Ischaemia in Head Injury

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Ischaemia in Head Injury

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Preface

One of the best attended satellite symposia at the 1995 Neurosurgical Congress in Berlin was on ischaemia in head injury. Its aim, according to its chairman, Professor Francois Cohadon of Bordeaux, was primarily to review the current concept of brain ischaemia in trauma, its diagnosis and its clinical management.

Professor Cohadon himself is pre-eminent in the field of accident and emergency surgery in France. Introducing the other speakers, he welcomed Professor Graham Teasdale of Glasgow and Dr Mark Dearden, now of Leeds, as products of the Scottish schools of traumatic neurosurgery. He was especially pleased to see in the audience Professor Jennett, the father of these schools, to which, Professor Cohadon said, all neurosurgeons are indebted for innumerable major contributions to our understanding of traumatic brain injury. Professor Nicholas Dorsch of Westmead Hospital, New South Wales, Australia, and Dr Kakarieka of the Bayer Research Group, were the two final speakers.

Professor Cohadon introduced the concept of secondary damage after brain trauma. Professor Teasdale described the pathological and clinical evidence of ischaemic damage in brain trauma, and Dr Dearden described its mechanisms and methods for the clinical monitoring of the threat to patients.

Professor Dorsch described the role of traumatic subarachnoid haemorrhage (TSAH) in causing vasospasm after brain trauma, and the consequences for eventual recovery. The meeting was completed by Dr Kakarieka, who gave the first report on a randomized, controlled trial of nimodipine in patients with TSAH.

The following pages are a record of the Berlin satellite presentations and the discussion that followed. The audience was left in

no doubt that ischaemia following brain injury is a real threat to full recovery, and that such ischaemia can be prevented at every stage in patient management – at the site of trauma, during transport to hospital, and during every phase of hospital care. It is hoped that this report will be of value to everyone working in accident and emergency services and in hospital trauma units.

T.C.G. Smith

Contents

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The Concept of Secondary Damage in Brain Trauma

F. Cohadon

It is accepted that secondary damage in brain trauma is ischaemic in nature, but exactly way and how it happens is still unclear. Ischaemia entered the field of brain trauma with the work of David Graham, who in 1970 and in two major publications in 1978 and 1989 demonstrated the presence of ischaemia in autopsy series from traumatic patients (Table 1). The 1978 series included 156 patients, 91% of whom had ischaemic hypoxic damage. In 1989, in another series of patients, at a time when there had been progress in resuscitation and in early management of brain trauma, still 80% of the brains at autopsy showed evidence of ischaemic damage.

In both series, in more than half of the patients the ischaemic damage was described as moderate to severe, and probably contributed to the fatal outcome. At that time the measurement of cerebral blood flow (CBF) yielded contradictory results. Only recently has there been compelling evidence, from in vivo measurements, of brain ischaemia in these patients. In a study by Freshman et al. of nearly 200 patients with severe head injury, early measurements of CBF revealed ischaemia within the first hour. In the same period, by measuring the arteriovenous oxygen difference, the first ominous sign of impending, brain ischaemia could be detected.

Secondary Damage

The concept of secondary damage after brain trauma, shaped in the 1970s, is that following the initial insult, secondary processes may arise that destroy more tissue and worsen the outcome. Initially ischaemia and hypoxia, and the progressive disturbance of many cell

Table 1. Publications on ischaemia in brain trauma

Graham et al. (1970, 1978, 1989)	Histopathological evidence	91%, 80% (autopsy)
Enevolden et al. (1977) Overgaard et al. (1981) Obrist et al. (1984) Muizelaar et al. (1989)	CBF measurements/ outcome	Contradictory findings
Yoshino et al. (1985)	*Early* CBF m. < 2h	Severe early ischemia
Bouma et al. (1991)	*Early* CBF m. 6–24 h AVD O_2	Early ischemia

CBF, cerebral blood flow; AVD O_2, difference in arterviovenous oxygen.

functions were considered to be mechanistically distinct. These disturbances evolve by themselves to destroy the cells (Fig. 1) Ischaemia constantly aggravates the progressive cellular changes, because they are very energy-demanding. At the same time the progressive cellular changes further increase ischaemia and hypoxia. In the 1980s, experimental work showed that ischaemia and hypoxia and the progressive cellular changes share common biochemical mechanisms with the surrounding stuctures (Fig. 2).

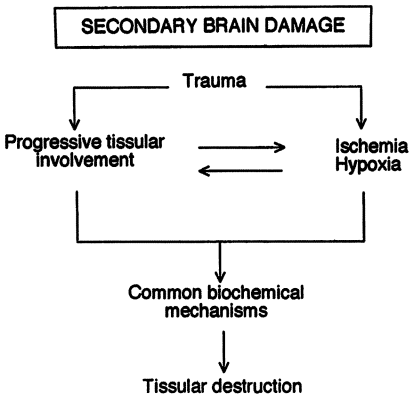


Fig. 1. Mechanisms of secondary brain damage

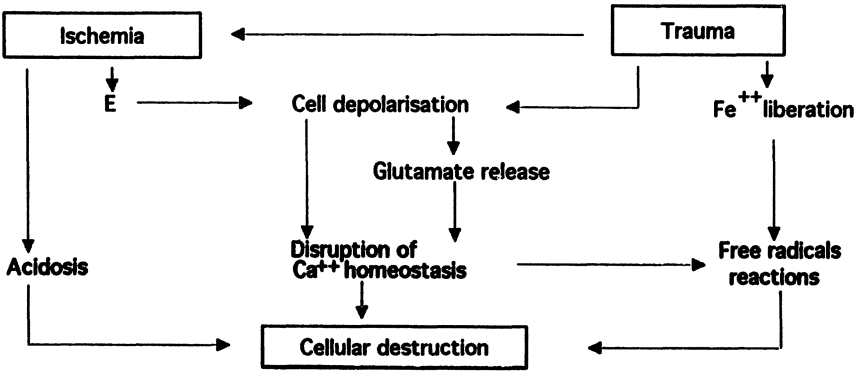


Fig. 2. Common biochemical cascades of tissue destruction, E, Energy

Secondary damage begins with cell depolarization. This leads either directly or through glutamate excitotoxic amino acid release to the destruction of calcium homoeostasis, which is the real core of the danger for the cell. This causes the activation of enzyme processes, leading to direct cell destruction and impaired mitochondrial function, free radical release and other processes.

In trauma, an extra factor is the liberation of iron around haematomers, which tremendously enhances free radical reactions. When true ischaemia is present, the lack of energy aggravates the destruction of calcium homoeostasis and leads to acidosis and eventually cell destruction. Thus, failure of calcium homoeostasis, free radical reactions and acidosis are the three major components of the biochemical cascades in cell destruction. Neurosurgeons are becoming more familiar with this scheme.

The fact that there is a time lapse between the primary and secondary damage in brain injury led to the idea that prevention of the secondary damage may be possible, given the time window for treatment. This gave a considerable thrust to pharmacological research on drugs that may, when given in this period, prevent or protect against such secondary damage.

Brain trauma starts with primary damage, the pure dissipation of the energy in the crash or trauma (Fig. 3). From then on there is progressive, and sometimes delayed, injury. Secondary insults may occur that contribute to secondary damage, and after the initial

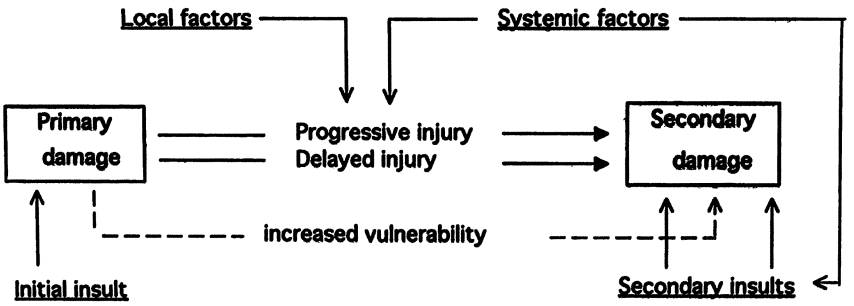


Fig. 3. Primary and secondary insults to the injured brain

trauma the brain has an increased vulnerability which worsens the secondary damage.

Progressive Injury

Progressive injury has three components: Firstly there are autonomous biochemical processes that destroy the cells; secondly, microcirculatory disturbance leads to vasogenic oedema; and thirdly, mass lesions occur. All three contribute to the destruction at and around the site of injury.

The autonomous biochemical processes which can occur without ischaemia include:

- cytotoxic oedema, affecting mainly the glia and dendrites
- membrane damage and mitochondrial failure, probably mainly from calcium disruption, and affecting all cell types including the neurones
- inhibition of protein synthesis.

These processes by themselves can kill neurones that were normal immediately after the trauma.

A second set of events in progressive injury includes disorders of the microcirculation and vasogenic oedema (Fig. 4). In the microcirculation vasoparalysis occurs with loss of autoregulation and vasospasm. This is not the vasospasm described by Professor Dorsch, but rather that which occurs just under an acute subdural

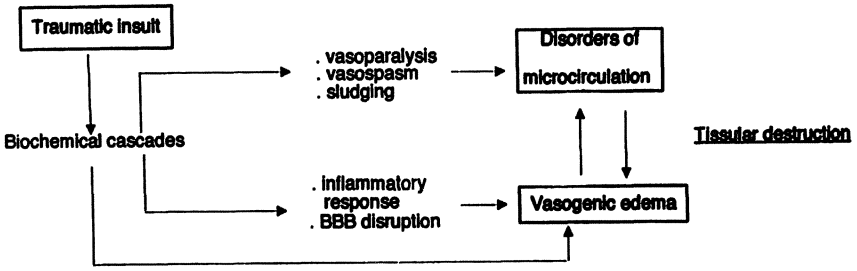


Fig. 4. Mechanisms of progressive injury. *BBB*, blood–brain barrier

haematoma, as shown by Bullock et al. There is also sludging in the microcirculation, with leukocyte accumulation. An inflammatory response occurs, with disturbance of the blood-brain barrier, and vasogenic oedema, which of course enhance one another.

The third type of progressive brain injury is purely ischaemic in nature and includes mass lesions. They develop in the brain, arising at sites of haematoma, oedema and contusions, with local compression around the mass lesion itself. This leads to focal ischaemia and to high intracranial pressure (ICP), diminished cerebral perfusion pressure, and global ischaemia.

Secondary Insults

In 1978 Douglas Miller published an account of 100 patients with severe head injury in *JAMA*. He showed that at least half of them had sustained, at some point between the trauma and the rest of the course of management, one or another type of secondary damage, which included hyperaemia, hypotension and hypercarbia (Table 2). Since then the same group has shown that such secondary injury can occur from the roadside to the hospital, within the hospital during transfer to the CT scan suite, and (in a paper by Patricia Jones of the Edinburgh team, in the *Journal of Neurosurgical Anaesthesia*) even in intensive care units.

Secondary insults may manifest in a reduction of the oxygen supply, resulting in hypoxaemia, hypotension, anaemia and hypercarbia. They may also have systemic or intracranial causes, such

Table 2. Secondary insults in brain injury

	Systemic	Intracranial
$\searrow O_2$ supply	Hypoxaemia Hypotension Aneaemia Hypocarbia	Elevated ICP Vasospasm Loss of autoregulation
$\nearrow O_2$ consumption	Pyrexia	Seizures
$\nearrow$ Acidosis	Hyperglycaemia Hypercarbia	

as an elevated ICP. By enhancing the demand of oxygen, secondary insults can also lead to pyrexia or seizure. Hyperglycaemia also contributes to acidosis.

Increased Vulnerability

In 1986 Ishige showed that a combination of fluid percussion injury and concurrent hypoxia led to a lesser recovery of neuronal function and an increase in histopathological damage compared to a fluid percussion injury alone. In combination with the injury, even a level of hypoxia that is normally well tolerated by normal rats caused an increase in damage. Whether this is due to an impaired response of CBF to hypoxia, or to extraction of oxygen, is not settled.

L.W. Jenkins and colleagues (1986–1989) subjected cats and rats to a sublethal level of brain injury. One hour later he added a sublethal level of ischaemia. The combination was lethal, with severe delayed hippocampal neuronal necrosis. Why this happens is not known – perhaps it is due to impairment of autoregulation, seizures, durable energy failure or cumulative DID – but the two sublethal types of injury make the brain more vulnerable to agonist/receptor interactions and biochemical cascades. Even very slight injury of short duration may cause grave deterioration in the brain.

In most severe cases of brain trauma, a traumatic penumbra around the site of the contusion results. In this area microcirculatory disorders, oedema, a biochemical cascade, and metabolic compro-

mise occur. This local evolution is considerable enhanced by systemic factors. When systemic factors such as hypoxaemia and changes in blood pressure are added to the local evolution of the intracranial mass and a rise in ICP, both focal and global ischaemia occur.

Summary

The general paradigm of brain trauma is primary brain damage leading to brain ischaemia through mechanical and systemic disorders. This ischaemia can be prevented by taking care of the systemic disorders, the ICP and mass lesions. The ischaemia also leads to biochemical cascades, which are triggered by the primary damage. Hopefully some protection may be offered against them in the future.

Systemic and Intracranial Mechanisms of Brain Ischaemia: Monitoring the Threat

M. Dearden

Brain ischaemia is found in 88%–92% of brains at post-mortem. About 33% of such brains show medial-occipital necrosis, and boundary zone ischaemia between middle and anterior territories occurs in 22% of patients. Global ischaemia due to raised intracranial pressure (ICP) was shown by Douglas Miller to occur in 10%–15% of adults during intensive care; if this global ischaemia is associated for long periods with a low cerebral perfusion pressure (CPP) (under 50 mm Hg), the mortality rate is as high as 90%. The Lund group are advocating CPP management below 50 mm Hg, but this is a different scenario from a CPP of 50 plus a very low ICP.

The causes of brain ischaemia are threefold:

- Inadequacy of flow delivery
- Inadequacy of cerebral artery content of oxygen and substrate
- The inability of the brain to utilize oxygen which is a cytotoxic problem.

As Professor Cohadon showed, all three mechanisms may be involved after brain trauma.

The secondary insults after brain injury have systemic and intracranial causes with crossover between them. The systemic secondary insults, some of which can be avoided, are referred to as the nine deadly H's (Table 3). Hypoxaemia and hypotension are the most important, especially in the early phase of management. Reduction in oxygen content can be due to an inadequate oxygen supply, inadequate carriage, or damage to the carriage mechanism. Hypotension can be due to hypovolaemia, which, in head-injured patients other than children, usually means bleeding from some

Table 3. Secondary insults after brain injury: the nine deadly H's

Hypoxaemia (hypoxia, anaemia, carbon monoxide)
Hypotension (hypovolaemia, cardiac disorder, pneumothorax)
Hypercapnia (respiratory depression)
Hypocapnia (hyperventilation)
Hyperthermia (hypermetabolism/stress response)
Hyperglycaemia (hypothermia/dextrose)
Hypoglycaemia (parenteral nutrition)
Hyponatraemia (hypotonic fluids)
Hypoproteinaemia (malnutrition)

place other than the head. Hypotension can also result from cardiac trauma or compression from pneumothorax.

Hypercapnia is particularly important in the early phase of injury, when there may be respiratory obstruction and/or depression, and can be the result of the use of sedative agents. It increase intracrainal pressure and volume and may compromise cerebral perfusion as a result. In contrast, hypocapnia results when the anaesthetist ventilates patients excessively and may lead to cerebral ischaemia from an inadequate cerebral blood flow.

High temperature increases oxygen demand by increasing the metabolic rate of the brain and the body and may lead to local areas of ischaemia in the brain. Hyperglycaemia together with increased lactic acidosis and further destruction. For advocates of hypothermia, the concomitant use of dextrose should be avoided because of this increased risk.

Hypoglycaemia, which may occur with parenteral nutrition regimens using insulin, is equally as bad, since the brain is provided with inadequate substrate. Finally, hyponatraemia, and hypoproteinaemia to a much lesser extent, may lower serum osmolality, which can lead to an ingression of hypotonic solution across semipermeable membranes. Hyponatraemic diffuse brain swelling may occur, particularly in women.

The following intracranial secondary insults, which have already been covered, may lead to intracranial hypertension:

- Haematoma, surgical or otherwise
- Oedema, defined as an increase in brain water content

- Engorgement of the brain vascular system?
- Hydrocephalus, more rarely

Other secondary insults include seizure activity, causing an increase in brain oxygen demand, vasospasm, and the potential for infection, such as meningitis and ventriculitis, either from monitoring techniques or from CSF contamination.

The first stage at which brain injured patients can become hypoxic is at the accident scene, and on their subsequent journey by road, boat and plane to reach a neurosurgical centre. Professor Jannett showed in his pivotal 1981 study that there is a clear inverse relationship between recovery rate and the development of hypoxia and hypotension (Table 4). If neither condition has developed on arrival at the neurosurgical unit, there is a substantial difference in outcome compared to those with hypoxia and hypotension.

Clearly in the early phase after head injury it behoves the intensivist and the Accident and Emergency Department to carry out early resuscitation and monitoring. Insults can still occur in the intensive care environment. Patricia Jones performed her study in Edinburgh in such an environment with complex monitoring; yet about 80% of the patients were still receiving some form of insult, such as ICP elevations, low or high blood pressure and low CPP. Insults, therefore, occur very often (Table 5).

There are studies of predictive outcome of different insults. The important ones are hypotension and intracranial hypertension, presumably because of their contribution to reduced CPP. They adversely affect the outcome, not just the mortality. Hyperpyrexia was a very important predictor of outcome in the Edinburgh study. This is not surprising, given that hypothermia has been advocated as

Table 4. Effects of hypoxia and hypotension on outcome of brain injury (Gentleman and Jennett 1981)

	Patients (*n*)	Dead (%)	Good recovery (%)
Hypoxia and hypotension	5	100	0
Hypotension only	12	75	8
Hypoxia only	29	59	17
Neither factor	104	34	34

Table 5. Proportion of patients monitored after brain injury with various types of additional insult

Variable	Monitored patients (*n*)	Patients with insults (*n*)	Patients with insults (%)
ICP	60	50	83.3
Hypotension	91	69	75.8
Hypertension	91	83	91.2
CPP	58	45	77.6
Hypoxaemia	90	39	43.3
Cerebral Oligaemia	11	8	72.7
Cerebral Hyperaemia	11	9	81.8
Hypocarbia	57	21	36.8
Hypercarbia	57	17	29.8
Pyrexia	87	76	87.4
Bradycardia	99	8	8.1
Tachycardia	99	64	64.6
Global Cerebral Hypoxaemia	9	2	22.2
Global Cerebral Hyperaemia	9	8	88.9

ICP, intragranial pressure; CPP, cerebral perfusion pressure

a protective regime, and has been shown in many experimental studies to be beneficial. Recently, the use of jugular venous oxygen saturation to monitor cerebral oxygen and consumption has shown that jugular bulb venous desaturation also predicts outcome (Table 6).

ICP should be measured in the following head-injured patients (Table 7): patients with an intracranial haematoma or contusion who are in coma; patients without contusions or operable haematomas with a coma score below 6 on resuscitation or a motor score below 4;

Table 6. Predictors of outcome in brain injury: secondary insults in intensive care unit

Hypotension (reduced CPP)
Hyperpyrexia
Intracranial hypertension (reduced CPP)
Jugular bulb venous desaturation

CPP, cerebral perfusion pressure

Table 7. Brain injury: indications for intracranial pressure monitoring

Coma with intracranial haematoma or contusion
G.C.S. < 6 (motor < 4)
Loss of 3rd ventricle and basal cisterns on CT
Tight brain after haematoma evacuation
Multiple injuries necessitating IPPV

G.C.S., Glasgow Comia Score; CT, computed tomography; IPPV, intermittent positive pressure ventilation

patients with CT evidence of intracranial hypertension; patients with a "tight" brain at operation; and patients with multiple injuries who will require intermittent positive pressure ventilation, who also have a head injury. This last group of patients is particularly vulnerable to secondary injuries and have many of them.

However, ICP is only as good as its ability to monitor CPP. ICP is becoming less important in the management of patients, whereas CPP is becoming more important.

Jugular Bulb Oxygen Saturation Monitoring

Although jugular bulb oxygen saturation monitoring is a difficult technique, some workers have been able to make good use of it. Claudia Robertson looked at the number of valid desaturations occurring in the intensive care unit. She divided patients into those with no, one and multiple desaturations and defined desaturation as below 50% for more than 10 min. She related the total number of desaturations to a 3-month outcome and found a substantially higher mortality (70%) in patients with more than one desaturation than in those with none (Table 8). Most of the episodes of desaturation occurred within the first 24 h of intensive care.

Catherine de Deyne of Ghent used ultra-early monitoring in 150 head-injured patients. She found that on admission an SJO_2 below 55% valid for a 30-min period occurred in 61 of the 150 patients. In first 6 h of intensive care, a further 24 patients showed episodes of desaturation, so that 56% of patients were undergoing episodes of

Table 8. Relationship between the number of episodes of jugular desaturation and neurological outcome at 3 months after injury

Desaturations (*n*)	3-month Glasgow Outcome Score Dead (*n*) (%)	Total (*n*)
None	10 (17.8)	56
One	10 (45.5)	22
Multiple	12 (70.6)	17

sustained hypoperfusion or worse during that time (Table 9). Furthermore, 45% of the episodes of desaturation occurred in the first 6 h of intensive care. It is now clear that the ischaemic insults occur early, both during transport and in the first few hours of intensive care. Therefore a big therapeutic "push" in this time window will probably be beneficial.

Most of the Ghent patients had a CPP below 70, largely associated with a normal ICP (Table 10), so that there was some systemic hypotension. The second most common cause was hyperventilation, with a low pCO_2. The most important conclusion of this paper was that when CPP was restored above 70 mm Hg by volume loading or induced hypertension, and when normal ventilation was restored by normalizing pCO_2, all of the desaturation episodes could be corrected. Hyperventilation, despite a reasonable mean arterial pressure, can give rise to extremely low jugular desaturation; simply restoring the CO_2 to a normal level can correct it.

Table 9. Ultra-early jugular oximetry after severe brain trauma showing the proportion of patients with episodes of desaturation (De Deyne et al. 1995)

SjO_2 < 55% on admission to ITU (*n*) (%)	SjO_2 < 55% during first 6 h of ITU (*n*) (%)	Total patients (*n*)(%)
61 (40.6)	24 (16)	150 (85/150 = 56.6)

Mean 4.8 h, range 2–9 h post trauma. Desaturation <55% >30 min (verified).

Table 10. Ultra-early jugular oximetry after severe brain trauma showing causes of desaturation (SjO_2 < 55%) in the first 6 h of ITU (De Deyne et al. 1995)

Cause	Patients (*n*) (total=85)
CPP below 70 mm Hg (ICP <20 mm Hg)	42
CPP below 70 mm Hg (ICP >20 mm Hg)	7
$PaCO_2$ below 30 mm Hg (4 kPa)	29
Both	7

Mean 4.8 h, range 2–9 h posttrauma
CPP, cerebral perfusion pressure; ICP, intracranial pressure

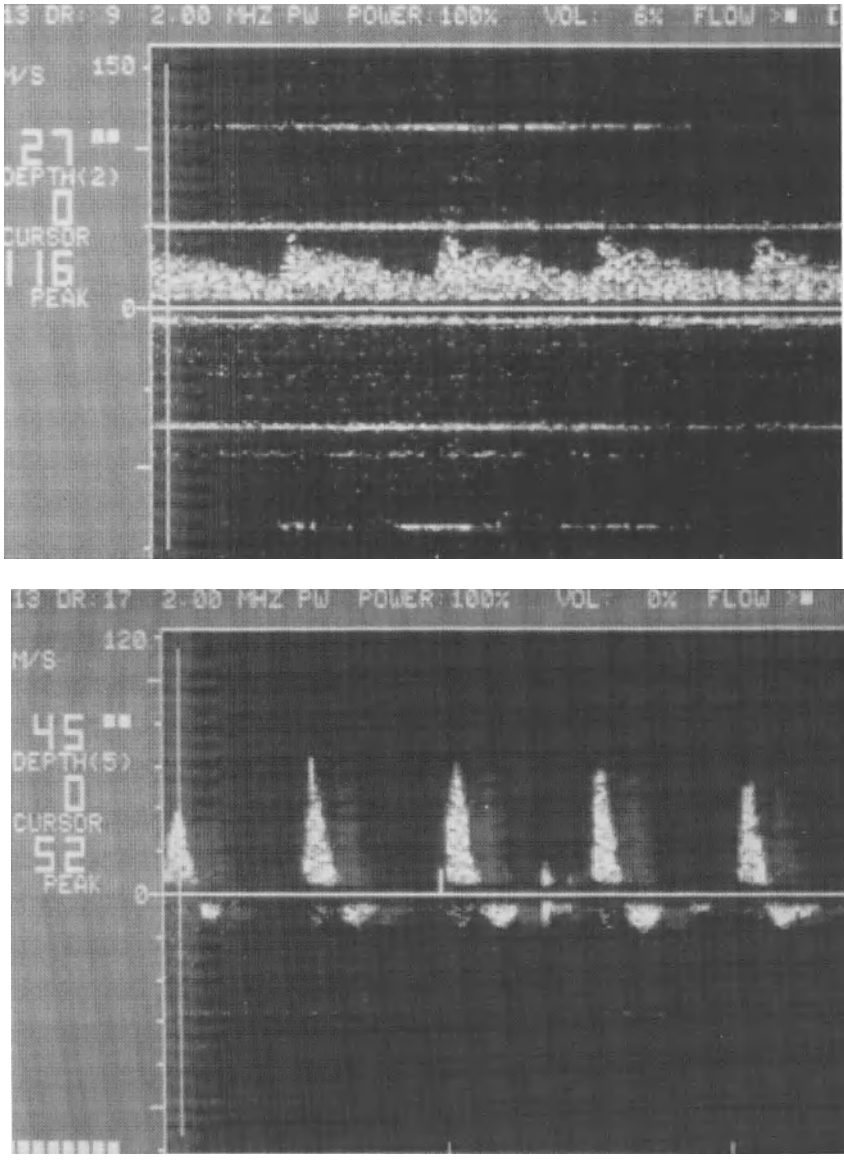
Transcranial Doppler

Transcranial Doppler measures cerebral blood flow (CBF) velocity, and therefore the relationship between CBF and vessel diameter. It can measure systolic, diastolic and time-average mean velocities, and calculate a pulsatility index (systolic minus diastolic, divided by the mean), which is dimensionless.

A trace of Doppler flow shows a systolic peak, a decline and a diastolic value (Fig. 5a). As the ICP rises, and, more importantly, as CPP falls, the diastolic component disappears, and an oscillating flow pattern occurs (Fig. 5b). In a plot of jugular saturation, pulsatility index and CPP, the first two parameters bear no relationship to CPP when the latter is above 70 mm Hg. However, with a progressive fall in CPP below 70 mm Hg, there is a rise in pulsatility index and a progressive fall in jugular saturation (Fig. 6), regardless of whether the cause of the compromised CPP is due to low blood pressure or to a high ICP. This suggests a progressive autoregulatory failure to deliver oxygen as CPP falls in these patients.

Therefore the concept emerges of a critical CPP in head-injured patients, below which autoregulation can no longer sustain oxygen delivery.

Doppler can also detect very high flow velocities (Fig. 7). When these are unilateral and associated with normal jugular saturation, it is feasible to postulate that this represents vasospasm in the insonated vessel. If patients who have developed a non-contusion-related infarct are examined in the territory of the high flow velocity,



a

b

Fig. 5. a A normal Doppler trace. **b** Doppler trace showing oscillating flow pattern with falling cerebral perfusion pressure

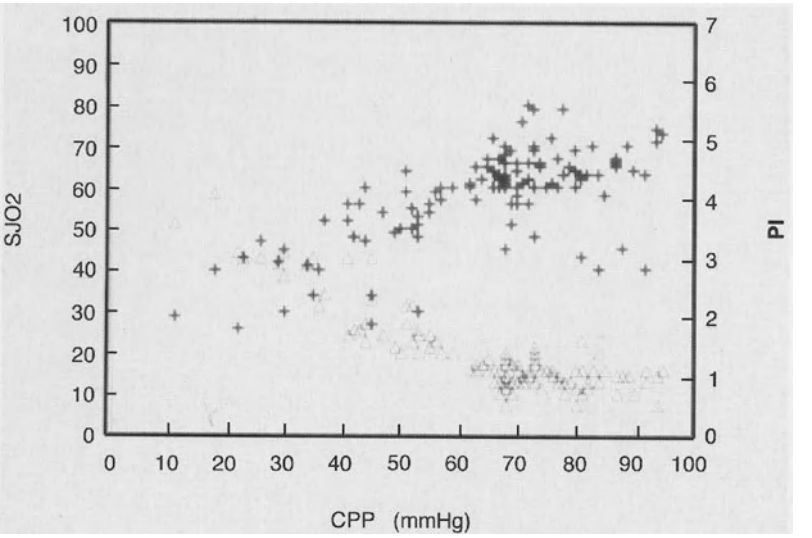


Fig. 6. Relationship between cerebral perfusion pressure, jugular saturation (+) and pulsatility index (Δ)

and their CPP is related to jugular saturation and pulsatility index, the breakpoint is higher, nearer to 80 than 70 mm Hg (Fig. 8). This suggests that in patients with presumed vasospasm the critical threshold is probably higher. Such patients need a higher CPP to avoid hypoperfusion.

Patient Management

Michael Rosner reported on head-injured patients in whom CPP was maintained above 70 mm Hg, paying less attention to ICP, using volume loading and/or induced hypertension. As controls, he used the trauma coma data bank, choosing patients with a Glasgow coma sum score of 3 or 4. He found 208 of 551 patients with this score, and compared them with his own patients with the same score (53 patients out of 157; Table 11).

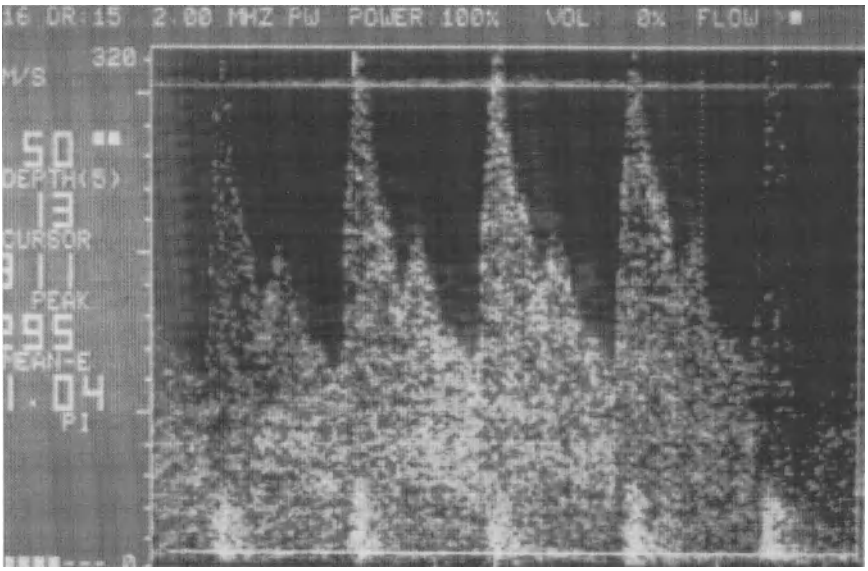


Fig. 7. Doppler trace with very high flow velocity

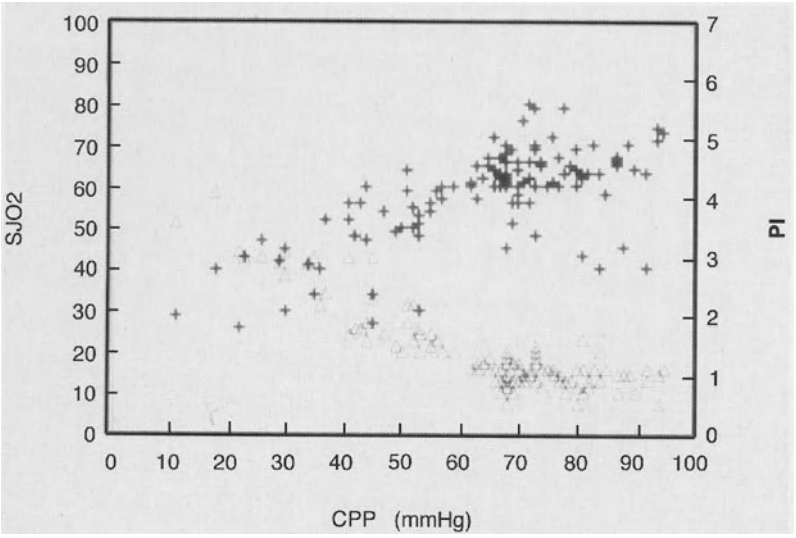


Fig. 8. Relationship between cerebral perfusion pressure, jugular saturation (+) and pulsatility index (Δ) in a patient with presumed vasospasm (noncustion infarct)

Table 11. Comparison of mortality in trauma coma data bank subjects and patients in whom cerebral perfusion pressure was maintained above 70 mm Hg. (M. Rosner et al.)

	GCSS 3 or 4 (*n*)	Mortality (%)
TCDB	208/551	65
CPP > 70 mm Hg	53/157	45

GCSS, Glasgow Coma Sum Score; TCDB, trauma coma data bank; CPP, cerebral perfusion pressure

His endpoint was mortality, which is not ideal for head injury. Nevertheless there was a trend towards a lower mortality. Whether there is an improvement in outcome is more important, of course, but these preliminary data do suggest a direction for future trials.

Table 12. Management of intercranial hypertension after brain injury

ICP > 25 mm Hg (first 48 h)
CPP < 70 mm Hg
  Eliminate avoidable secondary causes
  Consider CT +/– surgery
  Drain CSF

ICP > 25 mm Hg
CPP < 70 mm Hg
  Mannitol 0.25–0.5 g/kg over 20 min

ICP > 25 mm Hg
CPP < 70 mm Hg
  Hyperventilation ($PaCO_2$ >3.5 kPa)

ICP > 25 mm Hg
CPP < 70 mm Hg
  Consider hypertensive therapy with CVS monitoring
  Consider further hyperventilation with SjO_2 monitoring
  Consider moderate hypothermia (34–35 °C)
  Consider barbiturate therapy
  Consider decompressive craniotomy

ICP, intracranial pressure; CPP, cerebral perfusion pressure; CT, computed tomography; CSF, cerebrospinial fluid; CVS, cardiovascular

I have put together a plan for monitoring and managing raised ICP and reduced CPP after head injury, given the current data (Table 12). Most problems arise during the early phases of transport, resuscitation and early intensive care, usually times when tired junior staff are managing patients.

An ICP above 25 mm Hg (as an arbitrary figure) and a CPP below 70 mm Hg should be the targets. The avoidable secondary causes, and any surgical lesion, must be eliminated. Draining CSF, if it can be done, is probably one of the easiest ways to reduce ICP and improve CPP in the short term, but the final aim should not be just ICP reduction. The same principle applies to the use of mannitol. Hyperventilation has a lower priority and should be used with considerable caution, especially at levels of $PaCO_2$ around 3.5 kPa or less.

If these methods fail, induced hypertension could be considered, with cardiovascular monitoring. We often find that not only does the CPP go up, but the ICP goes down. Further hyperventilation could be considered, but the ICP goes down. Further hyperventilation could be considered, but only if monitoring shows that it is not producing ischaemia. The use of moderate hypothermia, barbiturate therapy and decompressive craniotomy are more controversial, and depends on personal preferences. CPP management is crucial.

Pathological and Clinical Evidence of Ischaemic Damage in Brain Trauma

G. Teasdale

Professor Cohadon talked about the mechanisms and pathophysiology of ischaemic damage, and Dr Dearden presented evidence that these events occur in patients. These insults leave their mark on the brain and are detected both at post-mortem (which has been known for a long time) and using modern ways of detecting ischaemic insults, in living patients.

The evidence for the frequency of ischaemic damage in head-injured brains came more than two decades ago from the work of Graham and Adams in association with Brian Jennett in Glasgow. In fatal head injuries it was present in 91% of cases. In many cases it was found to occur in different distributions in the cerebral cortex, in boundary zones, multifocal patterns and arterial territories (Table 13). In 8 of 10 cases it was also present in the hippocampus. This is extremely interesting, because of memory problems in head injury, and because the hippocampus is a site of excitotoxic brain damage due to glutamate activity – the "hot topic" of the moment. In some patients the ischaemia was of a diffuse pattern that could be related to different mechanisms.

The boundary zone pattern, with ischaemia between arterial territories, is thought to represent episodes of low cerebral perfusion pressure (CPP), of the type referred to by Dr Dearden, in which blood flow is reduced globally throughout the brain, but not totally ceased. When there is circulatory arrest, as in cardiac arrest, respiratory arrest or sometimes in status epilepticus, there is a pattern of diffuse or multifocal destruction throughout the cerebral cortex. In many patients there is an ischaemic pattern corresponding to the territory of a major cerebral artery. This may be in the posterior cerebral region due to compression from shift, but it may also be in

Table 13. Patterns of cortical ischaemic damage and pathogenesis

Pattern	Mechanism
Boundary zone	Perfusion failure
Diffuse/multifocal	Circulatory arrest
Arterial territory	Occlusion/compression

the territory of the middle cerebral artery, perhaps related to an overlying haematoma.

A Pathologist's View of Ischaemic Brain Patterns

The pathologist sees many patterns of ischaemia at autopsy. Figure 9 shows the brain of a patient with a burst temporal lobe and an overlying subdural haematoma that was evacuated. After death, discolouration and damage was found throughout the territory of the middle cerebral on that side.

Focal ischaemia occurs not just in major arterial territories. It also occurs around areas where there is a combination of contusion and laceration. Studies of biopsies from pericontusional tissue show

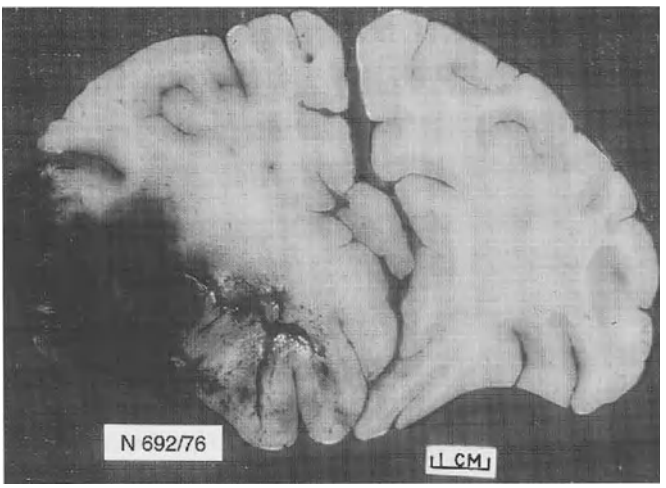


Fig. 9. Brain after middle cerebral artery ischaemia

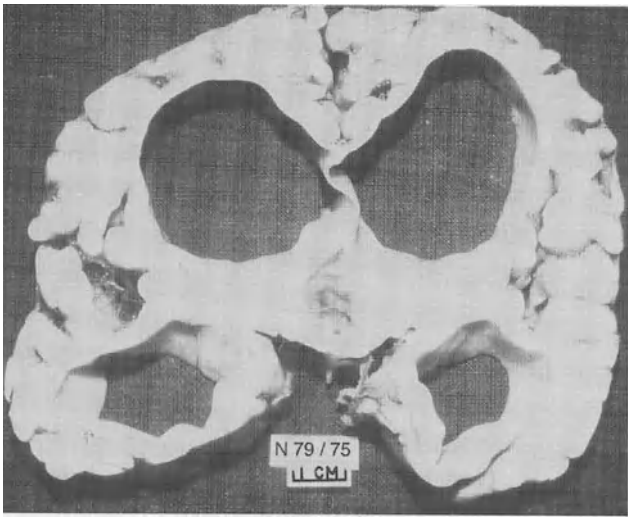


Fig. 10. Brain after long-term survival of cardio-respiratory arrest

features of cytotoxic damage and, later, of vasogenic oedema. Focal ischaemia is common. The different patterns of ischaemia after injury are subtle, but scattered areas of wedge-shaped damage clearly correspond to boundary zones between the anterior and middle cerebral arteries. This is caused by perfusion pressure failure.

Figure 10 shows a brain from a patient who survived a long time, but who had severe white matter atrophy and a diffuse loss of cerebral cortex texture. This is a pattern of diffuse cortical damage, arising from a cardiorespiratory arrest very soon after the injury.

The post-mortem evidence for brain ischaemia was well known in the late 1970s, at which time cerebral blood flow measurement was widely used in the investigation. Yet very few of the studies carried out in the 1970s and 1980s actually showed blood flow levels below the ischaemic thresholds that Professor Cohadon described. Flow was certainly reduced, but not down to the levels expected to produce ischaemic brain damage.

This made people ask the question: Had insults already occurred when the person came into intensive care? Dr Dearden showed that this was not the case. More information was needed before the

answer could be given. It emerged that ischaemia was not detected in the patients for three reasons: (1) To detect diffuse ischaemic condition the measurement have to be made very early after injury; (2) the measurements must be made continuously or very frequently to detect the brief ischaemic events of the type Dr Dearden described; (3) to detect focal ischaemia, Xenon external detection methods cannot be relied upon Tomographic imaging techniques, such as CT and SPECT, must be used.

Diffuse Ischaemia

Data from Richmond, VA, USA, emphasize the need to carry out flow studies early. Global cerebral blood flow (CBF) measured in patients at different times post-injury showed that even 5 h after injury the average blood flow is in the region of 40–50, a level that would certainly not be expected to give ischaemic damage, and which is just consistent with coma. Only when measurements were made within 4 h of injury was diffuse ischaemia detected, and there was a wide standard error. At 5 h after injury there was no corrleation between CBF and clinical state. It was only in the first 4 h that the correlation emerged.

Claudia Robertson of Houston related occurrences of jugular desaturation to outcome at 3 months. She showed very clearly in these very severely injured patients that an increasing frequency of brief ischaemic insult was associated with an increasingly poor outcome (Table 14). To detect such episodes, monitoring must start early and be continuous.

Table 14. Episodes of jugular desaturation ($SjVO_2$<50%) and outcome at 3 months

Episodes (*n*)	*n*	Dead/Veg	Severe disability	Moderate/good recovery
None	40	10	14	16
One	21	15	2	4
Two	11	8	3	–
Three	5	4	1	–

Focal Ischaemia

How can focal ischaemic events be detected in living patients? Shift, subdural haematoma, some contusion and haemorrhage, which is evacuated, is common among patients before operation. A large area of low density corresponding very well with the pathological picture of middle cerebral artery infarction is subsequently detected. This is associated with continuing and even increased shift. Ischaemia can be seen with CT scanning after the brain has become irreversibly damaged. Unfortunately the ischaemia cannot be monitored during its evolution.

SPECT scanning techniques offer the opportunity to map cerebral perfusion. CT scans of a head-injured patient from a Japanese colleague showed little, except for some compression of the cisterns (Fig. 11, left half), whereas a SPECT scan of the same patient showed a very large area of hypoperfusion in the right hemisphere (Fig. 11, right half). This could not have been seen on a CT scan. SPECT scans

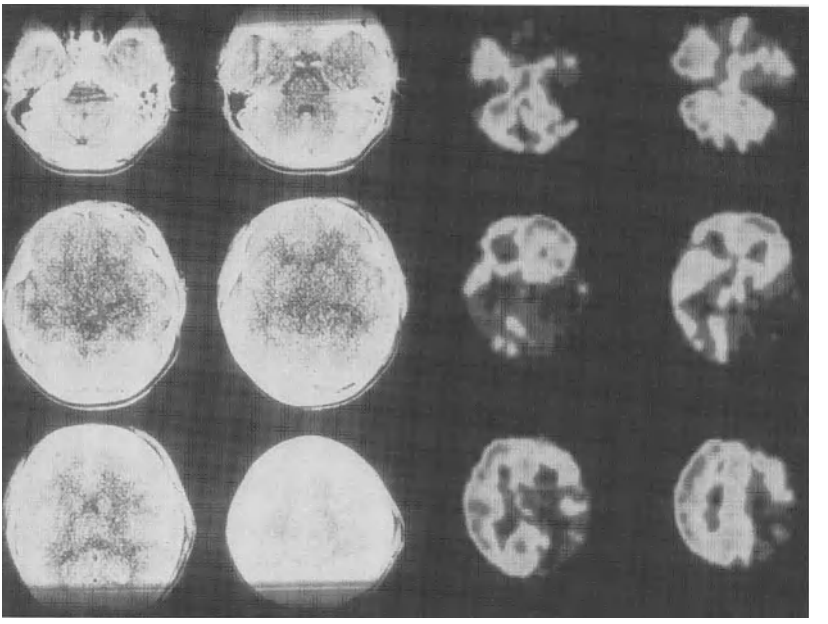


Fig. 11. Computed tomographic scan (*left*) and Single photon emission computed tomography scan (*right*) of patient after head injury

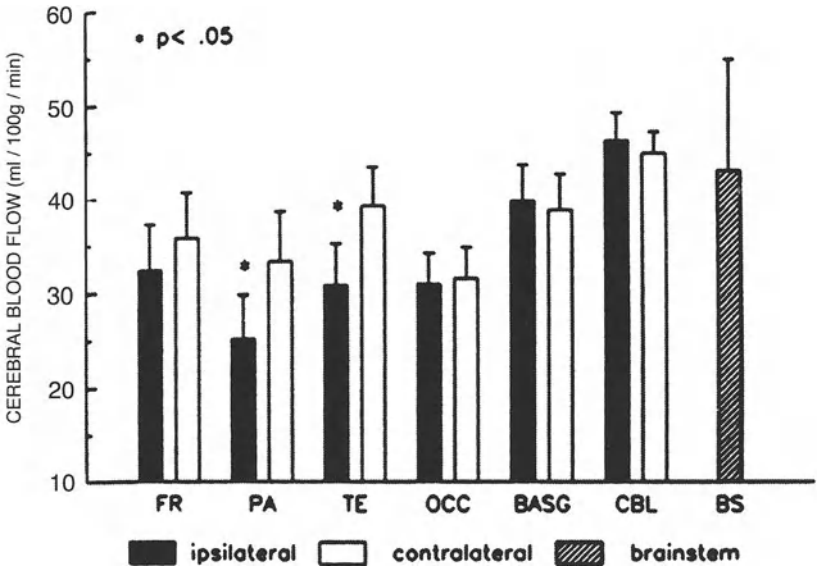


Fig. 12. Xenon-enhanced computed tomographic scan substraction studies in patients with subdural haematomas

can pick up areas of reduced perfusion living patients before they have produced structural damage. They can show areas of reduced perfusion before evacuation of the haematoma, and studies after evacuation show that the ischaemia persists, with the development of CT signs.

Xenon CT scanning can give the localization and absolute measurements of flow. Xenon-enhanced CT scan substraction studies from Ross Bullock of Richmond showed Xe distribution, and therefore blood flow, in a series of patients with subdural haematomas. Reduced flow was shown in cerebral areas ipsilateral to the compressive lesions (Fig. 12). Again, however, these flow levels are not those expected to produce ischaemic damage.

Other techniques may have to be used to detect ischaemic mechanisms in the living patient. We are investigating two ways of identifying ischaemia and ischaemic/metabolic/neurochemical processes in living patients.

An example is a CT scan in a patient with a large subdural haematoma and midline shift and with a small contralateral frontal

contusion and subdural haematoma (Fig. 13). Magnetic resonance imaging showed that within an hour of evacuation of the haematoma, the midline shift was much less and the ventricles were expanded again. The brain on this T1-weighted sequence did not appear to be severely damaged.

However, the proton spectrum revealed a different situation (Fig. 14). On the left there were peaks corresponding to choline and creatinine; in the middle there was a peak corresponding to anatidyl aspartate, which is considered to be a neuronal marker. These are normally present in the brain. What is not normally present is the peak corresponding to lactate, which was confirmed by repeating the sequencing and inversion. Spectra which were taken from an exactly comparable site in the contralateral hemisphere did not show lactate. This was the first time that lactate had been demonstrated intracellularly in a patient with acute head injury, showing that, despite evacuating the haematoma, there were still ischaemic metabolic conditions present.

The next step, if ischaemia continues, is to investigate the neurochemical consequences. Can excitotoxicity be detected in living patients? Our current research is focused on this area. We are using

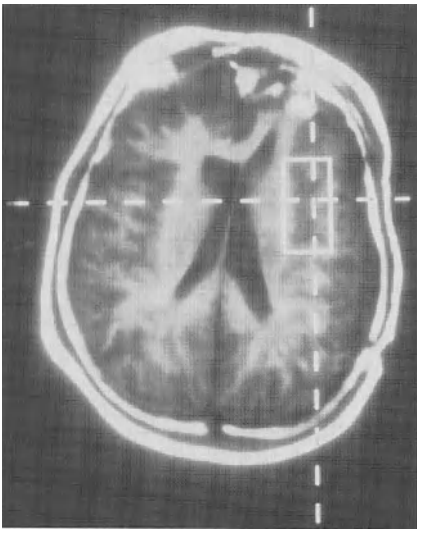


Fig. 13. Computed tomographic scan of a patient with a large subdural haematoma

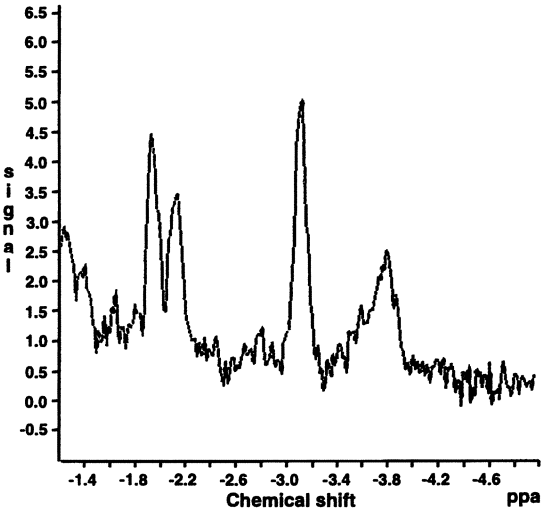


Fig. 14. Proton spectrum in the same patient as in Fig. 13

radiolabelled MK801 to detect glutamate receptor activation in life. MK801 is the first practical glutamate channel blocker, which is labelled with iodine for detection by SPECT. The glutamate receptor opens when activated by glutamate. Other blockers stick to different recognition sites; MK801, however, sticks in the open channels of the receptor. This is therapeutically advantageous, because it adheres to sites that are activated, and, like Ehrlich's "magic bullet", it sticks in the site where damage is taking place.

By labelling the receptor and locating it in the brain, the areas of damage can be identified. A CT scan and a SPECT scan with radiolabelled MK801 were compared in a patient with a large deep haemorrhage. The first SPECT picture 10 min after injection of the labelled MK801 showed the large deficit expected of a haematoma (Fig. 15 left half). It also showed that flow around the haematoma was reduced compared to that at contralateral sites. In this flow region, the penumbral conditions in which brain metabolism is unstable may be found. Between 10 and 90 min after injection, increasing amounts of glutamate bound to activated receptors. The difference between the 10- and 90-min scans was that on the later scan, an area of intense "hot" activity appeared, indicating the

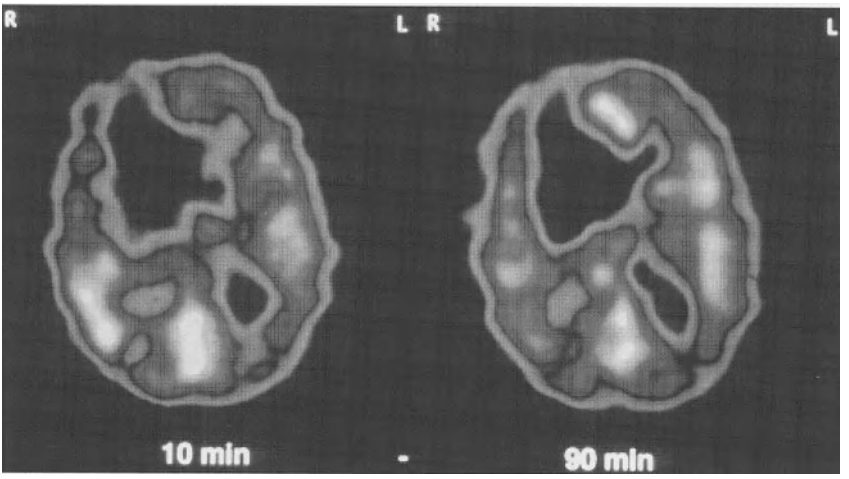


Fig. 15. Single photon emission computed tomographic scans with radiolabelled MK801 of a patient with subdural haematoma showing glutamate receptor activation

trapping of radiolabelled MK801 (Fig. 15, right half). This was the first evidence of glutamate receptor activation and excitotoxicity in man. This may be the way to decide which patients are suitable for glutamate antagonist treatment.

Summary

Many mechanisms of head injury involve ischaemia as the common path to brain damage. Ischamia in head injury occurs at the site of trauma, before hospitalization, in hospital, when undergoing surgery, and even under anaesthesia and in intensive care. There are many opportunities for detecting and treating ischaemia. Our treatment for ischaemic head injury is being increasingly targeted to its cause.

Subarachnoid Haemorrhage and Associated Vasospams: Do They Play a Role in Traumatic Brain Ischaemia?

N. Dorsch

Much has been heard about the immediate changes after brain injury and the secondary insults that occur when things go slightly wrong in intensive care. This presentation focuses more on the secondary changes that occur in the days after brain injury that are not necessarily related to disasters in management.

Vasospasm, which occurs after aneurysmal haemorrhage, causes delayed ischaemic deficit (DID) and occurs in nearly one-third of patients. As shown by Fisher it is related to the amount of subarachnoid blood on a CT scan. Once vasospasm or DID has occurred, the outcome is very poor without specific treatment: nearly one-third dies and around the same number is left with a permanent deficit (Fig. 16a).

During the 1970s and 1980s, patient management with variations of HHH therapy started, and this led to a considerably lower incidence of DID (Fig. 16b). Although this has never been submitted to a proper trial, the results with large numbers of patients are quite likely to be valid. HHH also improves the outcome after ischaemic deficits have occurred.

In the mid-1980s nimodipine was introduced, and several studies showed that it improved the survival rate in all subarachnoid haemorrhage (SAH) patients, not just in those with delayed ischaemia (Fig. 17). It also increased the proportion with a good outcome. Tettenborn and Deeker's meta-analysis of five or six very well controlled trials showed a 40% reduction in the risk of bad outcomes when nimodipine was used after aneurysmal haemorrhage.

More specifically, extrapolating from the figures on prophylaxis and treatment of SAH which nimodipine, taking 1000 patients with aneurysmal haemorrhage without specific treatment, about 20%

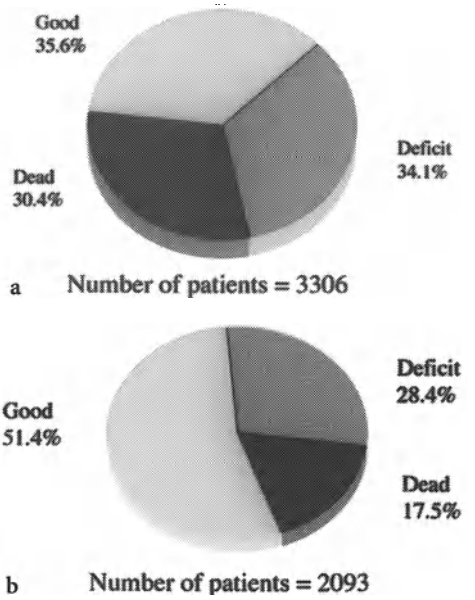


Fig. 16. **a** Natural history (105 reports) of delayed ischaemic deficit (DID). **b** DID outcome (72 reports) after HHH theraphy

would be affected by delayed vasospasm. With nimodipine and fluid management, which is the best modern treatment, the number who would be affected by vasospasm is reduced considerably (Table 15).

There is no doubt that when subarachnoid blood is present after SAH, vasospasm is a real problem but can be treated. In some situations, this can apply after head injury. A long time has passed since vasospasm was first shown in head injury. In the 1960s there

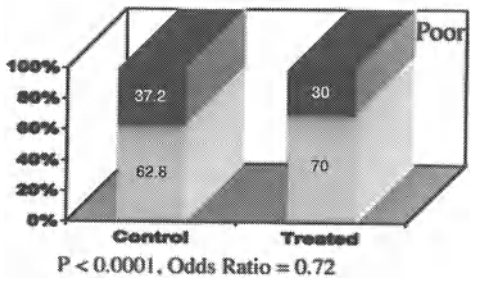


Fig. 17. Patient outcome in nimodipine trials (poor outcome 114 studies)

Table 15. Outcome in 1000 patients with aneurysmal haemorrhage

	No treatment	Nimodipine
DID	327	133
Fatal	99	24
Residual deficit	111	42
Total affected	210	66

DID, delayed ischaemic deficit

were isolated reports, also in Glasgow, but the numbers of patients in which it was shown in angiograms were quite large. Recently transcranial Doppler has shown it more often (Table 16).

Some of the trials did not apply the proper criteria for distinguishing vasospasm from delayed hyperaemia. This is important, as Lindegard has shown. There is no doubt, however, that many patients with raised transcranial Doppler velocity had vasospasm. In this group, the patients who had the most severe SAH on a CT scan had significantly more delayed infarcts than control patients.

In one centre involved in the HIT-I study with nimodipine, the two treatment groups were clinically much the same, but the transcranial Doppler velocities were significantly lower in the patients receiving nimodipine. This suggested that vasospasm was a problem.

In the HIT-II study, nimodipine not significantly improve outcome; however, the patients in the control group with traumatic subarachnoid haemorrhage (TSAH) had a significantly different outcome from those without it (Table 17). The overall Glasgow coma scale was very different, and there was a very significant difference in outcome between those with a coma score of 1–2 and those with a

Table 16. Traumatic vasospasm defined by transcranial Doppler

Author	Year	Patients (*n*)	%Spasm
Compton et al.	1987	25	68
Weber et al.	1990	35	40
Martin et al.	1992	30	27
Chan et al.	1992	50	34

Table 17. HIT-II nimodipine study: outcome with and without traumatic subarach-noid haemorrhage

	tSAH (%)	No SAH (%)
Good	40	70
Poor	60	30

tSAH, traumatic subarachnoid haemorrhage
Fisher OR = 3.5 (CI 2.3–5.3), $p < 0.0001$

score of 3–5. The odds ratio for a bad outcome was >3 in the group with a score of 1–2.

Among the patients in a valid protocol who received nimodipine and had a TSAH, their better outcome was significant. This suggested that further studies be done in patients with TSAH.

Our studies were mainly with patients with severe head injury. Early cerebral blood flow (CBF) measurements were done on 50 patients with severe closed head injury, with a Glasgow coma score of 8 or less. The global flow was measured by radioactive xenon clearance and daily Doppler studies. Twenty of these patients (40%) developed what was classified as vasospasm according to the Lindegard criteria, which depend on the ratio of intracranial/extracranial arteries and increased flow velocities. A slightly lower number had delayed hyperaemia by the same criteria (with a smaller ratio). Later CBF studies confirmed increased flow velocities in these patients.

The blood flow studies on the first day were of some use in predicting whether the increased flow velocity would follow later. If patients had a flow within a fairly narrow band in the centre of the range the risk of developing vasospasm or hyperaemia was much less (Fig. 18). The early patients with a very low flow had an increased risk of later developing hyperaemia or vasospasm. The use of this technique for predicting an increased Doppler velocity later was much more accurate than was the prediction of TSAH by CT scan.

Hyperaemia tended to have a later onset than vasospasm, was often transient, and was of shorter duration than the vasospasm. The patients with vasospasm tended to have a much higher peak mean velocity, which was often more localized than the hyperaemia, which

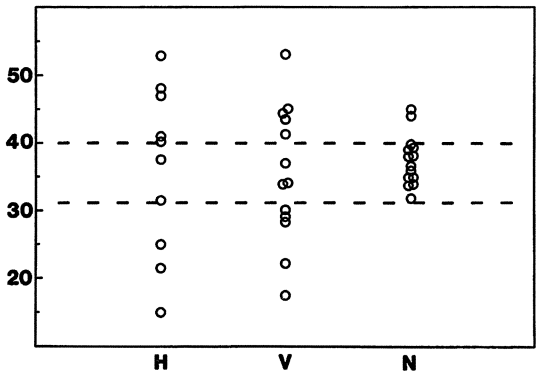


Fig. 18. Blood flow studies: the risk of hyperaemia (*H*), vasospasm (*V*) and neither complication (*N*). Initial slope index

was more general. Both hyperamia and vasospasm were associated with a much worse outcome. Only a small proportion of the patients who did not developed these conditions ended with a poor outcome. Over half the patients with hyperaemia or vasospasm did badly. A regression analysis based on the highest velocity and the lowest cerebral perfusion pressure (CPP) as well as on age, was reasonably accurate in predicting whether the outcome would be good or poor (Table 18).

In another study in which 47 patients with cerebral contusions were tested for the presence or absence of associated TSAH, nearly half had a definite TSAH (Table 19). The patients were otherwise similar in their initial clinical state and in CT scan abnormalities. In the following days, the patients with TSAH had a significantly increased likelihood of developing post-traumatic vasospasm compared to those without TSAH (Table 20). The TSAH group had a

Table 18. Logistic regression analysis in brain trauma

Probability of good outcome $p = 1/(1+e^{-z})$
Chi-sq = 29.2 $p < 0.0001$
Accuracy = 82%
Sensitivity = 96.2%
Specificity = 76.2%
$z = -0.084$ Age $- 0.042$ HVEL $+ 0.11$ LCPP $+ 1.75$

Table 19. Forty-seven patients with cerebral contusion with and without traumatic subarachnoid haemorrhage according to computed tomography

Group I:	25 patients with cerebral contusions but without SAH
Group II:	22 patients with cerebral contusions and SAH

SAH, subarachnoid haemorrhage

Table 20. Blood flow changes in patients of Table 19

	Group I (*n*)	Group II (*n*)	Statistics
Total	25	22	
Hyperaemia	10	5	p = 0.2
Vasospasm	6	13	p = 0.019
Severe vasospasm	2	8	p = 0.021
Normal velocity	9	4	p = 0.2

lower likelihood of developing hyperaemia. They also showed an increased incidence of contusion-related and non-contusion-related hypodense areas on later CT scans.

There was a significant difference in outcome between the two groups. Patients with TSAH were much more likely to have a poor outcome than those without TSAH. The conclusions from this small study are that the presence of TSAH is associated both with an increased incidence of delayed vasospasm, as measured by transcranial Doppler, and considerably worse outcome.

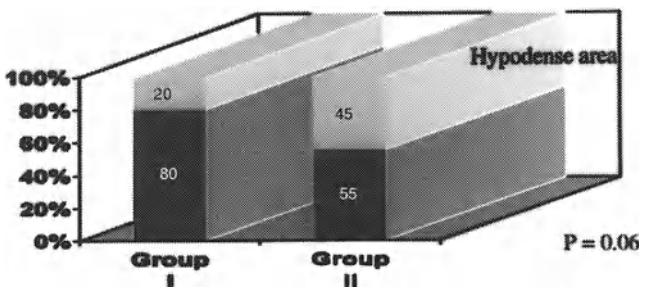


Fig. 19. New hypodense areas on second computed tomographic scan in the HIT-II study: Group I, nimodipine; Group II, placebo *top part*, hypodense area; *bottom part*, no hypodense area

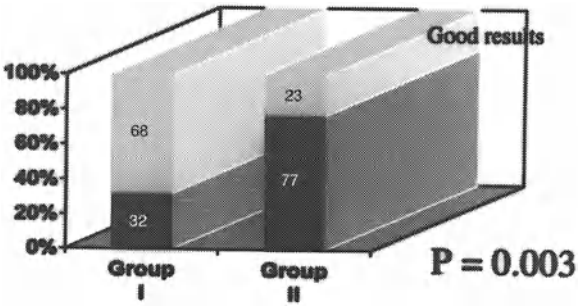


Fig. 20. Proportion of good outcomes in the HIT-III study: Group I, nimodipine; Group II, placebo; *bottom part*, poor outcome; *top part*, good outcome

Of interest are the preliminary results of the nimodipine study of patients with TSAH – which may be called HIT-III. In the patients who received nimodipine and had TSAH, there was a significant improvement in outcome overall (Figs. 19, 20). This improvement was even more marked in those whose condition strictly fulfilled the criteria for SAH.

Summary

Vasospasm is a very significant factor after head injury, especially in those patients who have TSAH, and it has a significant influence on outcome.

The German Study of Nimodipine in Traumatic Subrachnoid Haemorrhage

A. Kakarieka

With the excellent co-operation of 21 centres (Table 21) in Germany, a randomized, double-blind, placebo-controlled trial in traumatic subarachnoid haemorrhage (TSAH) was performed. The rationale for this trial was the frequent occurrence of TSAH in head injury (Table 22). In the HIT-II trial in Europe, one third of the patients had a TSAH on the first CT scan. The Americans reported an incidence of 40% of TSAH in their traumatic coma data bank. HIT-II also showed that TSAH worsened the outcome in head-injured patients. Sixty % of patients with a TSAH had an unfavourable outcome, compared with 30% when there was no such finding on CT scan. At that time it was speculated that the pathophysiology of TSAH was similar to that of aneurysmal SAH, and we saw that TSAH patients had a better outcome after nimodipine. The aim of the study was to describe TSAH as a clinical entity, to study the effect of

Table 21. Centres participating in the German nimodipine traumatic subarachnoid haemorrhage study

Aachen	Halle
Berlin-Neukölln	Kassel
Bochum	Köln-Merheim
Chemnitz	Münster
Dortmund	Münster-Clemenshospital
Duisburg	Regensburg
Erfurt	Schwerin
Essen	Trier
Frankfurt-Unfallklinik	Tübingen
Fulda	Wiesbaden
Göttingen	

Table 22. Rationale for the use of nimodipine in traumatic subarachnoid haemorrhage

tSAH is a frequent finding in head injury
33% in the HITII-study
40% in the American Traumatic Coma Data Bank
tSAH worsens outcome in head injured patients
HITII: 60% unfavourable outcome in tSAH
30% unfavourable outcome in noSAH
tSAH pathophysiology might be similar to aneurysmal SAH
tSAH patients showed improved outcome after nimodipine therapy (HITII)

tSAH, traumatic subarachnoid haemorrhage

nimodipine on the outcome and on vasospasm, and to confirm the results of HIT-II on the effect of nimodipine on TSAH.

Patients enrolled in the study had to have TSAH on the first CT scan, had to be admitted into the study within the first 12 h of injury, regardless of their neurological condition, and had to be between 16 and 70 years old. Gunshot injuries were excluded. The same treatment regimen was used as for aneurysmal SAH. Patients were given nimodipine or matched placebo for 7–10 days, followed by oral therapy until day 21.

Demographic Data

123 patients were enrolled between January and October 1994. Their mean age was 45 years, 80% of the patients were male, and 37% were under the influence of alcohol at the moment of injury (Table 23). In one quarter of the patients the injury was mild. The treatment groups were well balanced at baseline.

Table 23. Demographic data of patients enrolled in the study from January 1994 to October 1994

Number of patients	123
Mean age	45 years
Male	80%
Alcohol influence	37%
Mild injury	25%

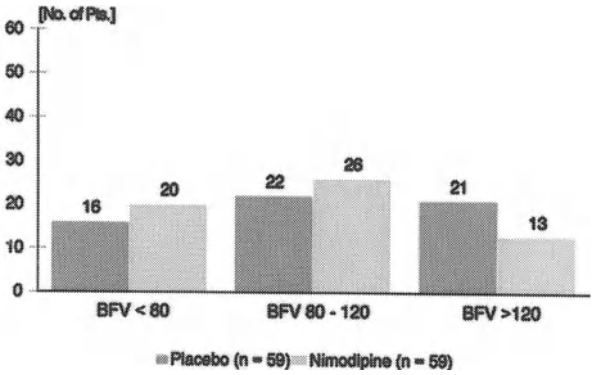


Fig. 21. Mean blood flow velocities (*BFV*) in patients with traumatic subarachnoid haemorrhage according to treatment groups

In 29%, there was a small amount of blood in the subarachnoid space: in 46% it was moderate, and in 25% TSAH was extensive. In 30% of the patients there were increases in BFV of between 80% and 120 cm/s, and in 30% there were increases of more than 120 cm/s (Fig. 21). More of the placebo patients had BFV increases >120 cm/s, than patients who received nimodipine. In one patient with a mean BFV value of over 120 cm/s, the shape of the BFV curve was very similar to that seen in aneurysmal SAH, with the peak at day 11.

Outcome at 6 Months

Two patients were lost to follow-up. In the nimodipine group there was a reduction in mortality, in vegetative survival, and in severe disability (Fig. 22). Taking these three categories together as an unfavourable outcome, 45% of the placebo-treated patients, and only 26% of those given nimodipine, fell into this group. The difference was statistically significant.

Considering only those patients who in the opinion of the study review committee had a clear-cut SAH, there was the same difference in death, vegetative survival and severe disability. There was a 59% incidence of unfavourable outcome in the placebo-treated patients (almost the same figure as in HIT-II) and a 29% incidence in the

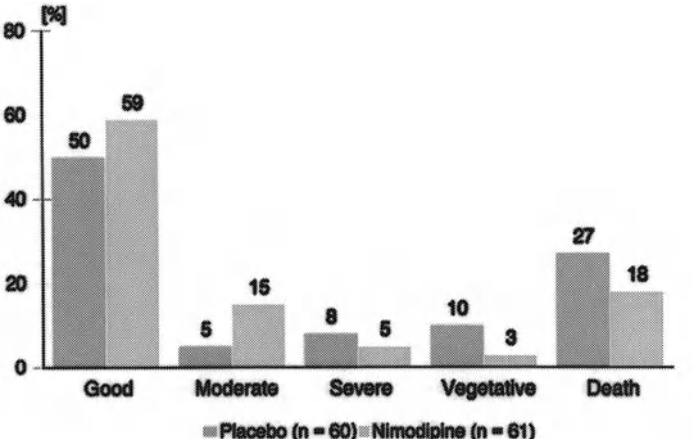


Fig. 22. Traumatic subarachnoid haemorrhage: outcome at 6 months (n=121) *left-hand bars*, placebo (n=60); *right-hand bars*, nimopidine (n=61)

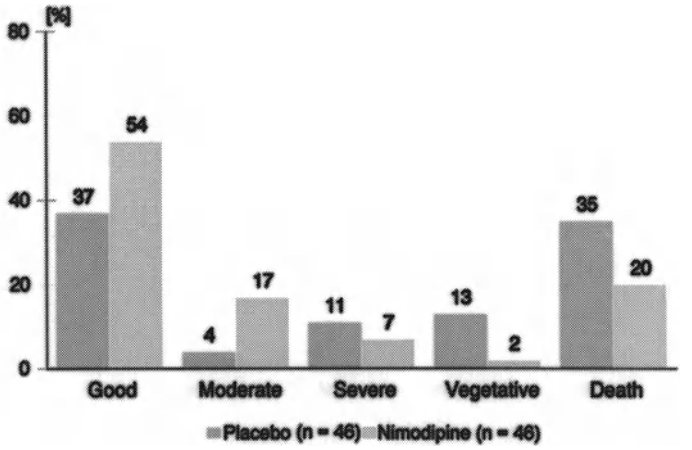


Fig. 23. Outcome at 6 months of patients with clear-cut traumatic subarachnoid haemorrhage (n=92). *Left-hand bars*, placebo (n=46); *right-hand bars*, nimodipine (n=46)

nimodipine patients – a relative reduction of 51%, which was highly significant (Fig. 23).

The outcome was linked to the amount of bleeeding. In those with a small amount of blood in the subarachnoid space, there was no big

difference in outcome between the two treatment groups. The difference was significant in the moderate and severe bleeding groups. BFVs also influenced outcome. A BFV of below 80 cm/s was not linked with a difference in outcome between the treatment groups. The difference was entirely among the patients with BFVs >80 cm/s.

Conclusions

TSAH is a clinical entity in head injury. It shows a pathophysiological similarity to aneurysmal SAH, and patients with TSAH benefit significantly from nimodipine therapy.

Discussion

Dr Dearden: We now have HIT-II and this study, with relatively small patient numbers because they are subgroups. Should we go on these data alone? It is convincing, and the statistics are consistent between the two trials. Or should we do things "properly", with a full-size phase 3 study? This is up to the audience.

Professor Dorsch: Although this is a particularly impressive study, the numbers were small, particularly the number of patients that were accepted as completely valid in that much more significant group. With aneurysmal SAH, four or five well-controlled studies were done, and this helped to convince the neurosurgical world that it was important in this situation. I would suggest that a larger phase 3 study should be the way forward.

Professor Teasdale: I would like first of all to congratulate Dr Kakarieka, not just for the results, but also for motivating the study. The HIT-II studies did not show an overall benefit. The SAH data came from a subgroup analysis, subject to all the caveats and reservations. Dr Kakarieka carried the flag for TSAH, and worked hard within the company to get the study done. He had an excellent relationship with his colleagues in Germany.

Part of the reason why it was so hard to motivate people for this trial was the HIT-I study. The HIT-I data were looked at retrospectively, and the CT scans were reviewed and classified according to whether or not they show TSAH, and whether or not nimodipine made a difference. It did not. If HIT-I and HIT-II had demonstrated the benefit of using nimodipine, a third study would not have been needed. But in the HIT-I patients classified blindly as having TSAH,

nimodipine was not considered to have influenced outcome after the study was over.

So there is one highly interesting study, the results of which we have seen for the first time today. We are trying to find data that apply to all patients in all parts of the world. Is the existing data on nimodipine sufficient for application to all SAH patients throughout the world? I would not like to answer that this morning. I would like to see more data. We have two studies which speak in favour of using nimodipine, and one which does not. In the end, it is partly up to Bayer and the regulatory authorities to make the decisions, and not to the people here this morning.

However, I would like to see a "barefoot doctor" type study of nimodipine in large numbers of patients without an immense amount of monitoring or safety data, and with low cost and low technology. It would be similar to the studies that showed that fibrinolytic treatment works in myocardial infarction. With a large number of centres co-operating, we should get the answers quickly. This would provide convincing results and information about the size of the effect. From this small number of patients we cannot say, for example, that nimodipine will improve outcome by 50% in a large number of patients. It might be between 10% and 100%; with larger numbers we will have a much better idea of how much benefit is achieved.

Dr Tettenborn: May I comment on the differences between the outcomes of HIT-I and HIT-II, and between them and this trial? The important difference between the first two trials and this trial is that the treatment duration for the HIT trials was only 7 days. As we have seen from the presentations of Drs Dorsch and Kakarieka, the vasospasm continues to develop until a maximum is reached at day 10–12. In HIT-I and HIT-II the treatment was stopped before the maximum vasospasm had occurred. In the third trial, the patients were treated for up to 21 days, and this may explain the improved outcome.

Professor Teasdale: This is a very valid point. I am delighted to see Dr Tettenborn here, because he did so much to promote the use of nimodipine in neurosurgery. Your comment raises a question: At

what stage does the difference in outcome between treated and untreated patients appear? Most mortality occurs in the first 3 days after injury. Does the difference in this trial only start to appear after the first 7 days, or is it there before the seventh day?

Dr P. Reilly, Australia: I would like to ask a general question about the concepts of ICP and CPP. Mark Dearden showed a standard protocol for management, based on ICP and CPP levels, and rightly emphasized the importance of maintaining CPP. Is ICP important at all, except in so far as it is a way of regulating CPP? In other words, does increased intracranial pressure damage the brain except through either CPP or brain shift? If it does not, then we need not worry about setting it to 25 or 30 mm Hg on day 1 or whatever; we should simply concentrate on a convenient way of managing the CPP. If it does, I would like to know how.

Dr Dearden: CPP matters much less than we previously argued, although this is not based on evidence but on a clinical gut feeling. We know that there are patients who in the first 24–48 h have relatively low ICPs of 25–30 mm Hg and have dilated pupils, coma, and die. We also see patients with ICPs of 50 mm Hg, and with good CPPs of 7 or 8, who when taken off the ventilator will speak! Judging from isolated clinical cases, the ICP issue seems to be more difficult. When we combine the ICP predictive outcome data with the ICPs, we find that the CPP is a much better indicator than the ICP. Patients with high ICPs and high CPPs do much better than patients with high ICPs and low CPPs. We should be using the ICP monitor much more as a monitor of the CPP, and we should be doing this a lot earlier than we do now.

We should be concentrating much more on the first 12-h window, as far as the anaesthetist, surgeons, and the Accident and Emergency Department specialists are concerned, to maintain good perfusion pressures. After that, unless there is shift, patients are probably stable, provided that the CPP is good and other monitoring shows no evidence of global ischaemia. Of course the monitoring should be continued. The only problem, as Professor Teasdale showed, is where there is continuing evidence of focal ischaemia. We do not yet know whether this can be influenced by that regimen.

Professor Teasdale: To answer any questions about all types of head injuries with one answer is now clearly wrong. In diffuse ischaemia, it is certainly CPP that is important. But we must consider that many head injuries have focal problems. It is with focal problems that ICP is relevant, in which case it is a good indication as to whether the shift is increasing or decreasing, whether we should do a CT scan, or take a haematoma out. The answer to any head injury question depends on the type of injury.

Professor Dorsch: I would concur with that most definitely. Many of us have seen isolated cases where CPP has been maintained well, but where the ICP was high, and eventually shifts caused blowing of pupils.

Japanese doctor: With respect to the problem of CPP, in using nimodipine for treating aneurysmal SAH we sometimes see patients whose blood pressures drop so low that we have to tailor the dosage or even stop it. Was there a similar problem in using nimodipine in the head injury series?

Professor Dorsch: This is a problem with aneurysmal SAH, and sometimes it is necessary to give pressor drugs. I notice that a number of units, particularly in America, are giving perssor drugs where necessary to keep up the CPP. They can be added to nimodipine.

Dr Kakarieka: We found in the HIT-II trial that the patients given nimodipine had a lower average ICP measurement than the placebo-treated patients. We have not yet analysed CPP.

Doctor from Germany: Is TSAH due to diffuse leakage form contusions or to rupture of a major artery? Do patients with TSAH have different types of injury from those without?

Professor Cohadon: We have no answer to that. However, the neurosurgeons of my generation were trained to make diagnoses from acute angiography. In the first few hours there was already strong vasospasm in a significant number of patients, which we forgot.

Professor Dorsch: Most TSAH is associated with an epidural or subdural haematoma with local blood. In our series, only two of 16 patients without a contusion had a TSAH, and they were very mild. Most of our TSAH cases were associated with contusions, or contusions were present as well. However, if you do a lumbar puncture in a patient with a fractured skull, there will be a little bit of blood in the CSF.

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