Cerebral protection in severe brain injury: physiological determinants of outcome and their optimisation

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The primary role of intensive care in acute head injury lies in the prevention, detection and reversal of secondary neuronal injury. The maintenance of optimal systemic and cerebrovascular physiology can substantially contribute to these aims. There is, however, a role for novel neuroprotective interventions, many of which are currently under investigation.

Approximately 1.4 million patients suffer a head injury in the UK each year[1], and 270–313 individuals per 100,000 population are admitted to hospital with this diagnosis each year[2]. About 2500 of these suffer a severe head injury, defined as a post resuscitation Glasgow Coma Score[3] of ≤ 8. Head injury is responsible only for 1% of all adult deaths, but represents 15% of deaths in the 15–45 year age bracket[2], and is one of the most important causes of death in this group. The overall inpatient case fatality rate for all head injuries in the European and US literature varies between 2.6% and 6.5%[4], and is obviously influenced by referral and admission patterns. However, there is substantial variability in outcome rates even for severe head injury (which ought to represent a more homogeneous subgroup of patients) from US and UK centres, with mortality ranging from 15% to over 50%[5]. Conversely, good outcomes, defined as a Glasgow Outcome Scale[6] of 1 or 2, (Table 1) vary from under 50% to nearly 70%[5]. It is essential that we identify the source of this variability so as to explore ways in which overall outcome can be improved.

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Table 1 Glasgow Outcome Scale

1 = Good recovery
2 = Moderate disability
3 = Severe disability
4 = Vegetative state
5 = Dead

Many studies dichotomize the scale to Good Outcome (1 & 2) and Poor Outcome (3–5).

Maintenance of physiological homeostasis important in acute head injury

Little can be done about the extent of primary injury to the brain when patients present to intensive care units following head trauma, but the presence and severity of secondary neuronal injury, much of which is triggered by physiological insults to the injured brain, can be a major determinant of outcome[7,8]. Eloquent proof of the importance of such secondary neuronal injury is available from the 30–40% of patients who talk or obey commands before they die[9], implying that the primary injury was, on its own, insufficient to account for mortality.

The most important derangements in physiology that affect outcome are listed in Table 2, and can be graded for severity with respect to their expected effect on secondary neuronal injury[10,11]. While this table focuses on physiological derangements that contribute to secondary neuronal injury in an ICU setting, it is essential to emphasise the fact that rapid resuscitation and transport to definitive neurosurgical care are the most critical determinants of outcome (Fig. 1)[11–13]. It has also been shown that the severity of physiological insults can be related to outcome, both in the early (Fig. 2)[11] and late (Table 2)[10,11] period after head injury. Physiological insults are additive in their effect on outcome, both when multiple insults occur at the same time point (Fig. 2), or when the same insult occurs repeatedly (Fig. 3). It would seem self-evident that outcome is likely to be improved in a setting where such insults can be prevented, detected and reversed.

Targets for basic intensive care practice in this area have been widely debated and been the subject of systematic review over the last few years. These reviews have resulted in recommendations for treatment[14,15], and there is general (although not universal) consensus on several of the main principles involved in managing these patients[14,15]. These involve the institution of monitoring for the presence of secondary physiological

Table 2 Physiological insults following head injury and their relation to outcome

Insult	Significant relation to	
	Mortality	Grades within GOS
Duration of hypotension (SBP ≤ 90 mmHg)	Yes	Yes
Duration of hypoxia (SpO_2 ≤ 90%)	Yes	No
Duration of pyrexia (T_{core} ≥ 38°C)	Yes	No
Intracranial hypertension (ICP > 30 mmHg)	Yes	No
Cerebral perfusion pressure (CPP < 50 mmHg)	Yes	No

Significance was demonstrated using a logistic regression model except for CPP, where this was not possible due to the confounding effects of ICP and MAP. However, a CPP < 50 mmHg was shown to independently predict outcome using non-parametric statistics. Data are from Jones *et al*[10], who showed that 91% of all patients had one or more physiological insult(s) during the course of their ICU stay.

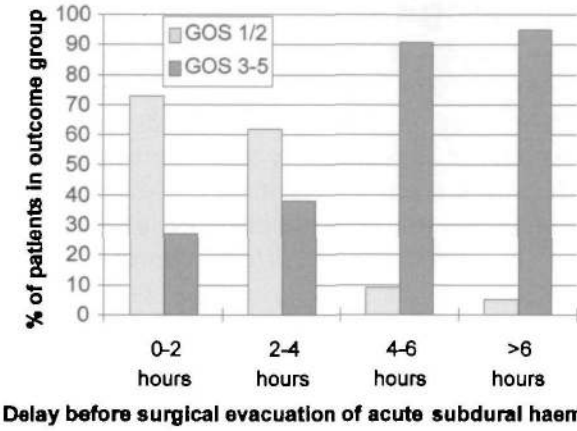

Fig. 1 Effect of delay in surgical evacuation on outcome from traumatic subdural haemorrhage. Redrawn from data in Seelig *et al*[13].

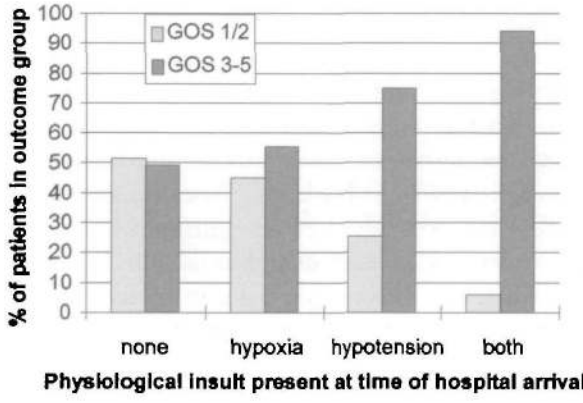

Fig. 2 Effect of physiological insults at time of presentation to neurosurgical centre on outcome from acute head injury. Of 699 patients enrolled in the Traumatic Coma Data Bank study, 35% presented with either hypoxia (PaO_2 8 kPa) and/or hypotension (systolic BP 90 mmHg). Redrawn from data in Chesnut *et al*[14].

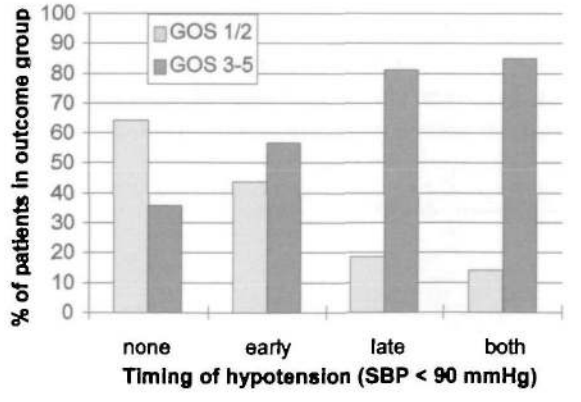

Fig. 3 Effect of early and/or late hypotension (SBP 90 mmHg) on outcome from severe head injury. Redrawn from data in Chesnut *et al*[11].

insults, and preventing or treating these. Novel neuroprotective interventions have been the focus of much recent literature and may hold considerable promise, but their general failure in clinical Phase III trials[16,17] has lead to considerable pessimism that introduction of such agents is likely to materially alter outcome in the short-term.

However, there appears to be much room for improvement in conventional clinical practice. There is good evidence of heterogeneity in the quality of basic intensive care practice on both sides of the Atlantic[18–20]. Data from a series of telephone and postal surveys suggest that basic recommendations for monitoring and general intensive care in severe head injury have not been consistently followed in many neurosurgical centres in the US and UK. As an example, intracranial pressure (ICP) was monitored in only half the centres surveyed[18–20]. While recent preliminary results suggest that this situation may now be improving[21], it is important to emphasize that the application of novel neuroprotective therapies is futile if stable cardiorespiratory and cerebrovascular physiology cannot be achieved.

Pathophysiology in acute head injury

A detailed discussion of the pathological features of acute traumatic brain injury is beyond the scope of this chapter and has been discussed elsewhere[22]. However, it is important to appreciate that the severity and type of impact will substantially influence the structural lesions that ensue (Fig. 4). The acceleration-deceleration forces that ensue from impact during falls and motor vehicle accidents can produce axonal dysfunction and injury, brain contusions, and axial and extra-axial haematomas. The generation of such macroscopic injury is associated with microscopic and ultramicroscopic changes, including ischaemic cytotoxic oedema, astrocyte swelling with microvascular effacement and dysfunction, blood brain barrier disruption with vasogenic oedema, and phasic inflammatory cell recruitment (Fig. 5)[16,22]. These microscopic changes are underpinned by early, multiphasic gene activation, and later recruitment of repair mechanisms (in many cases by the very processes that result in secondary neuronal injury; Fig. 5). Several secondary neuronal injury processes have been classically associated with brain trauma. Perhaps the most consistent pathological finding in fatal head

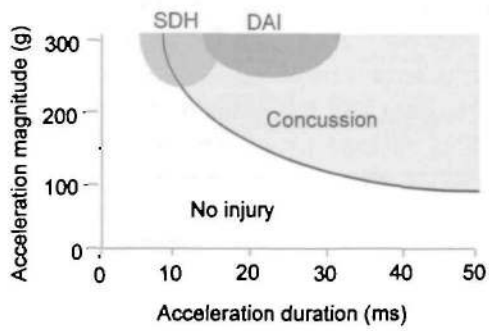

Fig. 4 Effect of the duration and magnitude of acceleration/deceleration forces on the type of injury produced in the brain.

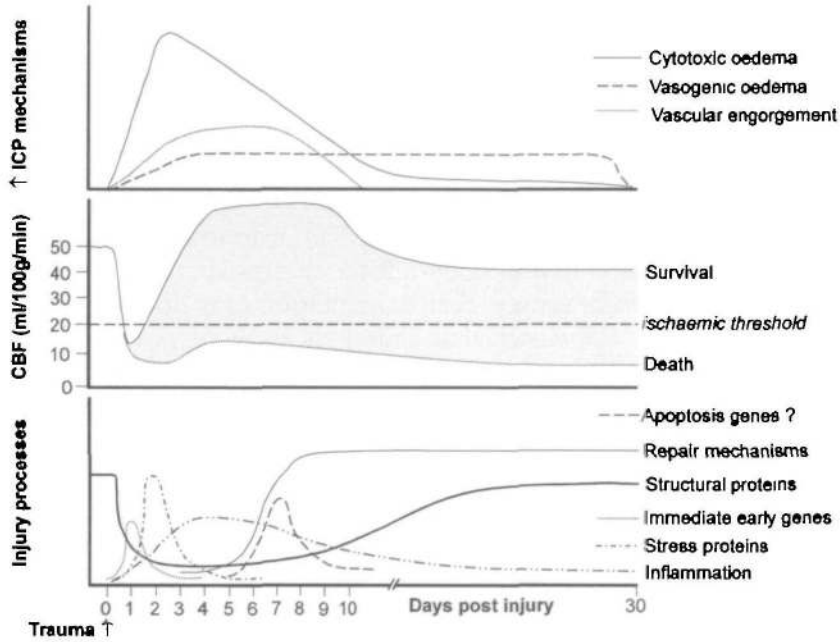

Fig. 5 Sequential activation of injury processes (bottom panel), cerebrovascular responses (middle panel) and mechanisms involved in brain swelling (top panel) following head injury. Cerebral blood flow is initially low, but after a period of hyperaemia, may have a variable course, depending on the type and severity of injury, and the presence or absence of vasospasm. Redrawn with modifications from Bullock[22].

injury is the presence of ischaemic changes[24]. Mechanisms involved in secondary neural injury include excitatory amino acid (EAA) release, intracellular calcium overload, free radical mediated injury and activation of inflammatory processes. Many of these processes have been extensively discussed in many previous articles[22–24] and will not be addressed in detail here.

There is, however, new and emerging interest in the role of cerebral inflammation following acute brain injury from a variety of causes (Fig. 6)[16]. There is good evidence now that there is a local inflammatory response in the human brain following a variety of insults[25,26], with production of pro-inflammatory cytokines (including IL-6 and IL-8) and adhesion molecule upregulation (including ICAM-1, ICAM-2 and E-selectin)[27,28]. These changes result in early neutrophil influx, and later recruitment of lymphocytes and macrophages. The microglial cells become transformed and adopt the morphology and function of dendritic antigen presenting cells[29]. They then contribute to the later stages of a prolonged inflammatory response, which may be associated with the laying down of amyloid. Indeed, head injury is a recognised risk factor for amyloid deposition in the brain and for Alzheimer's disease[30,31]. Further, the risk of these outcomes is related to an individual's apolipoprotein E (ApoE) genotype[30,31], with an increased risk conferred by possession of the ApoEε4 genotype. Even more intriguingly, the ApoEε4 genotype has been shown to affect outcome directly in patients admitted with a severe head injury[32]. This may be the first recognition of many genotypic influences that modulate the severity of secondary neuronal injury mechanisms, and

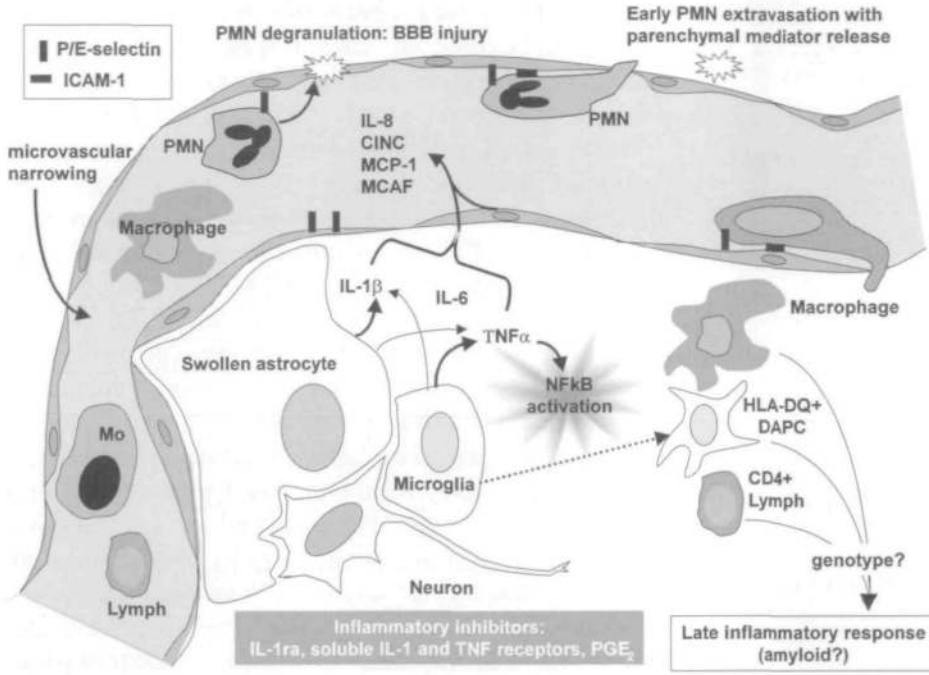

Fig. 6 Induction of inflammatory responses following acute brain injury: TNFα, IL-1β and IL-6 are secreted by astrocytes and microglial cells, with later production of chemokines, including IL-8, cytokine induced neutrophil chemotactic factor (CINC), monocyte chemoattractant protein-1 (MCP-1) and monocyte chemotactic and activating factor (MCAF, which attracts monocytes and macrophages). Leukocytes attracted by these chemokines subsequently interact with adhesion molecules such as P- and E-selectin and intercellular adhesion molecule-1 (ICAM-1). The initial cellular response is mainly polymorphonuclear (PMN), and later cellular responses predominantly consist of invading macrophages and $CD4^+$ lymphocytes. These cells, along with microglia derived $HLA\text{-}DQ^+$ tissue macrophages with the morphology of dendritic antigen presenting cells (DAPC), may be responsible for a sustained inflammatory response, the magnitude of which may show genetic polymorphism. TNFα also produces activation of the nuclear factor NFκB, which has wide ranging effects. Modified from Menon and Summors[16].

elucidation of these processes may enable us, in the future, to select high risk patients for intensive neuroprotection strategies.

There is an intimate and continuing interplay between the various steps of the cascade described above. Unevacuated intracranial haematomas may not only raise ICP and worsen cerebral hypoxia, but may also be responsible for the activation or intensification of EAA release, inflammation and microvascular dysfunction. The microvascular dysfunction, in turn, may limit the ability of the injured brain to cope with minor variations in physiology. Indeed, while the normal brain has the autoregulatory capacity to cope with mild hypotension that results in cerebral perfusion pressure (CPP) reduction to 50 mmHg, it has been well documented that patients with acute head injury, as a group, tend to

require CPP values above 60 mmHg in order to maintain cerebral perfusion. Further, at later stages after head injury, the presence of extravascular blood may predispose to large vessel spasm, with the potential for distal hypoperfusion and ischaemia.

These varied pathophysiological consequences of a single structural pathology are well reflected by sequential changes in cerebrovascular physiology that are observed following head injury. Classically, cerebral blood flow (CBF) is thought to show a triphasic behaviour (Fig. 5)[33]. Early after head injury (< 12 h), global CBF is reduced, sometimes to ischaemic levels. Between 12 h and 24 h post injury, CBF increases and the brain may exhibit supranormal CBF. While many reports refer to this phenomenon as hyperaemia, the absence of consistent reductions in cerebral oxygen extraction suggest that metabolism and blood flow often remain coupled, and a more appropriate label would be hyperperfusion. CBF values begin to fall several days following head injury, and, in some patients, these reductions in CBF may be associated with marked increases in large vessel flow velocity on transcranial Doppler ultrasound that suggest vasospasm.

These time-varying haemodynamic responses also define the vascular contribution to ICP elevation in time (Fig. 5)[22]. Immediately after head injury there is no vascular engorgement and, though a transient blood brain barrier (BBB) leak has been reported in the immediate period after impact in animals, there is no evidence of BBB disruption at this stage in humans. Apart from surgical lesions (*e.g.* intracranial haematomas), ICP elevation during this phase is commonly the consequence of cytotoxic oedema, usually secondary to cerebral ischaemia. Increases in CBF and cerebral blood volume (CBV) from the second day postinjury onward make vascular engorgement an important contributor to intracranial hypertension. The BBB appears to become leaky between the second and fifth days post trauma, and vasogenic oedema then contributes to brain swelling. If these patterns were consistent and predictable, they would allow the rational selection of therapies at each stage following trauma. Unfortunately, patients vary enormously, and different mechanisms responsible for intracranial hypertension may operate concurrently even within a single individual at any given time point. However, the discussion above does apply to groups, and provides a useful basis on which to select initial 'best guess' therapy in an individual patient, especially when data from multimodality monitoring are also available to help guide therapy choices.

Monitoring in acute head injury

None of the monitoring techniques and interventions that are widely used by specialist centres in severe head injury have ever been subjected to prospective randomized control trials. Indeed, some procedures such

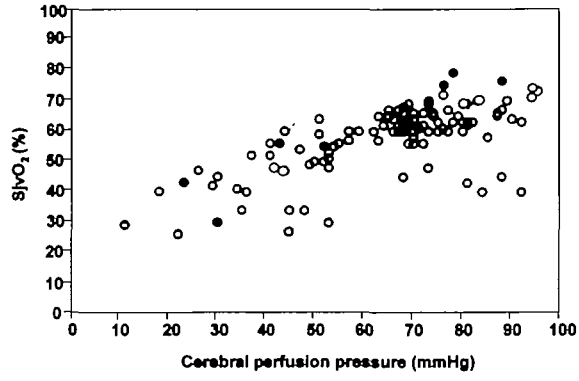

Fig. 7 Effect of changes in CPP produced by increases in ICP (open circles) or decreases in MAP (closed circles) on $SjvO_2$. Note the reduction in $SjvO_2$ at CPP values below 60–70 mmHg implying exhaustion of autoregulatory vasodilatation and reliance on increased oxygen extraction to maintain oxygen metabolism. Redrawn from Chan *et al*[37].

as intracranial pressure (ICP) monitoring are now so widely accepted as being central to the management of patients with severe head injury, that it may have become ethically impossible to mount a randomized trial addressing the efficacy of the procedure. However, the large body of clinical evidence that supports the use of many of these interventions provides a relatively strong basis for their recommendation as treatment guidelines. Selection of individual monitoring modalities is probably best based on their ability to measure physiological endpoints that have been shown to influence outcome and are amenable to modulation by therapeutic interventions.

Defining therapeutic targets: a rational approach to selecting monitoring modalities

Basic physiological premises suggest the benefit of maintaining cerebral blood flow and oxygenation, and these assumptions are confirmed by data from the Traumatic Coma Data Bank (TCDB)[11,34] and from other sources[10] which demonstrate the detrimental effects of hypotension (systolic blood pressure < 90 mmHg) and hypoxia (PaO_2 levels < 60 mmHg [8 kPa]) in the early and later phases of head injury on outcome (Figs 2 & 3). Several studies that have addressed break points for cerebral autoregulation in patients with head injury have suggested preserved cerebrovascular autoregulation with maintenance of cerebral blood flow (CBF) at cerebral perfusion pressures (CPP: defined as MAP-ICP) above 60–70 mmHg (Fig. 7)[9,35–37]. Further, ischaemia is a consistent finding in fatal head injury[24], and retrospective outcome studies from several groups have suggested that outcome is improved in patients who have fewer episodes of CPP or MAP reduction[36], aggressive CPP management[38] or

maintained autoregulation[39]. Despite this large body of data that supports the maintenance of high CPP values in head injury, there is some concern that relatively high perfusion pressures may contribute to oedema formation post head injury. Indeed, at least one group have focussed on the minimisation of cerebral perfusion pressure to relatively low levels in order to minimise oedema formation[40]. Other small studies have shown that outcome may be worsened in patients who suffer episodes of jugular venous desaturation below 50%[41], or blood glucose elevation[42]. There appears to be general agreement that uncontrolled rises in body temperature may worsen outcome in acute brain injury[16,43].

These findings make several points. First, they suggest that autoregulation maybe impaired in these patients, since the CPP thresholds for loss of pressure autoregulation are higher than in healthy subjects. Second, they emphasize the importance of maintenance of cerebral perfusion pressure, rather than isolated attention to intracranial pressure as a therapeutic target. There are however, data that show that ICP is an independent, albeit weaker, determinant of outcome in severe head injury[43]. These studies suggest that an ICP greater than 15–25 mmHg is an appropriate threshold for initiation of therapy.

Monitoring systemic physiology

The need to maintain cerebral oxygenation and CPP predicate the monitoring required to achieve these therapeutic targets. Consequently, monitoring of direct arterial blood pressure along with measurement of ICP are essential for computing and manipulating CPP. Typically, the need to manipulate mean arterial pressure rationally will also require the measurement of central venous pressure, or left atrial pressure using pulmonary artery catheterization, where appropriate. Similarly, the maintenance of systemic oxygenation requires the continuous monitoring of this variable (by pulse oximetry, supported by arterial blood gas measurement). The propensity of the injured brain to be damaged by core temperature elevation and by extremes of blood sugar demands the continuous measurement of body temperature and regular blood sugar estimation.

Global CNS monitoring modalities

While the monitoring described above may help to ensure the maintenance of optimal systemic physiology, detection of local changes in CNS physiology will require other tools. Commonly used bedside monitoring techniques in this area include transcranial Doppler ultrasound for non-invasive estimation of CBF, jugular venous saturation ($SjvO_2$) monitoring,

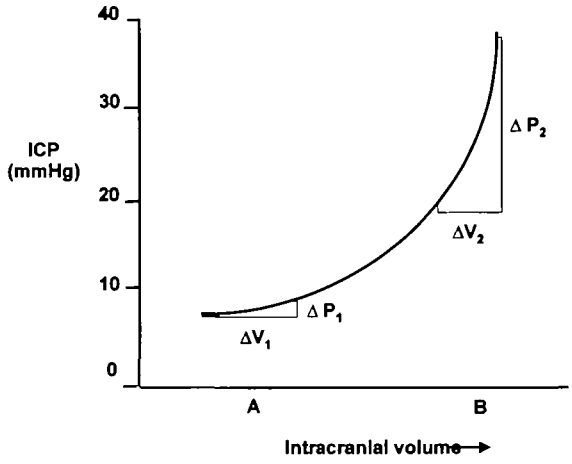

Fig. 8 The intracranial pressure volume curve (see text for details).

and monitoring of brain electrical activity. These techniques seek to estimate cerebral blood flow in the presence of an adequate CPP, estimate the adequacy of oxygen delivery to the brain, and document the consequences of possible oxygen deficit or drug therapy on brain function, respectively.

Intracranial pressure monitoring

The need to optimise CPP predicates the requirement of monitoring ICP in all patients with severe head injury[6,44]. Clinical signs of intracranial hypertension are late, inconsistent and non-specific. Further, it has been shown that episodic rises in intracranial pressure may occur even in patients with a normal X-ray CT scan[45]. The majority of devices used to monitor ICP can be placed under local anaesthesia at the bedside. A ventriculostomy with an intraventricular catheter remains the gold standard, and provides a means of treating high ICP with drainage of CSF. Intraparenchymal micromanometers (Codman, USA) or fibre-optic probes (Camino, USA) are increasingly being used instead of ventriculostomies. While these present a lower infection risk, they are more expensive and do not permit CSF drainage for the reduction of elevated ICP.

The relationship between intracranial volume and pressure is not linear, since initial increases in intracranial volume are buffered by compensatory mechanisms which limit ICP rise (the flat part of the intracranial pressure volume curve shown in Fig. 8). However, when these compensatory mechanisms are exhausted, further increases in intracranial volume result in increasingly steep increases in ICP (the knee and vertical part of the curve in Fig. 8). A more complete assessment of intracranial fluid dynamics may be obtained by assessing the intracranial compliance, where changes in ICP are observed following the infusion into or removal of fluid from a

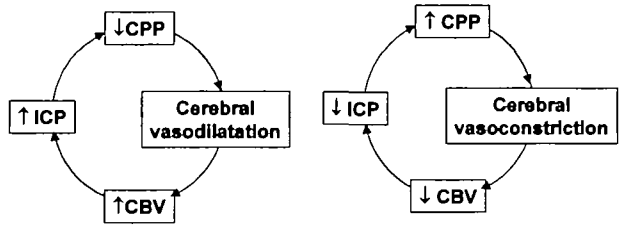

Fig. 9 Vasodilatory/vasoconstrictor cascades (after Rosner[38]). On the left changes in cerebral blood volume (CBV) induced by vasodilatory responses to CPP reduction tend to increase ICP and further reduce CPP, resulting in a vicious circle. Conversely (right panel) CPP elevation will not only improve cerebral perfusion, but also trigger autoregulatory vasoconstriction and reduce CBV and ICP.

ventricular catheter. The arterial pulse produces a small increase in intracranial volume with every cardiac contraction, and an exaggerated transmission of the arterial pressure waveform to the intracranial waveform (which normally has a pulse pressure of a few mmHg) suggests that intracranial compliance may be compromised.

In addition to static ICP elevation, patients with head injury may develop phasic increases in ICP, often triggered by cerebral vasodilatation in response to a fall in CPP (Fig. 9). 'A waves' tend to occur on a high baseline pressure and elevate ICP to 50–100 mmHg for several minutes, usually terminated by a marked increase in mean arterial pressure consequent to a Cushing response which results in catecholamine secretion. Shorter-lived fluctuations lasting about a minute are referred to as B waves. The frequency of both A and B waves may be decreased by increasing MAP, thus preventing the reflex cerebral vasodilatory cascade that initiates CBV increases and ICP elevation (Fig. 9).

Transcranial Doppler (TCD) ultrasonography

TCD measures the velocity of red blood cells (RBCs) flowing through the large vessels at the base of the brain using the Doppler shift principle. Since the diameter of these basal vessels is not affected by common physiological variables such as MAP and $PaCO_2$, flow velocity (FV) in these vessels provides an index of flow. Although many of the intracranial arteries may be studied, the middle cerebral artery (MCA) is most commonly insonated because it is easy to detect, receives a substantial proportion of the blood flow from the internal carotid artery and allows easy probe fixation. Marked reductions in MCA FV may provide a useful marker of critically reduced cerebral perfusion in the setting of intracranial hypertension in acute head injury, but episodic rises in ICP may also be caused by hyperaemia, which may be diagnosed by increases in TCD FV. Transcranial Doppler ultrasonography can also be used as a non-invasive monitor of

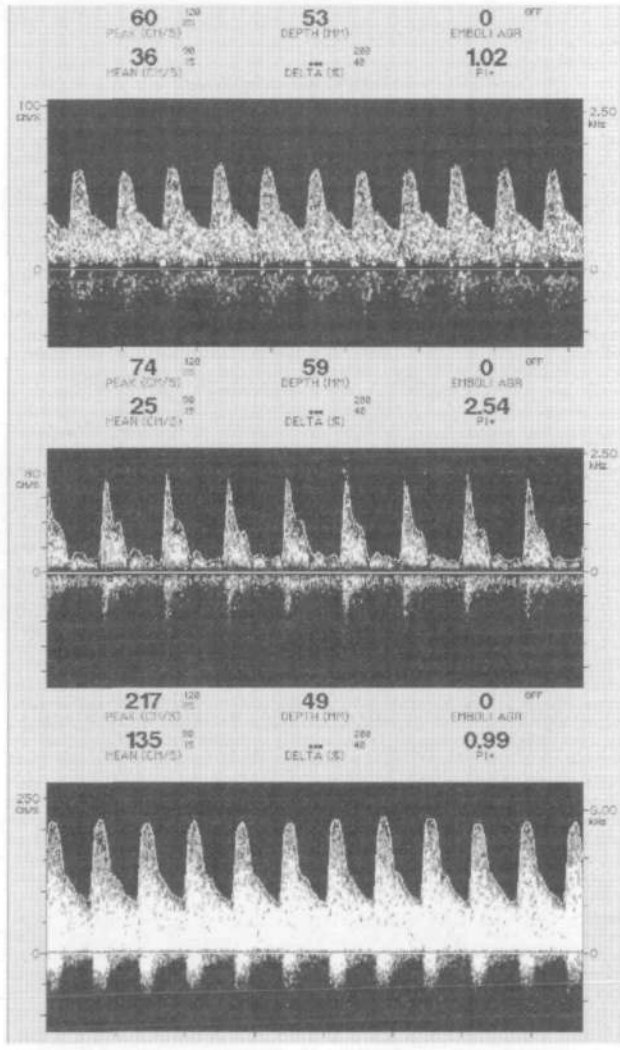

Fig. 10 Transcranial Doppler waveforms obtained in the presence of a normal ICP (top panel), intracranial hypertension (middle panel) and vasospasm/ hyperaemia (bottom panel). Note the high pulsatility index in the presence of ICP elevation. Both hyperaemia and vasospasm result in high middle cerebral artery flow velocities. The distinction between the two depend on extracranial internal carotid artery flow velocities, which are correspondingly high in hyperaemia and discordantly low in vasospasm.

cerebral perfusion pressure. As the ICP increases and cerebral perfusion pressure correspondingly decreases, a characteristic highly pulsatile flow velocity pattern is seen (Fig. 10). Continuing increases in ICP result first in a reduction and then loss of diastolic flow, progressing to an isolated systolic spike of flow in the TCD waveform, and eventually to an oscillating flow pattern which signifies the onset of intracranial circulatory arrest[37,46]. The pulsatility index (PI) is one way of mathematically describing the waveform pattern, and correlates with cerebral perfusion pressure than with ICP[47]. This form of monitoring may become particularly useful in centres where ICP measurements are not routinely used (such as district general hospitals), or in patients in whom ICP monitoring is unavailable or may not be clearly indicated (*e.g.* mild closed head injury).

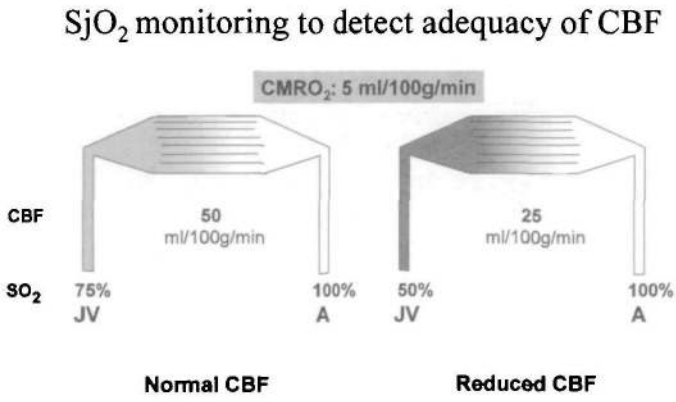

Fig. 11 The use of $SjvO_2$ monitoring to measure adequacy of CBF. When CBF is inadequate to meet metabolic needs, the brain extracts a greater proportion of arterial oxygen content, resulting in a reduction in $SjvO_2$ (50%) and an elevated $AVDO_2$ (> 9 ml/dl).

Cerebral vasospasm results in increases in TCD flow velocity, as blood is pushed through narrow arterial segments into a widely dilated microvascular bed[33,48,49]. Cerebral vasospam is present if the mean flow velocity in the MCA is >120 cm/s (Fig. 10)[50] and is distinguished from hyperaemia by the absence of a concomitant increase in flow velocity in the extracranial internal carotid artery (ratio between the flow velocity in the MCA and ICA exceeds 3[51]).

The loss of cerebral pressure autoregulation and vasoreactivity to CO_2 are indicators of poor prognosis after head-injury[52]. Classical tests of autoregulation involve recording TCD responses to induced changes in mean arterial pressure. Cerebral autoregulatory reserve is also assessed by the transient hyperaemic response test (THRT)[53]. More recent algorithms constantly assess autoregulation by on-line calculation of changes in MCA FV in response to small spontaneous alterations in MAP[39]. Such analysis permits the on-line calculation of indices of cerebrovascular reactivity and compensatory reserve, which may allow prediction rather than recording of physiological behaviour, and facilitates the selection of patients for intensification of therapy.

Jugular venous oximetry

Cerebral oxygenation has conventionally been assessed by jugular bulb oximetry. Conventionally, the superior saggital sinus is thought to drain primarily into the right intenal jugular vein, and it is common practice to place jugular bulb catheters on this side in order to monitor the oxygenation in the supratentorial compartment. More recent data suggest that supratentorial venous drainage is less lateralised, and a case has been made for bilateral jugular bulb catheterisation[54]. Normal jugular bulb oxygen saturations ($SjvO_2$) tend to run at 65–70%. Reductions in $SjvO_2$ or increases in arteriojugular differences in oxygen content ($AJDO_2$) to greater than 9 ml/dl provide useful markers of inadequate CBF[55] (Fig. 11) and can

guide therapy[56], and $SjvO_2$ values below 50% have been shown to be associated with a worse outcome in head injury[41]. Conversely, marked elevations in $SjvO_2$ may provide evidence of cerebral hyperaemia. While $SjvO_2$ monitoring has been widely used in head injury, it is technically difficult. The use of continuous $SjvO_2$ monitoring with a fibre-optic catheter will detect episodes of cerebral desaturation associated with intracranial hypertension, hypocapnia, systemic hypotension and cerebral vasospasm, but as many as half of the episodes identified as cerebral desaturation ($SjvO_2$ ~50%) may be false positives[57]. The position of the catheter should be checked using a lateral radiograph of the neck.

Newer techniques for brain oximetry

The major deficiencies of jugular venous oximetry are its invasiveness and the poor reliability of signal obtained. Other techniques that have been employed investigationally in acute head injury include near infra-red spectroscopy (NIRS)[57,58], direct tissue oximetry[59,60] and cerebral microdialysis[61–63].

Two groups have published data on the use of NIRS in the context of acute head injury. Kirkpatrick *et al*[57] were able to demonstrate that during 1–5 days after head injury, NIRS was better than $SjvO_2$ at detecting periods of abnormal physiology as defined by multimodality monitoring. The changes were confined to cerebral haemoglobin desaturation and no changes seen in cytochrome aa_3 redox state. Gopinath *et al*[58] used a simplified dual wavelength NIR unit to detect and lateralize the side of intracranial haematomas in 46 patients with head injury. It is likely that with the wider availability of NIRS, many other applications of this technology will be explored. While several companies have devised algorithms that seek to provide an absolute measure of cerebral oxygen saturation using NIRS, it is the author's opinion that these remain inadequately validated.

An entirely opposite approach is taken by the technique of direct cerebral oximetry, which uses a combined pO_2, pCO_2, pH and temperature micro-sensor implanted in the brain. This technique has been used in several clinical studies, and results are beginning to emerge that relate tissue oxygen levels to outcome[59,60]. However, it measures oxygenation in a very small volume of tissue, and it remains to be established whether this is representative of the large bulk of brain that requires monitoring.

Tissue microdialysis presents the opportunity of directly sampling brain ECF composition, with opportunities for the measurement of glucose (which tends to parallel perfusion), lactate/pyruvate ratios (which provide information regarding ischaemia) and glutamate (which tends to be elevated after physiological insults)[61–63]. In addition to insights into brain

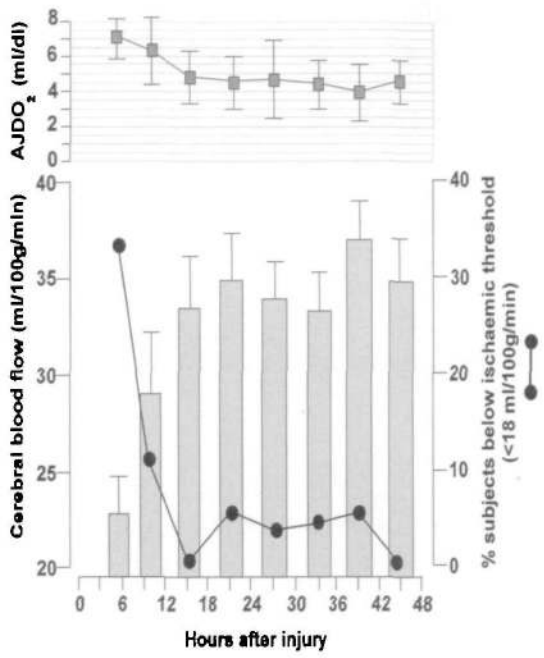

Fig. 12 Global CBF (*bars show means* ± standard error), percentage of patients below ischaemic threshold (solid circles and lines), and $AVDO_2$ (boxes in upper panel) in the first 48 h following head injury. Redrawn from data in Bouma *et al*[65].

physiology, this technique may provide a method of measuring local pharmacokinetics of drugs in head injury.

Cerebral blood flow measurement

Global cerebral blood flow measurements in acute head injury have commonly used ^{133}Xe washout techniques at the bedside and documented the phasic changes in CBF after head injury. Despite the common observation of ischaemic neuropathological changes in fatal head injury, evidence of ischaemia from CBF studies was unconvincing in early studies[64], since CBF reductions were generally modest in the first few days following injury, and these were not commonly associated with the marked increases in $AJDO_2$ which would imply ischaemia. On the contrary, most patients exhibited $AJDO_2$ in the normal range, implying that the CBF reductions were appropriately coupled to decreases in cerebral metabolic rates for oxygen ($CMRO_2$)[64]. Two different approaches have provided explanations for these observations. Ultra early (<12 h) CBF measurements after head injury have provided clear evidence that over 30% of patients exhibit global CBF reductions below commonly accepted ischaemic thresholds (<18 ml/100 g/min)[65]. Later measurements in this study showed elevation of CBF to non-ischaemic levels by 24–48 h post injury (Fig. 12)[65]. These findings have been generally confirmed by other studies[33]. However, even at early time points, $AJDO_2$ remained relatively low despite a

markedly low CBF (Fig. 12), with few patients demonstrating increases above 9 ml/100 ml (a commonly accepted threshold for defining ischaemia)[33,65].

These results fail to reconcile the clinical findings seen in the vast majority of patients with the neuropathological changes observed in fatal cases[66]. One explanation for this discordance may lie in the physiological heterogeneity observed in the injured brain. While both conventional monitoring methods and newer techniques are useful, they are limited by the fact that they detect either globally averaged or highly localized abnormalities in cerebral physiology and are, hence, likely to miss focal derangements that occur in the metabolically heterogeneous injured brain.

Imaging physiology and metabolism in head injury

The presence of such focal pathophysiology has two major implications. First, a relatively small area of critically abnormal physiology may be diluted by surrounding normal tissue, and may have no effect on global measures of CNS well being. Conversely, the benefits and side effects of therapeutic intervention need to be assessed in the small portion of brain that is at risk of secondary injury but is still salvageable. Since structural changes (as detected by X-ray CT or conventional MRI) are relatively late and often irreversible, these considerations have lead to the conclusion that there is a need to image physiology and metabolism in such patients.

The best established technique for physiological imaging is the use of stable xenon CT studies for measurement of regional CBF (rCBF). Marion *et al*[67] confirmed that CBF values were reduced in the first 24 h following head injury. While global CBF misrepresented regional CBF values in 48% of subjects, lobar or basal ganglia levels were often higher than might have been expected from global values[67]. They also demonstrated variations in global and regional perfusion patterns in different structural pathologies, with lowest blood flows in patients with diffuse swelling or bihemispheric contusions. Bouma *et al*[68] confirmed the presence of ischaemia within 4 h of injury, and demonstrated reductions in hemispheric CBF on the side of intracranial haematomas. Several studies have demonstrated marked heterogeneity in perfusion patterns and CO_2 reactivity in the injured brain, especially in the vicinity of contusions[67–69].

We have used positron emission tomography (PET) and magnetic resonance imaging for this purpose. In recent studies we have shown (Fig. 13) that moderate reductions in $PaCO_2$ (to 4.2 kPa in some instances) can result in increases in the volume of brain tissue with CBF values below well recognised ischaemic thresholds (< 20 ml/100 g/min)[70]. Importantly, the development of these ischaemic areas, which are typically peri-contusional or in white matter, is not reflected by reductions in jugular

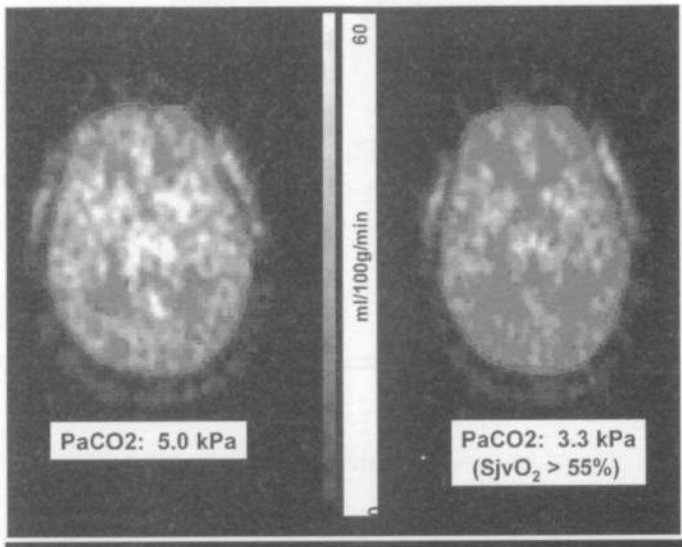

Fig. 13 PET rCBF scan showing effect of hyperventilation in the first 24 h following head injury. Despite the maintenance of $SjvO_2$ at acceptable levels, hyperventilation results in marked increases in the volume of brain tissue below an ischaemic CBF threshold (20 ml/100 g/min).

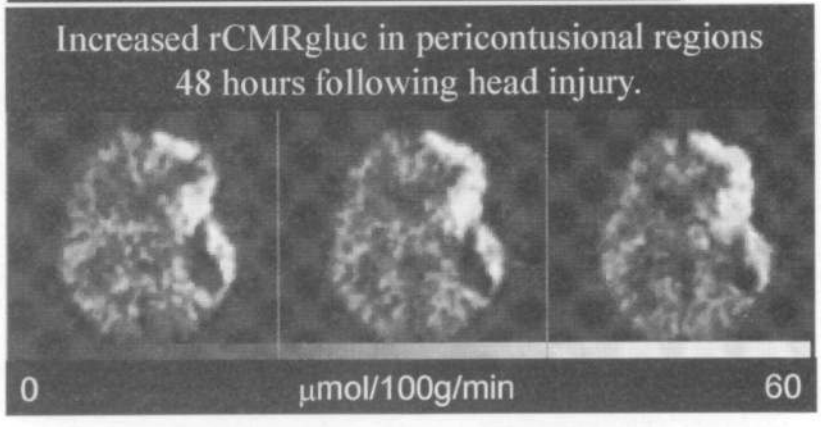

Fig. 14 [^{18}F]-Deoxyglucose (FDG) PET scan 48 h post head injury demonstrating pericontusional increases in FDG uptake.

bulb oxygen saturations below commonly accepted thresholds for ischaemia (55%). In addition, PET provides the opportunity to image cerebral glucose and oxygen utilisation and radioligand binding. Recent interest has focused on increased uptake of the PET tracer ^{18}F-deoxyglucose around contusions and adjacent to haematomas (Fig. 14), which are probably unaccompanied by increases in oxygen metabolism[71,72]. These data concur with previous animal studies, and imply cerebral hyperglycolysis (anaerobic glucose utilisation) and may represent metabolic changes associated with local epileptiform activity, high ECF glutamate or inflammatory activation.

Multimodality monitoring

While individual monitoring techniques provide information regarding specific aspects of cerebral function, the correlation of data from several

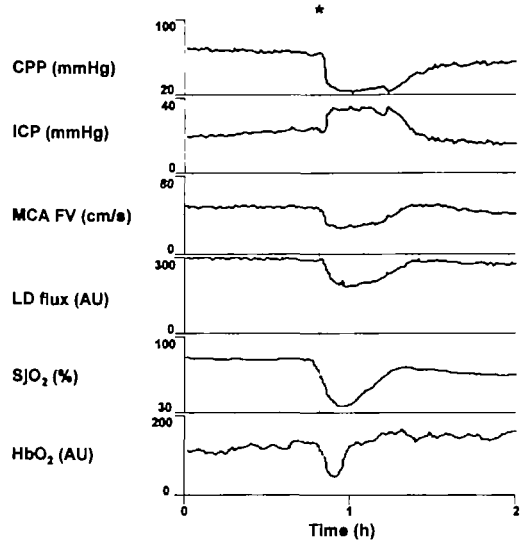

Fig. 15 Multimodality monitoring in head injury. An increase in ICP triggers a reduction in CPP, and hence in TCD MCA flow velocity and laser Doppler flux (an investigational device that measures capillary flow). Inadequate cerebral perfusion results in a fall in cerebral oxygenated haemoglobin (HbO_2). The early reduction in $SjvO_2$ shows that jugular desaturation (produced in this case by arterial desaturation, which is not shown) was the primary event.

modalities has several advantages in head injury management. Integration of monitored variables allows cross validation and artifact rejection, better understanding of pathophysiology and the potential to target therapy (Fig. 15).

Therapy

Achieving target CPP values

Most centres would agree on the need to maintain cerebral perfusion by keeping CPP well above 60–70 mmHg, either by decreasing ICP or by increasing MAP. MAP maintenance involves the use of adequate preload expansion, inotropes and vasopressors. The relative merits of each of these interventions to increase MAP have not been investigated, although we have no data on the safety of high doses of vasoactive agents in the presence of damage to the blood brain barrier. Drainage of CSF (where possible), mannitol administration, hyperventilation and the use of CNS depressants (typically barbiturates) have all been used to reduce ICP.

In general terms, the debate in this area has focussed on the means of optimising CPP at a level above 70 mmHg (although some proponents would quote a substantial body of data to justify a target of 60 mmHg)[9,35–39,56]. Rosner *et al*[38] have been the most enthusiastic proponents of the use of hypervolaemia and hypertension to increase MAP and induce

secondary reductions in ICP (Fig. 9). The contrary view is championed by Cruz,[56] who has used 'optimised hyperventilation' (guided by $SjvO_2$ monitoring), to reduce ICP and hence increase CPP. In an excellent editorial, Chesnut[56a] summarises the relevance of these issues to those of us 'not situated firmly on either side of this fence'. It is likely that several different pathophysiological mechanisms co-exist in individual patients, and both approaches are likely to have a role if applied appropriately. It must be remembered that both hyperventilation and induced hypertension have clearly recognised systemic and cerebral side effects, and their extent of use will also be limited by a risk/benefit ratio.

CSF drainage has long been used as a means of reducing ICP, and such an approach was facilitated by the routine use of ventriculostomies for measuring ICP. The more recent advent of intraparenchymal manometers or fibre-optic devices for measuring ICP has reduced infection risk, but removed automatic access to ICP drainage in such patients. Data quoted in the Brain Trauma Foundation guidelines for the management of severe head injury provide circumstantial evidence supporting the increased use of CSF drainage for ICP control[5].

Alternative philosophies for CPP targets: the Lund protocol

In contrast to the studies discussed above, publications from one Swedish centre[40,74] describe the use of a protocol that focuses primarily on the prevention and reduction of cerebral oedema rather than maximising cerebral perfusion. These authors accepted CPP values as low as 50 mmHg in adults, and reduced mean arterial pressures using a combination of clonidine and metoprolol, and reduce cerebral blood volume with dihydroergotamine and low dose thiopentone (which was used as a sedative). Plasma oncotic pressure was increased by transfusing albumin or plasma to maintain normal albumin levels. They report excellent results with this regimen (8% overall mortality and 79% good outcome) which compare well with those from centres using conventional CPP guided therapy. However, they used historical controls, and there is some doubt as to whether their data are truly comparable to those obtained from other centres. However, their impressive outcome figures demand further investigation, and it may well be that optimal CPP levels may vary widely both between patients, and at different stages after head injury in the same patient[75].

Ventilatory support and the use of hypocapnia for ICP reduction

It is generally agreed that patients with a GCS of ≤ 8 require intubation for airway protection, and that such patients should receive mechanical

ventilatory support in order to ensure optimal oxygenation and $PaCO_2$ control. Airway control and ventilation are also advised for patients with ventilatory failure, central neurogenic hyperventilation or recurrent fits.

Hyperventilation, once the mainstay of ICP reduction in severe head injury, is now the subject of much debate[76,77]. The aim of hyperventilation is to reduce cerebral blood volume and hence ICP, but this is accompanied by a reduction in global cerebral blood flow, which may drop below ischaemic thresholds[41,56,64]. Such ischaemia can be documented using jugular bulb oximetry, and while conclusive data are not available, it is possible that these consequences may worsen outcome in patients who undergo prolonged hyperventilation[78]. More recent studies have shown that hyperventilation may result in significant focal reductions in rCBF, shown by contrast enhanced dynamic computed tomography or positron emission tomography[69,70,79], which are undetected by global measures of cerebral oxygenation such as SjO_2 monitoring. In addition to concerns regarding ischaemia, hyperventilation may have only short-lived effectiveness in decreasing ICP. With prolonged hyperventilation, compensatory reductions in cerebral extracellular fluid (ECF) bicarbonate levels rapidly restore ECF pH in normal subjects.[80] Although there is some evidence that these compensatory changes may be delayed after head injury,[64] it is likely that they will, over time, attenuate the effect of low $PaCO_2$ levels on vascular tone. Indeed, restoration of $PaCO_2$ levels to normal under these circumstances may result in rebound increases in cerebral blood volume and ICP. It has been suggested that the use of the diffusible hydrogen ion acceptor, tetra-hydro-aminomethane (THAM), may restore ECF base levels and restore the reactivity of the cerebral circulation to CO_2. In addition, one study reports that the use of THAM may reduce ICP and the need for intensification of ICP therapy after head injury, but without a change in outcome[80].

Fluid therapy and feeding

Accurate fluid management may be complicated by manifest or concealed haemorrhage from associated extracranial injuries, but every effort must be made to restore normovolaemia as hypovolaemia will cause hypotension and aggravate cerebral ischaemia[81]. Fluid replacement should be guided by clinical and laboratory assessment of volume status and by invasive haemodynamic monitoring, but generally involves the administration of 30–40 ml/kg of maintenance fluid per day. The choice of hydration fluid is largely based on inconclusive results from animal data[81]. Unlike other vascular beds, capillaries in the brain are impermeable to most small molecules, and fluid flux across the normal BBB is governed by osmolarity rather than oncotic pressure. Consequently, hypotonic fluids are avoided and serum osmolality is maintained at high normal/high

levels (290–300 mosm/l in our practice) to minimise fluid flux into the injured brain. Dextrose containing solutions are avoided since the residual free water after dextrose metabolism can worsen cerebral oedema, and because the associated elevations in blood sugar may worsen outcome[42]. Some clinical data are now available to support these practices. Quershi *et al*[82] used 3% saline in patients with brain oedema due to head injury and demonstrated a rise in plasma sodium and osmolality and at least temporary reduction in ICP and midline shift. Simma *et al*[83] reported that 1.6% saline, when compared to lactated Ringer's solution as maintenance fluid in head injured children, resulted in lower ICP values, less need for barbiturate therapy, a lower incidence of acute lung injury, fewer complications and a shorter ICU stay. These encouraging results must be balanced against imperfections in the design of both studies and the potential side effects of hyperosmolar fluid therapy[42,84]

The potentiation of plasma oncotic pressure by colloid infusions might be expected to provide a distinct advantage when reflectance for sodium is seriously compromised in the presence of blood brain barrier disruption[81]. Maintenance of oncotic pressure with albumin supplements is one of the cornerstones of the Lund protocol[40], and other authors have discussed the advantages of colloid use in this setting. Both albumin and gelatins have been used, but hetastarch should be used with caution, since its effects on haemostasis may potentiate intracranial haemorrhage. There is some evidence indicating that certain colloids (pentastarch) may be effective in reducing the cerebral oedema associated with cerebral ischaemic and reperfusion injury[85]. Agents which 'plug leaks' by acting as oxygen free radical scavengers and or by inhibiting neutrophil adhesion may be the resuscitation fluids of the future[86].

Head injured patients have high nutritional requirements and feeding should be instituted early (within 24 h), aiming to replace 140% of resting metabolic expenditure (with 15% of calories supplied as protein) by the seventh day post trauma[87]. Enteral feeding is preferred as it tends to be associated with a lower incidence of hyperglycaemia and because of its protective effect against gastric ulceration, the incidence of which may be increased in these patients. Impaired gastric emptying is a common finding in head injury, and can be treated with prokinetic agents, such as cisapride and metoclopramide[88]. In those who cannot be fed enterally, parenteral nutrition should be considered together with some form of prophylaxis against gastric ulceration (H_2 antagonists or sucralfate) and rigorous blood sugar control.

Hyperosmolar therapy

In the setting of clinical, radiological or measured evidence of intracranial hypertension, mannitol (0.25–1 g/kg, usually as a 20% solution) has

traditionally been used to elevate plasma osmolarity and reduce brain oedema[89,90]. In addition to its osmotic effects, mannitol probably reduces ICP by improving CPP and microcirculatory dynamics[90,91]. While it is reported to possess antioxidant activity, these are unlikely to be clinically important. Side effects include secondary increases in ICP when the BBB is disrupted, fluid overload from initial intravascular volume expansion, and renal toxicity from excessive use. These can be minimized if its use is discontinued when it no longer produces significant ICP reduction, volume status is monitored and if plasma osmolality is not allowed to rise above 320 mosm/l[90] (although there is little objective evidence to support this threshold). In addition to their use as maintenance fluids, hypertonic saline solutions (7.5%) are being used for small volume resuscitations, and may provide improve outcome in comatose patients suffering from multiple trauma[92]. Recent reports also highlight the successful use of 23.4% saline for treatment of intracranial hypertension refractory to mannitol[93]. While more studies are required, it appears hypertonic saline will find a place in the treatment of brain swelling[94].

Sedation and neuromuscular blockade

Intravenous agents preserve pressure autoregulation and the cerebrovascular response to CO_2, even at doses sufficient to abolish cortical activity[95,96], and decrease cerebral blood flow, cerebral metabolism and ICP[96–99]. The reduction in flow is secondary to a reduction in metabolism (flow-metabolism coupling). However, this coupling is not perfect and the decrease in CBF may exceed the corresponding decrease in $CMRO_2$, with a widening of the cerebral arteriovenous oxygen content difference[100]. Such uncoupled CBF reductions may be at least partially due to changes in systemic haemodynamics.

Barbiturates are now less commonly used in the head injured patient for routine sedation, owing to the availability of other agents, such as propofol, which possess similar cerebrovascular effects but better pharmacokinetic profiles[101]. However, propofol is not without side effects. At high doses, propofol can induce hypotension and decrease in cerebral perfusion pressure. The lipid load imposed by a 20 ml/h continuous infusion of propofol is not insignificant and must be taken into account in the daily caloric intake. In our hands, the use of 200 μg/kg/min propofol to produce burst suppression for long periods has often resulted in unacceptable levels of plasma lipids. These problems with lipid loading have been substantially ameliorated by the introduction of a 2% formulation of propofol.

Midazolam is often used in combination with fentanyl and propofol for sedating the patient with head injury. Midazolam reduces $CMRO_2$, CBF and CBV with both cerebral autoregulation and vasoreactivity to

CO_2 remaining intact[102,103]. However, these effects are inconsistent and transient, and even large doses of midazolam will not produce burst suppression or an isoelectric EEG. Opioids generally have negligible effects on CBF and $CMRO_2$. However, the newer synthetic opioids fentanyl, sufentanil and alfentanil, can increase ICP in patients with tumours and head trauma[104]. This increase, originally assumed to be secondary to an increase in CBF, is more likely to be the result of changes in $PaCO_2$ and systemic hypotension[105,106]. and can be avoided if blood pressure and ventilation are controlled[107–109].

Neuromuscular blockade in the head injured patient receiving intensive care is currently the subject of much debate[110–112]. The use of neuromuscular blockers can play an important role in the head injured patient. Coughing and 'bucking on the tube' can result in an increase in ICP, and the administration of non-depolarising muscle relaxants prevents such rises in ICP[112]. However, despite facilitation of ICP control, use of these agents is not associated with better outcomes, perhaps because of increased respiratory complications. Further, long term use of neuromuscular blockade has been associated with continued paralysis after drug discontinuation[113] and acute myopathy[114], especially with the steroid-based medium to long acting agents. However, atracurium is non-cumulative and has not been associated with myopathy, and theoretical concerns about the accumulation of laudanosine, a cerebral excitatory metabolite of atracurium, in head injured patients have not been shown to be clinically relevant[112].

Antiepileptic therapy

Seizures occur both early (< 7 days) or late (> 7 days) after head injury, with a reported incidence of between 4–25% and 9–42%, respectively[115]. Seizure prophylaxis with phenytoin or carbamazepine can reduce the incidence of early post-traumatic epilepsy, but has little impact on late seizures, neurological outcome or mortality[115,116]. The incidence of post traumatic seizures is greatest in patients with a GCS < 10, and in the presence of an intracranial haematoma, contusion, penetrating injury or depressed skull fractures[115] Since it is important to balance the possible benefit from seizure reduction against the side effects of antiepileptic drugs, such patients may form the most appropriate subgroup for acute (days to weeks) seizure prophylaxis following head injury.

Cerebral metabolic suppressants

Intravenous barbiturates have been used in the setting of acute head injury for ICP reduction for over 20 years[117]. While they clearly result in

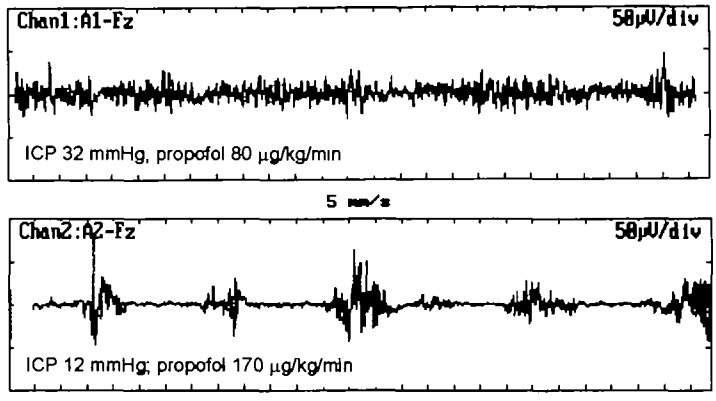

Fig. 16 Raw EEG recording from a patient with elevated ICP (top panel) showing the development of EEG burst suppression and reduction in ICP (lower panel) in response to an increased in propofol dose.

cardiovascular depression, increased ICU stay and increases in pulmonary infections, it appears that they have a significant role to play in a small number of head injured patients whose problem is intractable intracranial hypertension that responds to intravenous anaesthetics[118,119]. They are best given as an intravenous infusion, titrated to produce burst suppression on EEG (Fig. 16). One major disadvantage of barbiturates is prolonged recovery. This might suggest a role for other intravenous anaesthetics (etomidate and propofol) with more desirable pharmacokinetic profiles as useful agents in this setting. However, the efficacy of these agents remains unproven, and they have their own drawbacks. The adrenocortical suppression produced by etomidate has been well documented, and the high doses of propofol required to achieve burst suppression (up to 200 μg/kg/min), necessitate the delivery of high lipid loads with resultant abnormalities in plasma lipid status. The availability of 2% preparations of propofol may substantially ameliorate this problem.

Novel neuroprotective interventions

Although none of these have been accepted as standard therapy in acute head injury, a variety of novel pharmacological neuroprotective agents are currently under investigation. Disappointingly, none of the agents that have been tested thus far in Phase III trials have proved to provide benefit on an intention to treat basis[16,17].

Excitatory amino acid (EAA) antagonists

While the role of EAAs and protection by EAA antagonists have been well documented in experimental ischaemia, and to a lesser extent in experimental head injury, early clinical studies have been disappointing[17,120,121].

The prototype non-competitive glutamate antagonist acting at the N-methyl D-aspartate (NMDA) receptor, dizocilpine (MK-801) never reached large scale clinical trials because of fears regarding hippocampal neurotoxicity. More recent compounds have either been competitive or non-competitive antagonists, act as allosteric modifiers of NMDA channel activity, acted at presynaptic sites to reduce glutamate release, or act at non-NMDA glutamate receptors. However, none of these has been proved to be effective in outcome trials.

Calcium channel blockers

The success of nimodipine in subarachnoid haemorrhage prompted trials of this agent in head injury. While initial studies were disappointing, more recent studies have suggested that the agent may improve outcome in a subgroup of head-injured patients who have traumatic subarachnoid haemorrhage[122,123], though this remains controversial[124].

Antioxidants

Animal studies have suggested a prominent role for oxidants in acute brain injury, and demonstrated protection by antioxidants. Application in humans has not fulfilled this promise. Although initial clinical trials of polyethylene glycol conjugated superoxide dismutase (pegorgotein) were encouraging[125], a more recent large randomized outcome study has failed to demonstrate any benefit[126], and large Phase III trials of the novel antioxidant, tirilazad (which had proven efficacy in experimental models) have shown no improvement in outcome in clinical head injury[127].

Corticosteroids

These agents were initially used in head injury for their anti-inflammatory effect, and a large outcome trial demonstrated small, but significant, benefit of early high dose methylprednisolone in traumatic spinal cord injury[128]. Although isolated studies have reported benefit from steroids in acute head injury, a systematic review of the literature suggested that corticosteroids were ineffective or harmful in severe head injury[129]. More recently, a meta-analysis has re-awakened interest in mounting a well-designed randomized trial of early corticosteroid therapy in patients with head injury[130], but this approach is the subject of some debate[131]. While high dose methylprednisolone was originally

designed as an antioxidant intervention, the increasing recognition of inflammatory mechanisms in brain trauma suggests that it may also provide benefit by suppressing these processes.

Hypothermia

Much interest has focused on mild to moderate hypothermia (33–36°C) as a neuroprotective intervention since animal studies demonstrated improved outcome from cerebral ischaemia with small (1–3°C) reductions in temperature. Three preliminary studies demonstrated benefit from moderate hypothermia in head injury[132–134], and interim results from a large ongoing outcome trial have been encouraging, suggesting benefit in a subgroup of patients with Glasgow Coma Scores of 5–7[135]. While final results from this study are due for publication in early 1999, there has been lively correspondence in various journals regarding the methodology and conclusions of this report[136–140]. However, it is well recognised that temperature elevation has been shown to worsen outcome following brain injury. Recent studies have shown that cerebral temperature tends to be above core temperature in the injured brain, and is more accurately estimated by brain tissue probes[141] or jugular bulb catheters[142]. These findings are of particular relevance since it is now widely accepted that the prevention of hyperthermia is a highly desirable target in acute head injury[143].

Integration of intensive care: sequential escalation vs targeted therapy

It is clear that a diverse range of pathophysiological processes operate in acute head injury, and that there exist a wide range of therapeutic options, few of which have proven efficacy. This raises the question as to which interventions are best employed at different stages following head injury in any given patient. Two approaches are possible. The first of these is to use a standard protocol in all patients, and introduce more intensive therapies in a sequence that is based either on intensity of intervention or on local experience and availability. While such a scheme is simple, it does not provide for individualisation of therapy in a given patient.

An alternative approach is to target individual therapies at individual pathophysiological processes. Examples are the use of hyperventilation in the presence of hyperaemia, mannitol for vasogenic cerebral oedema or the use of blood pressure elevation in the presence of B waves. While this approach is intellectually appealing, it is hindered by the fact that

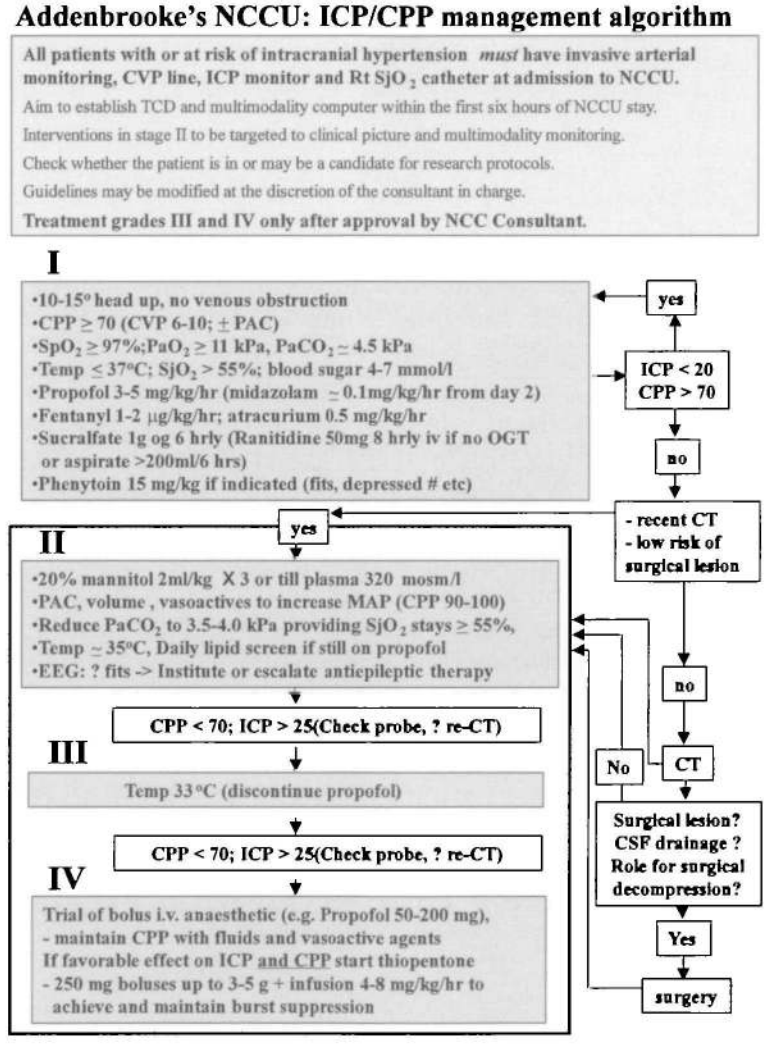

Fig. 17 Addenbrooke's NCCU ICP/CPP management algorithm.

pathophysiology is usually mixed, and global monitors of CNS physiology may miss critical focal abnormalities. Further, some interventions (*e.g.* hypothermia) work via multiple mechanisms, and do not easily find a place in a strictly targeted therapy plan.

In practice, many established head injury protocols represent a hybrid approach. Initial baseline monitoring and therapy are applied to all patients, and refractory problems are dealt with by therapy escalation, with the choice of intervention determined by clinical presentation and physiological monitoring. Often, interventions that are more difficult to implement or present significant risks (*e.g.* barbiturate coma) are used as a last resort. Figure 17 represents the ICP/CPP management protocol used in the Neurosciences Critical Care Unit (NCCU) at Addenbrooke's Hospital.

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