NEUROLOGICAL INVESTIGATIONS

Multimodal monitoring in neurointensive care

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The pathophysiological mechanisms occurring in cerebral ischaemia are multiple, complex, and incompletely understood. However, despite the diverse aetiology for brain injury, different processes operate to cause common manifestations such as a raised intracranial pressure (ICP), derangements in cerebral blood flow (CBF), and brain hypoxia. Such changes in the pathophysiological state of the cerebral tissues may be transient and last only a few minutes. Although intermittent monitoring with serial cranial imaging methods (such as enhanced computed and emission tomography) in specialised institutions provide good spatial information, they are likely to miss transient events. Also, the necessary intensive support for these precarious patients is difficult to maintain within such imaging facilities. Thus methods for assessing brain function in an uninterrupted fashion have attracted increased clinical attention, particularly those that can be adapted for bedside monitoring, which reduces the need for patients’ transfer.

A single monitored cerebral event, such as a period of raised ICP, may be a manifestation of various different pathophysiological changes. Cerebral swelling from ischaemia (oligemia), and increased cerebral blood volume from hyperaemia are examples in which the contrast in pathology is extreme. Blind ICP treatment in both instances using agents such as mannitol may be beneficial in the first case, but potentially aggravate the raised ICP in the second. Thus directing treatment according to one measured variable may be inappropriate. Similarly, whereas controlled hyperventilation has traditionally been used to treat raised ICP by encouraging reactive vasoconstriction, recent evidence suggests that in situations of cerebral oligemia these manoeuvres can increase cerebral ischaemia and lactic acid production. By monitoring several different variables, each providing relevant information on different aspects of brain physiology, a greater understanding of the individual situation can be gathered. The aim would be a more accurate targeting and policing of treatment. Computer support of multimodality monitoring helps the observer to identify important cerebral events among the background noise and artefacts (often induced within the hostile environment of an intensive care unit), and helps in the interpretation of complex information.

The purpose of this chapter is to provide an introduction to the novel methods that are available for the continuous assessment of cerebral perfusion, haemodynamics, and oxygenation. Continuous monitoring techniques for different variables concerning the health of the brain are now available, and these include measurements of ICP, cerebral perfusion pressure (CPP), jugular venous oxygen saturation (SjO2), and cortical electrical activity.

General systems monitors, such as pulse oximetry, end tidal CO2, and temperature are clearly of importance but will not be discussed here. More recently additional methods have been introduced such as transcranial Doppler, laser Doppler flowmetry, and near infrared spectroscopy.

Computing support of data analysis

In an established neurointensive care facility enormous quantities of data can be captured from each patient from which information on cerebral autoregulation, oxygenation, metabolite production, and function can be obtained. Recognition of changing cerebrovascular haemodynamics and oxygenation demands not only reliable monitoring techniques, but also complex and time consuming signal analysis. This can only be provided by dedicated computer support.

The first specialised computer based systems for neurointensive care were introduced at the beginning of the 1970s. Initially these systems were oriented to the monitoring of ICP and arterial blood pressure (ABP) allowing calculation of CPP and a basic analysis of the pulsatile ICP waveform. By contrast, contemporary systems are highly complex multichannel digital trend recorders with built in options for complex signal processing. The considerable flexibility of such systems permits almost unlimited signal analysis which in itself can generate a state of data chaos. Thus the modern user is faced with the problem of which variables should be considered, and how the data should be interpreted. This information should then be presented in a manner which is comprehensible to medical and nursing staff. The mechanism of presentation is also important.
Although personal computers with designated software are portable, they have yet to gain widespread clinical acceptance as an intensive care tool. They are seen as stand-alone instruments requiring specialised skills for their operation, and occupying precious space. By contrast, commercial hardware systems with a customised console are more user-friendly, but are far more expensive and less flexible.

The intensive multimodality monitoring system adopted in the Cambridge Neurosurgical Intensive Care Unit is based on software for the standard IBM compatible personal computer, equipped with a digital to analogue converter and RS232 serial interface. It was introduced into clinical practice in Poland, Denmark, and the United Kingdom in the late 1980s and has recently been extended into a system for multimodal neurointensive care monitoring and waveform analysis.34 Most data have been derived from patients with head injuries, common occupants of the neurointensive care unit. However, the same techniques are being increasingly applied to those with severe stroke, subarachnoid haemorrhage, cerebral infections, and encephalopathies.35

**Intracranial pressure and cerebral perfusion pressure**

Pathophysiological mechanisms responsible for stabilisation of ICP within a rigid skull vault are complex.4 Changes in the CSF and cerebral blood volume may compensate for longstanding volumetric changes of cerebral tissue. However, in acute injury small changes in cerebral parenchymal volume can cause gross changes in ICP and CPP. Accompanying cerebral haemodynamic deterioration may occur with the possible sequel of secondary ischaemic brain damage. Thus the continuous assessment of ICP is a key component of any cerebral multimodality monitoring system.

Reliable measurement of ICP still depends on invasive systems. Non-invasive methods, such as transfontanometry,36 tympanic membrane displacement,37 and assessment of transcranial Doppler flow velocity pulse waveform,38 are difficult to calibrate and have not achieved suitable accuracy. The least invasive systems available use epidural probes, but there is still uncertainty regarding the precise relation between ICP and pressure in the extradural space. Intraventricular or subdural fluid filled catheters with external pressure sensitive elements can measure ICP directly but display signal drift, have limited frequency response,26 and present a risk of infection. By contrast, ICP microtransducers measure CSF or intraparenchymal pressures with high accuracy, minimum signal drift, and a good frequency response.39-41 and as their support bolt provides an airtight seal with the skull bone they can be safely used for long term monitoring without concern for infection.

Intracranial pressure measurements are used to estimate CPP; providing that ICP estimates intracerebral venous pressure:

\[ \text{mean CPP} = \text{mean ABP} - \text{mean ICP} \]

Sufficient CPP is required to maintain a stable CBF with an autoregulatory reserve. A CPP below 60–70 mm Hg may result in a compromise in various haemodynamic modalities.3 13 32 There is also an increased chance of a poor outcome if CPP falls below these thresholds in patients with head injury.33-35 However, policies to therapeutically maintain a high CPP are controversial. Non-reactive vessels may result in hyperaemia, increasing vasogenic oedema, and secondary increase in ICP. It is also probable that there are considerable patient dependent differences in the optimal level of CPP. Thus although many authors evaluate such thresholds in their group analysis31 32 35 36 and demonstrate critical values ranging from 55 to 80 mm Hg, a general threshold between adequate and non-adequate CPP for each patient is difficult to define. The threshold of CPP causing haemodynamic deficit should be considered as a time dependent factor,37 39 hence the real time assessments of the relation between haemodynamic modalities and CPP is essential.

One approach to identifying a “safe pressure” zone in the individual patient is to use information derived from the ICP and CPP waveforms. For example, the analysis of the relation between the mean ICP and the amplitude of its waveform,39 40 the analysis of the shape of pulse wave39 and its relation to respiratory oscillations,41 the transmission of the ABP wave into the intracranial compartment,42 43 and the spectral analysis of the fundamental44 45 and subsequent ICP waveform harmonics46 have all been considered. The basic phenomenon of an increase in ICP amplitude with rising mean ICP was seen in the early recordings made by Ryder et al in 1953.44 Using a monoeponential model of cerebrospinal pressure-volume relation Langfitt et al48 later postulated that if an increase in cerebral blood volume during one heart contraction was constant, it would produce a higher pressure response when the ICP level was raised. However, when the ICP becomes very high with a compensatory maximal vasodilatation a secondary decrease in the ICP pulse amplitude is seen (fig 1). The linear correlation coefficient between mean ICP and ICP pulse amplitude values can be calculated and has been termed RAP (R = symbol of correlation, A = amplitude, P = pressure).44 49 This index describes time dependent changes in the relation between mean ICP and the pulse amplitude. The advantage is that the coefficient has a normalised value from -1 to +1 (fig 1) allowing comparison between patients. The relation of RAP and ICP or CPP in pooled analysis of patients with head injury shows that a positive index close to +1 is expected in patients with head injury with moderately raised ICP (>15 mm Hg) and CPP above 50 mm Hg. Decrease in RAP to 0 is found with very high ICP and very low CPP (fig 2), which are predictive of a poor outcome (fig 3).50 The RAP index as a time related factor often anticipates brainstem herniation due to
an excessive rise in ICP (fig 4). Because the RAP coefficient is calculated using the fundamental harmonic of the ICP pulse wave the practical advantage of this index is that there is no need to use a pressure transducer with a wide bandwidth; a simple subdural catheter connected to an external membrane transducer will suffice.

Transcranial Doppler ultrasonography

Transcranial Doppler ultrasonography allows non-invasive measurement of blood flow velocity in basal cerebral arteries. Most data have been derived from the middle cerebral artery as this vessel is technically the simplest to insonate, and is the most relevant as 80% of supratentorial cerebral blood flow passes through it. Although blood flow velocity cannot express volume flow, the dynamic changes of CBF are almost always reflected in transcranial Doppler readings. Experience with transcranial Doppler in neurointensive care monitoring is still limited because of problems of long term fixation of the ultrasound probe and of interfacing with a computerised system. However, the high dynamic resolution provided with confirm correlation with other haemodynamic modalities is encouraging increasing numbers of neurointensivists to adopt the technique. In addition to calculating the time averaged meanflow velocity, recent transcranial Doppler machines provide information on the flow waveform which is affected by pulsations of CPP and by the resistance and compliance (mechanoelastic properties) of the cerebrovascular bed. Thus transcranial Doppler provides great potential in cerebrovascular investigations for assessment of cerebrovascular autoregulatory reserve, reactivity, CPP, cerebral hyperaemia, post-traumatic spasm, and in the estimation of cerebral tamponade.

CEREBRAL AUTOREGULATION

With continuous transcranial Doppler, autoregulation can be assessed by observing the responses to spontaneous changes in ABP, transient changes in CPP induced by a second carotid compression, or longer periods of reduced CPP induced by inflating and releasing large blood pressure cuffs applied to the legs. Continuous assessment of transcranial Doppler pulsatility indices which vary according to the state of autoregulation can be useful for the on line monitoring of critical thresholds in CPP (see later). More recently an evaluation of the gradient of linear regression between the different components of the flow velocity waveform (systolic, mean, and diastolic) and the CPP show that these gradients are dependent on mean CPP and correlate with outcome after head injury (fig 6).

CEREBROVASCULAR REACTIVITY

The response of flow velocity to changes in CO₂ concentration characterises vascular reactivity. Decreased reactivity is reported with decreasing CPP and in patients with poor outcome after head injury.
Figure 4 Mean values of CPP, ICP, and RAP over a 24 hour period in 42 patients with head injury in different outcome groups. ICP is significantly lower for moderate/good (m/g) patients. RAP is significantly lower for dead or persistent vegetative (PVS/d) patients. RAP = correlation coefficient between pulse amplitude (first harmonic) and mean intracranial pressure; sd = severely disabled patients. Redrawn from Czosnyka et al.29

SPASM AND HYPERAEMIA
Flow velocity in excess of 100 cm/s occurs in 10% to 20% of patients after head injury,64,65 but the differentiation between hyperaemia and vasospasm can be difficult and often requires measurement of a further variable such as jugular venous oximetry.66 If the ratio of middle cerebral artery flow velocity to the internal carotid artery flow velocity exceeds 3 then vasospasm is likely.67 Detailed flow velocity waveform analysis and detection of a dicrotic notch in the pulse pattern68 are not very helpful.

NON-INVASIVE ASSESSMENT OF CEREBRAL PERFUSION PRESSURE
The pulsatility index (flow velocity amplitude/flow velocity mean) is a dimensionless index that is independent of sampling variation provided the signal to noise ratio is good and the gain setting of the instrument is constant. Most modern software packages provided with transcranial Doppler automatically calculate the pulsatility index which is averaged from several cardiac cycles. The potential importance of the pulsatility index in brain injury is that increases in the index provide a non-invasive artefact free measure of failing autoregulation.6,21,23 Clinical experience has shown a closer correlation between CPP and pulsatility index than between mean flow velocity and CPP which has facilitated the use of this variable for the non-invasive estimation of CPP in patients with head injury (fig 7).

DETECTION OF CEREBRAL TAMPOADE
Transcranial Doppler has been used to assist in the diagnosis of brain death. At very low levels of CPP the critical closing pressure for cerebral arterioles is reached resulting in the collapse of the microcirculation and vascular infarction. Net forward blood flow diminishes

Figure 5 Three specific patterns of relation between systolic (FVs), diastolic (FVd) and time averaged (FV) blood flow velocity and CPP. Left: both systolic and diastolic are pressure-passive (autoregulation exhausted). Middle: diastolic and time average FV pressure-passive but systolic FV not pressure passive (good autoregulatory reserve). Right: systolic and diastolic FV are not pressure passive (good autoregulatory reserve). Figure redrawn from poster presented at the 3rd International Neurotrauma Symposium, Toronto, 1995 by Czosnyka et al.
and the transcranial Doppler pattern shows reversal of flow during diastole.\cite{57}

**Laser Doppler flowmetry**

Laser Doppler flowmetry is a technique which provides a continuous measure of relative microcirculatory flow.\cite{56}\textsuperscript{70} The final signal generated is a measure of microcirculatory red cell flux (the product of red cell concentration and the red cell velocity). Experimental use of laser Doppler flowmetry in vitro and in vivo has consistently shown a close linear correlation between laser Doppler flowmetry flux and CBF measured with standard methods, and the laser light used does not seem to alter the morphological and physiological characteristics of the vascular bed examined.\cite{71}\textsuperscript{73} The method has shown particular use in the observation of changes in microcirculatory flow induced by physiological and pharmacological stimuli.\cite{74} However, laser Doppler flowmetry is not quantitative, records from a small tissue volume, and provides no information on the direction of blood flow. Further, experience has shown that the flux signal is very sensitive to the artefacts of local tissue pressure and movement, so that the reliability of the tech-
Figure 9 Effect of mannitol infusion on laser Doppler flux (upper) and estimated cerebrovascular resistance (eCVR calculated using relative changes in cortical laser Doppler signal—lower graph) after a 200 ml bolus of 20% mannitol compared with a 200 ml bolus of normal saline.

Figure 9: Effect of mannitol infusion on laser Doppler flux (upper) and estimated cerebrovascular resistance (eCVR calculated using relative changes in cortical laser Doppler signal—lower graph) after a 200 ml bolus of 20% mannitol compared with a 200 ml bolus of normal saline.

Technique is critically dependent on the method of application. Despite these drawbacks, laser Doppler flowmetry has already shown potential for blood flow measurements in several clinical disciplines including neurosurgery. Using rigid support bolts which are fixed into the skull, reliable long term recordings from ventilated patients with head injury have been achieved. Figure 8 (left) shows an example of a recording captured from one patient with a severe diffuse head injury during spontaneous changes in CPP. Fluctuations in ICP resulted in variations in CPP which were accompanied by changes in the laser Doppler flowmetry signal. Although cerebral events resulting in changes of CPP usually cause very similar trends in middle cerebral artery flow velocity, and laser Doppler flowmetry, uncoupling between flow velocity and laser Doppler flowmetry can occur (fig 8 (right)).

The advantage of laser Doppler flowmetry is that the technique provides a real time measure of relative changes in capillary perfusion which is particularly suitable for assessing the microcirculatory response to a therapeutic challenge. Figure 9 shows the effect of mannitol infusion on cerebral microcirculatory flow in patients with head injury indicating a fall in cerebrovascular resistance with increased red cell flow independent of any significant change in CPP.

Near infrared spectroscopy
Near infrared spectroscopy is a non-invasive method which attempts to measure cerebral concentrations of oxymhaoglobin and deoxyhaemoglobin by observing the absorption of near infrared light. The method has been used most extensively in the neonate where interperterial transmission of light (transmission spectroscopy) can occur. An absolute measure of changing brain haemoglobin saturation and blood volume is possible, and has provided a means of monitoring the cerebrovascular response to certain therapeutic manipulations in critically ill infants.

In adults, scattering of light during passage through a greater thickness of tissue prevents adequate transmission of light to the opposite side of the skull. Thus scattered light has to be sampled by a receiving probe placed ipsilateral to the source probe (reflectance spectroscopy). This results in limited topographical resolution, as it is not clear to what depth near infrared light penetrates the adult brain. Further, the thicker extracranial tissue will influence the sampled signal to a greater proportion when near infrared spectroscopy is used in adults, and the significance of this remains unresolved. Hence, although an estimate of the light path length transgressed is possible, the use of near infrared spectroscopy in the adult brain is presently considered non-quantitative. Despite these concerns, the technique has been used to demonstrate predictable physiological changes in cerebral oxygenhaemoglobin and deoxyhaemoglobin content during respiration, in response to various manoeuvres such as a CO2 stress test, and in response to internal carotid artery cross clamping during carotid endarterectomy.

Experience using near infrared spectroscopy in the neurointensive care setting is limited due in part to the practical difficulties of main-
Multimodal monitoring in neurointensive care

Figure 10. Two successive episodes of peripheral desaturation occur in this head injured patient as recorded with peripheral pulse oximetry. The second event arrowed shows the SaO₂ falling to below 80% and is accompanied by a fall in oxyhaemoglobin and reciprocal rise in deoxyhaemoglobin. The SjO₂ monitor failed to register this event. From Kirkpatrick et al. ICP = intracranial pressure (mm Hg); CPP = cerebral perfusion pressure (mm Hg); FV = right middle cerebral artery flow velocity (cm/s); LDF = laser Doppler flux from the right frontal region (AU); NIRS = near infrared spectroscopy (recording from the right frontal region); HbO₂ = oxyhaemoglobin (μmol/l); Hb = deoxyhaemoglobin (μmol/l), tHb = total haemoglobin (μmol/l), (SjO₂ = right jugular venous oxygen saturation (%), SaO₂ = peripheral oxygen saturation (%).

In patients where we have experienced minimal risk of trauma-induced artefacts, the probes' positions can be predetermined and used for long-term monitoring. However, our own experience indicates that it can provide warning of a fall in cerebral oxygenation with greater sensitivity than jugular venous oximetry (fig 10). In addition, calculations of total haemoglobin allow characterisation of different events causing a fall in CPP (hyperaemia v primary increases in ICP (fig 11)). The advantage of a non-invasive technique which provides estimates of cerebral oxygenation with high temporal resolution is clear to all those interested in monitoring cerebrovascular status, but the use of near infrared spectroscopy in adults is in a state of evolution requiring considerable efforts with future clinical validation studies.

Intraparenchymal probes

Direct measurement of substances in brain tissue has been slow to evolve in the clinical setting for practical and ethical reasons. However, modern probes can now be placed with minimal risks of added morbidity and experience is accumulating. The measurement of relevant chemicals (such as excitatory amino acids) in traumatised adult brain using microdialysis techniques indicate similar chemical profiles to those seen in experimental animals. Similarly, oxygen measuring electrodes can be employed for direct measurement of parenchymal oxygen concentration and are beginning to provide novel information regarding the response of the cerebral tissues to specific manoeuvres such as hyperventilation. However, whether such focal measures will provide a sufficiently accurate estimation of the condition of the brain for targeted treatment remains to be seen.

The future for multimodality monitoring

All the aforementioned techniques have largely evolved independently of each other and have all identified their own limitations and artefacts. However, the disadvantages of one modality does not necessarily overlap with
those of another. As a result there has been a growing tendency to adopt a multimodality approach to patients in neurointensive care which allows a more informed interpretation of an individual patient’s cerebral state and helps to identify artefacts. Thus an event characterised by changes in several monitored variables (fig 11) provides credence to the finding. As experience gathers we anticipate that certain modalities will eventually evolve as those providing the essential key information. If the errors provided by these selected modalities are acceptable, the system can be trimmed for simplicity and reliability, features which are clearly necessary before these systems gain a wider clinical acceptance.

The advantage of multimodality monitoring is the increased power of interpretation. Most patients with brain injury are treated according to general principles maintaining low ICP and adequate CPP. With increasing experience we are learning to recognise situations in which general principles of treatment may at best be inappropriate, at worst detrimental. We envisage that the future management for brain injury will become more precise and increasingly dependent on monitored information gathered real time.

Multimodal monitoring in neurointensive care


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Multimodal monitoring in neurointensive care.

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