liability to intracranial hypertension. The apparent fixity of a reduced cerebral blood flow despite increasing perfusion pressure, is one form of false autoregulation. The second type of false autoregulation encountered in the severely damaged brain occurs when an increase in arterial pressure is accompanied by an equal increase in ICP so that there is no net change in perfusion pressure and thus no stimulus to autoregulation (Fieschi et al., 1974). In both of these circumstances, however, any reduction in arterial pressure causes a further reduction in cerebral blood flow.

Brain shift, distortion and herniation

Since computerized tomography became the principal investigative method in severely head injured patients, the major revelation has been the high proportion of intracranial haematomas encountered in severely head injured (comatose) patients—40–50% in most series. Intracranial haematomas, particularly the intradural haematomas (subdural and intracerebral) are associated with a high incidence of increased ICP and high mortality (table IV) (Becker et al., 1977; Jennett et al., 1979; Miller et al., 1979).

During enlargement of mass lesions in the supratentorial compartment, medial temporal structures herniate through the tentorial hiatus. This process serves not only to interrupt the free communication of CSF pressure throughout the craniospinal axis, but the advancing temporal lobe can also compress the posterior cerebral artery to produce infarction of the ipsilateral occipital lobe. Subfalcine herniation of the cingulate gyrus may compress one or

TABLE IV. *Intracranial haematoma complicating severe head injury: incidence and influence on outcome*

	U.S. series			U.K. series		
Location of haematoma	No.	(%)	Mortality (%)	No.	(%)	Mortality (%)
Extradural	18	8	28	10	11	20
Intradural	75	35	64	38	41	53
No discrete haematoma	132	59	18	45	48	44
Total	225	100	34	93	100	45

both anterior cerebral arteries, producing ischaemia of the cortex of the media side of the cerebral hemispheres and the clinical picture of "cerebral paraplegia". In addition to herniation of brain across the midline, there is downward axial migration of the diencephalon, mid-brain, pons and medulla. The basilar artery, from which the central perforating blood vessels that supply these structures arise, does not migrate downwards and there is stretching and narrowing of the perforating vessels with ischaemia in the central portion of the brain stem, proceeding in severe cases to rupture of these vessels and brain stem haemorrhage, accompanied by the clinical picture of coma, with disturbances of arterial pressure, heart rate and respiration (Johnson and Yates, 1956; Miller and Adams, 1984).

Spasm of cerebral arteries is a well recognized feature of spontaneous subarachnoid haemorrhage. Vasospasm has been recorded also as a complication of post-traumatic subarachnoid haemorrhage, but there is less information on the prevalence and severity of this problem now that CT scanning has supplanted cerebral angiography as the most common definitive investigation of intracranial status in head injured patients. The papers by Suwanela and Suwanela (1972) and MacPherson and Graham (1978) suggest, however, that at least part of the aetiology of multifocal brain ischaemia in severely head injured patients may be ascribed to cerebral vasospasm. Extrapolation from experience in patients with spontaneous subarachnoid haemorrhage suggests that the combination of cerebral vasospasm and increased intracranial pressure is particularly important. Since vasospasm may occur in 5–35% of severely head-injured patients, and increased intracranial pressure occurs during the first 72 h in 50% of severely head injured patients (Miller et al., 1981), the likelihood of the simultaneous occurrence of both processes is high.

LATE PHASE BRAIN ISCHAEMIA (HOURS TO DAYS AFTER IMPACT)

Hypoxaemia

In the critical hours and days when the patient with severe head-injury is in the Intensive Care Unit, hypoxaemia remains a constant danger. In addition to the potential causes of hypoxia listed in the previous section, are the development of chest infection, neurogenic pulmonary oedema and adult respiratory distress syndrome (Frost, 1977, 1979). In the patient in whom PEEP is required during artificial ventilation to produce a satisfactory P_{O_2}, monitoring of intracranial pressure is advisable to ensure that the increase in end-expiratory pressure does not produce an undue increase in intracranial pressure. In the spontaneously breathing patient with multiple injuries causing pain, a particular problem arises if it is necessary to provide analgesia, because the risk of drug-induced depression of respiration and hypoxaemia is very great. Our recommended policy is to use no analgesia stronger than codeine phosphate i.m. in the spontaneously breathing patient with severe head injury, to use local anaesthesia where appropriate and, if more potent analgesia is required, to intubate the trachea and to ventilate the lungs mechanically.

Arterial hypotension

Assuming that multiple injuries have been detected and treated, the most frequent causes of reduction in arterial pressure are hypovolaemia, septicaemia and administration of certain drugs. Hypovolaemia may occur because of inadequate fluid replacement in patients who have received large doses of osmotic agents to reduce intracranial pressure, followed by extensive diuresis. Although barbiturates are cited frequently as a cause of drug-induced hypotension in head injured patients, this problem may attend the use of most sedative drugs used in those patients whose lungs are ventilated, particularly when hypovolaemia is present.

Anaemia

At a time when there may be difficulty in maintaining an adequate arterial P_{O_2}, it is necessary to ensure that the haematocrit is at an optimum. Progressive haemodilution in the hours and days following an injury may result in a considerable reduction in haemoglobin concentration, even in patients who have not apparently suffered a major single haemorrhage. A haematocrit less than 30% is associated with a poorer outcome (Miller et al., 1978, 1981).

Increased intracranial pressure

In addition to the causes mentioned above, intracranial hypertension in the later stage may be produced by increases in body temperature and by the development of brain oedema. Brain oedema is defined as an increase in brain volume produced by increase in tissue water content and should be distinguished from congestive brain swelling, in which the volume increase is intravascular (Fishman, 1975).

Brain oedema may occur in the vicinity of cerebral contusions as vasogenic oedema, following evacuation of a large extracerebral haematoma (post-compressive brain swelling), and after brain ischaemia produced by increased intracranial pressure or arterial hypotension (post-ischaemic oedema). Hyponatraemia ($Na^+ < 120$ mmol litre^{-1}) contributes to its formation, as does hyperthermia. As oedema develops, it produces a mass effect with brain shift and herniation, in addition to the increased intracranial pressure. Both processes may lead to brain ischaemia (Miller, 1979a).

Intracranial infection

Deterioration in neurological function that cannot be explained by a change in perfusion pressure or blood-gas tensions, or the development of a mass lesion, may be a result of meningitis. While the change in brain function may be a direct toxic effect of infection, inflammation around cortical blood vessels also induces a degree of ischaemia. Paulson and his colleagues (1975) recorded marked reductions in cerebral blood flow and metabolism in patients with meningitis and encephalitis, particularly in pneumococcal meningitis, the most common type after head injury.

Post-traumatic epilepsy

Epilepsy may occur at any time following a head injury. During an epileptic seizure there is usually an increase in local cerebral blood flow produced by a combination of increased metabolic demand and an increase in arterial pressure coupled with suspension of autoregulation. The increase in CBF is usually inadequate, however, to provide for the vastly increased metabolism of the firing cells. Ischaemic-hypoxic brain damage is therefore a recognized sequel of prolonged seizure activity (Meldrum and Horton, 1973). In the patient who is paralysed and receiving artificial ventilation, it may be difficult to recognize an epileptic seizure unless some record is made of brain electrical activity. The only clue may be sudden dilatation of the pupils. Unrecognized epileptic seizures in patients receiving artificial ventilation may be a greater source of ischaemic brain damage than is presently appreciated.

IMPLICATIONS FOR THERAPY

Principal physiological variables

After various vogues for pronounced hyperventilation, hypothermia and relative dehydration, the general principles of physiological maintenance of severely head injured patients are, in most centres, to ventilate artificially the lungs of many patients at P_{CO_2} values of approximately 4 kPa, to maintain normal hydration and normothermia, but to treat vigorously any increases in body temperature and at all costs to prevent critical reductions in arterial and cerebral perfusion pressure. In addition to respiratory indications for instituting artificial ventilation, we usually utilize this manoeuvre in patients who have been comatose (no eye opening, not obeying commands, not speaking—Glasgow Coma Score 8 or less) and have required surgical decompression of an intracranial haematoma, and in patients without an intracranial haematoma who are deeply comatose (Glasgow Coma Score 5 or less).

Neurological evaluation

One of the most worrying problems in managing the head injured patient in the Intensive Care Unit is the timely detection of episodes of neurological deterioration in patients who are paralysed and whose lungs are artificially ventilated. While changes in pupil size and reaction may provide some indication, these are late changes, indicative of brain stem dysfunction and by the time they are detected it may already be too late to reverse the neurological deterioration. Antagonism of neuromuscular blocking drugs may result in increase in intracranial pressure. The use of continuous EEG monitoring is hampered by the effects of sedative drugs on spontaneous electrical activity in the brain. Repeated measurements of evoked electrical response may be helpful, but the equipment required is expensive and the expertise demanded for correct interpretation of results is of a high order. Devices to produce a more easily interpretable derivative of spontaneous electrical activity in the brain, such as the compressed spectral array, or the cerebral function monitor, are discussed elsewhere.

Monitoring of arterial, intracranial and cerebral perfusion pressure

We have adopted a policy of monitoring intracranial pressure using a subdural bolt, transducer, or intraventricular catheter in all severely head injured patients in whom artificial ventilation of the lungs has been instituted. Cerebral perfusion pressure is calculated as the difference between arterial and intracranial pressure. The importance of considering both arterial and intracranial pressure before making therapeutic decisions cannot be over-

emphasized. When arterial pressure increases steeply in the head-injured patient, it is nearly always secondary to brain shift or an increase in intracranial pressure, or both. The correct way to treat this is to reduce intracranial pressure. To reduce arterial pressure alone results in rapid onset of severe brain ischaemia which is usually irreversible and leads to brain death.

Patients with severe head injuries may develop ECG multiple changes and cardiac arrhythmias suggestive of myocardial ischaemia. In fatal cases, subendocardial haemorrhage and focal myocytolysis are seen in the myocardium (Connor, 1968). The value of attempting to treat these cardiac changes, by β-adrenergic blockade for example, is not yet proven, but there are suggestions that this is beneficial.

worsening the patient's condition (table V). These measures include: more pronounced hyperventilation to a $PaCO_2$ of 2.5 kPa, continuous CSF drainage (from intraventricular catheters only) against a positive pressure of 3 kPa, and i.v. infusions of 20% mannitol solution.

Hyperventilation, by inducing hypocapnia, produces cerebral vasoconstriction, and reduces cerebral blood volume and intracranial pressure. The degree to which ICP decreases depends on the extent of vasoconstriction and the elastance of the brain ($\Delta P/\Delta V$). Fears are often expressed that the decrease in cerebral blood flow produced by hypocapnia may cause ischaemic brain hypoxia. While it is true that hyperventilation can produce EEG slowing and CSF lactacidosis, structural brain damage has not been demonstrated. The curve relat-

TABLE V. *Methods of controlling increased intracranial pressure*

Treatment	Limitations	Risks
Hyperventilation	Blood vessels must be responsive to changes in P_{CO_2}	Vasoconstriction may produce brain ischaemia (although structural damage has never been shown to occur)
CSF drainage	From ventricular catheter only	Leakage of CSF may interfere with ICP recording. Haemorrhage in track of cannula through brain
Mannitol	Serum osmolality must be less than 320 mosmol $litre^{-1}$	Fluid and electrolyte disturbance and renal failure
Barbiturates	Loss of neurological responsiveness	Arterial hypotension (especially in hypovolaemic patients); increased risk of infection
Gammahydroxybutyrate	Irritant solution, needs central venous line	Production of seizure-like EEG activity

Treatment of increased intracranial pressure

In the management of increased intracranial pressure, the objective is prevention of an increase in ICP sufficient either to cause a critical reduction in perfusion pressure and brain ischaemia or to produce worsening of brain shift or herniation, or both. The normal range of intracranial pressure is 0–15 mm Hg. When the pressure exceeds 22 mm Hg, measures should be initiated for the prevention of further increases in pressure. These measures must first include checking and correction of sources of increased intracranial pressure related to the position of the patient's head and neck, adequacy of the airway, body temperature and respiratory movements in opposition to the ventilator (Miller, 1978).

The next stage in management is the application of one or more of three measures which are known to be effective in most instances and carry a low risk of

ing CBF and arterial P_{CO_2} "bottoms out" as $PaCO_2$ decreases to less than 3 kPa.

Drainage of ventricular CSF may be a valuable means of controlling intracranial hypertension, but it is important to drain fluid only against a positive pressure in order to avoid collapse of the ventricular system, and loss of ICP recording. Because the normal practice is to insert the catheter to the contralateral ventricle when there is a unilateral intracranial haematoma or contusion, it is important to appreciate that, while CSF drainage may control ICP, it does not diminish midline brain shift and may even make it worse. This results because unilateral mass lesions causing increased ICP are frequently associated with enlargement of the contralateral ventricle. More often, however, in severe head injury of the diffuse axonal injury type, the ventricles are small, a ventricular catheter cannot be used and another means must be sought for reducing

increased ICP. This is accomplished usually by i.v. infusion of hypertonic mannitol solution.

The mechanism of action of i.v. hypertonic agents in reducing ICP has been disputed for many years and the debate continues today. Initially it was considered that, by increasing the osmotic gradient between blood and brain, water would be drawn from oedematous brain, mass effect reduced and ICP would decrease (Wise and Chater, 1962). Because the blood–brain barrier is deficient in the centre of (but not throughout) oedematous brain, at that site mannitol leaks into the tissue and the maximal tissue-dehydrating effect is restricted therefore to normal rather than oedematous brain (Pappius and Dayes, 1965). More recently, Takagi and his colleagues (1983) demonstrated that i.v. hypertonic mannitol reduces the volume of CSF in the ventricles and postulated that ICP is reduced by this mechanism rather than a change in tissue water content. This supports the earlier observation of Reed and Woodbury (1962), who found no relationship between brain water content and ICP before or after administration of hypertonic urea.

Most recently, Muizelaar and his colleagues (1983) have proposed that the ICP reduction caused by mannitol is caused by cerebral vasoconstriction. This occurs as a response to an initial increase in cerebral blood flow produced by reduction in blood viscosity and appears to be an autoregulatory phenomenon, present only when autoregulation of cerebral blood flow has been preserved to changes in arterial pressure.

While the arguments for and against these operative mechanisms continue, the message for the managing clinician is clear. The administration of mannitol should be accompanied by continuous measurement of ICP. Hypertonic mannitol solution should be given in a dose of 0.5 g/kg body weight initially and later doses adjusted according to the intracranial pressure response first obtained. If the serum osmolality exceeds 320 mosmol litre^{-1} before infusion, mannitol should be withheld, as further administration is likely to produce impairment of renal function without benefit to the increased ICP.

For many years, corticosteroids have been advocated by many in the management of severe head injury (Faupel et al., 1976; Gobiet et al., 1976; Tornheim and McLaurin, 1978). Recent evidence has shown that steroid therapy neither reduces increased intracranial pressure in this situation nor improves outcome. Steroids therefore have no role in the overall management of patients with severe head injury, except perhaps in those patients in whom there is perifocal oedema around brain contusion. Even in these cases, steroids have not been conclusively beneficial; evidence from clinical trials is limited to severe head injury in general (Cooper et al., 1979; Gudeman, Miller and Becker, 1979; Pitts and Kaktis, 1980; Saul, Ducker and Salcman, 1981; Braakman et al., 1983).

If the first-stage measures to control increased ICP prove ineffective, it is important to exclude alterations in blood-gas tensions as a cause of increased ICP, or the development of a recurrent or delayed-onset intracranial space-occupying lesion, by CT. If these are not responsible, the treating physician is left with little alternative but to proceed with second-stage therapies. These have mainly comprised short-acting anaesthetic agents (barbiturates, Althesin, etomidate, gamma-hydroxybutyrate) (Turner et al., 1973; Shapiro, Wyte and Loeser, 1974; Escuret et al., 1979; Moss et al., 1979; Strong, 1984). Despite the claims that have been made for their efficacy in the short term control of increased ICP, there has not yet been conclusive evidence that the administration of any of these agents results in long term benefits to patients in the form of an increased survival rate or decreased morbidity (Miller and Teasdale, 1985).

Marshall, Smith and Shapiro (1979) pioneered the use of pentobarbitone in patients with severe head injury, in whom first line methods of therapy for increased ICP had failed. They reported a gratifying level of control of intracranial hypertension and an apparent reduction in mortality in their series of 100 patients as compared with other published series. This encouraging report led many to use the induction of barbiturate coma as a routine therapeutic measure in the management of severely head-injured patients (Rockoff, Marshall and Shapiro, 1979; Rea and Rockwold, 1983). In 1979, Miller reviewed the evidence in favour of barbiturate therapy for increased ICP, concluded that the case was not proven and called for experienced centres to conduct randomized trials (Miller, 1979b).

In a randomized trial recently completed at the Medical College of Virginia, the administration of pentobarbitone to severely head-injured patients resulted in some temporary control of increased intracranial pressure but failed to confer any overall benefit in terms of reduction of the incidence of increased ICP, death from increased ICP, reduction in the requirement for i.v. mannitol infusions or in mortality. However, in both control and barbitu-

rate-treated patients mortality was somewhat lower than would have been expected. Barbiturates were associated with a significant increase in the incidence of episodes of arterial hypotension (systolic arterial pressure less than 80 mm Hg). These episodes occurred despite monitoring of pulmonary arterial pressure and the use of dopamine infusions to support the arterial pressure when necessary. It is possible that a beneficial effect of barbiturates on recovery from severe head injury may have been offset by the tendency of these drugs (particularly in the multiple-injured, hypovolaemic patient) to produce episodes of arterial hypotension of sufficient severity to produce disabling brain ischaemia.

This experience emphasizes the critical importance of brain ischaemia as a major determinant of morbidity and mortality following severe head injury. It may also be concluded that, while increased intracranial pressure is harmful in the head-injured patient, arterial hypotension may be an even worse insult, causing marked brain ischaemia during the reduction in pressure and impairment of reperfusion when arterial pressure has been restored. The successful conduct of any management regimen in these critically ill patients must take such factors into account. Proving the effectiveness of therapy in severe head injury remains an enormous challenge. The subgroups of patients selected for treatment must be defined rigorously so as to include the maximum number of patients in whom outcome can be influenced by therapy (Braakman et al., 1983; Miller and Teasdale, 1985.

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