An Appraisal of the Impact of Management Guidelines in Traumatic Brain Injury

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ABSTRACT

Objective: *To consider the evidence for the beneficial effects of the current management guidelines in traumatic brain injury, and to highlight the important issues.*

Data sources: *Articles and published peer-review abstracts about the mechanisms and management of traumatic brain injury.*

Summary of review: *Guidelines for the management of traumatic brain injury focus on the recognition, detection and prevention of secondary brain insults. Defence of cerebral perfusion pressure with optimisation of cerebral blood flow and substrate delivery, form the vanguard of these guidelines. The impact of guidelines per se on outcome is difficult to determine due to rapid changes in practice and a dearth of controlled evidence predating these guidelines. Technological developments in multimodal monitoring may identify trends in changing practice. However, there are still significant limitations in the accuracy of assessment of the underlying neuropathological processes.*

The impact of management strategies using current or novel therapies on these neuropathological processes is difficult to assess in randomised controlled trials due to small sample sizes and heterogeneous practice. Preliminary studies using continuous multimodal monitoring in accordance with current management guidelines have identified that episodes of sustained jugular venous desaturation were significantly reduced, indicating that potentially harmful episodes of cerebral oligaemia were prevented. Although the impact of these strategies on outcome was favourable, limitations in these studies do not allow firm outcome based assessments. However, these studies suggest that by defending cerebral perfusion pressure, potentially ischaemic or hypoxic cerebral insults may be prevented and may result in a reassessment of the indications and clinical utility of neuromonitoring.

Conclusions: *The impact of management guidelines in traumatic brain injury on patient outcome has been difficult to determine. However, there is a large body of uncontrolled evidence that suggests secondary global cerebral ischaemia-hypoxic insults are the major determinants in influencing outcome and that therapeutic interventions that maintain and defend cerebral perfusion pressures may improve outcome.* (**Critical Care and Resuscitation 1999; 1: 55-62**)

Key words: Neurotrauma, head injury guidelines, multimodality monitoring, secondary insults

The impact of secondary brain injury, specifically hypoxia and hypotension, on the outcome of patients with traumatic brain injury has been well established.[1] Of these factors, hypotension has been shown to be an independent predictor of an adverse outcome, with the outcome inversely proportional to the frequency of hypotensive episodes.[2] Importantly, whilst hypotension that occurs in the field is essentially an uncontrollable variable, significant episodes of hypotension have been found to occur subsequent to admission to emergency services or to the Intensive Care Unit.[3] These secondary insults are both detectable and preventable by the assiduous attention to maintenance of adequate cerebral perfusion pressure (CPP).

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Development of management guidelines and evolution of practice

The development of guidelines for the management of traumatic brain injury by bodies such as the American Association of Neurological Surgeons (AANS)[4] and the European Brain Injury Consortium (EBIC)[5] have focused on the recognition, detection and prevention of secondary brain insults within evidence based medicine strategies. Defence of CPP and therefore by implication, optimisation of cerebral blood flow and substrate delivery, form the vanguard of these guidelines. It would seem intuitive therefore that, provided the severity of the primary injury is compatible with a favourable outcome, the outcome may be improved if CPP is maintained at an optimal level as soon as possible following the primary injury.[6]

The aim of these guidelines is to provide the basis for optimal practice within the limitations of evidence based medicine and clinical preferences. For example, subsequent trials, such as a study analysing the effects of hypothermia in traumatic brain injury,[7] used the standards outlined in the guidelines as the baseline for standard of care. However, the impact of these guidelines *per se* on outcome for traumatic brain injury has not been determined and will be difficult to assess.

By nature, the development and evolution of clinical practice, whereby critical pathways are established and guidelines are developed, does not lend itself easily to the rigors of a randomised controlled trial. This is in part due to a paucity of controlled clinical trials in management of traumatic brain injury that predated the initiatives of the AANS and EBIC. In addition, surveys of management of traumatic brain injuries have shown that there were, and continue to be, wide variations in clinical practice.[8,9] Furthermore, innovations such as mandatory seat belts, motorcycle helmets and drink-driving legislation has resulted in a decrease in numbers of patients with severe head injuries presenting to major metropolitan centres. As a result, multicentre trials, based on a platform of homogenous practice, will be necessary to attain the appropriate sample size to achieve sufficient statistical power to address any issue.

Attempts to perform randomised controlled trials to compare 'traditional' therapies directed at lowering intracranial pressure (ICP) with 'targeted' strategies aimed at increasing CPP have been met with limited success with no convincing studies published to date. For example, a study performed by Robertson *et al*, showed that the six month Glasgow Outcome Scores were equivalent between two groups of patients (n = 20) randomised to be treated with either 'traditional' or 'targeted' therapy (i.e. maintaining cerebral perfusion pressure > 70 mmHg).[10] Episodes of jugular venous desaturations were abolished in the 'targeted' group compared with a significant number in the 'traditional' group that utilised routine hyperventilation. There was no difference in the development of refractory intracranial hypertension between the groups. However, the incidence of pulmonary oedema and 'ARDS' were higher in the 'targeted' group, with consequently longer Intensive Care Unit (ICU) stays and secondary complications such as nosocomial infections. These complications were attributed to aggressive fluid loading in order to achieve preset haemodynamic targets. To date this study has not been published, other than in abstract form and has been criticised for methodological errors in randomisation and treatment bias.

Multimodal neuromonitoring

The introduction of technologies such as continuous multimodality monitoring may assist clinicians in addressing the above questions. By comparing neurological variables in a succession of patients over a period of time when management strategies have evolved, outcomes may be compared in subsequent cohorts of patients. These monitoring systems have been established in neurocritical care for the last decade.

The development of solid state, minimally invasive intracranial pressure monitors allows the calculation of CPP and are routinely used in patients with severe closed head injuries.[11] Despite the accepted role that intracranial pressure monitoring has in clinical practice, management strategies directed at the active reduction of intracranial pressure have not been shown to confer an improved outcome. Intracranial pressure monitoring reflects global and gross changes in intracranial compliance. This is usually in the setting of severe cerebral oedema caused by the primary injury or with development of intracranial mass lesions. Significant changes in cerebral blood flow such as that following hyperaemia or upon reversal of hyperventilation induced hypocapnia may also result in sustained rises in intracranial pressure.

Intracranial pressure changes occur late in response to critical changes in cerebral blood flow and metabolism and as a result are relatively insensitive indicators of these changes.[12] Stocchetti *et al*, have also demonstrated marked interhemispheric differences in patients with bilateral intracranial pressure monitors, adding a further variable in the accuracy of the signal.[13,14] Furthermore, solid state strain-gauge transducer tipped or fibreoptic systems are prone to drift after 4 - 5 days and cannot be referenced to zero after insertion. Given these limitations, intracranial pressure monitoring should be regarded as a means to determine CPP, as a quantitative index of the severity of the

underlying insult, and/or as an early warning system to detect the development of a delayed or expanding intracranial mass lesion.

An accurate continuous bedside measurement of cerebral blood flow remains elusive. Modalities such as Xe^{133} enhanced CT, SPECT and positron emission tomography provide intermittent measurements of global and regional flow, but remain within the domain of research groups.[15] Transcranial Doppler provides intermittent or continuous assessment of velocities through large vessels (predominantly middle cerebral artery), but essentially provides a qualitative and indirect assessment of global cerebral blood flow.[16]

Nevertheless, the role of transcranial Doppler as a bedside modality is evolving, with studies identifying cerebral perfusion pressure breakpoints in head injured patients using changes in diastolic flow velocities and pulsatility index as early markers of critical global cerebral blood flow.[17]

Similarly, an accurate, bedside measurement of cerebral oxygenation and metabolism remains elusive. The advent of multimodal intraparenchymal oxygen and pH monitors provides information of local cerebral metabolism, but are also confined to research centres. Importantly, studies using these devices have shown that significant changes in cerebral oxygenation and acid-base homeostasis occur prior to changes in global measurements such as intracranial pressure or jugular venous oximetry.[18,19] Cerebral microdialysis across the cerebrospinal fluid of products of metabolism, excitatory and inhibitory neurotransmitters, provide an insight to the determination of the neuropathological insult, but phase three studies of therapeutic strategies directed at the modulation of these process have been unsuccessful.[20,21]

Jugular venous oximetry has been advocated as a surrogate measurement of global cerebral blood flow and oxygenation. In a landmark paper, Robertson *et al*, tested the hypothesis that differences in arterio-jugular oxygen contents could be used to predict cerebral blood flow[22,23] (Figure 1). A non-linear relationship between cerebral blood flow and arterio-venous oxygen difference was identified for a given cerebral metabolic rate for oxygen. In patients without evidence of cerebral ischaemia, cerebral blood flow varied independently where metabolic rate remained constant, indicating a coupled relationship between flow and metabolism.

Increased arterio-venous oxygen differences suggest that cerebral blood flow is low while decreased arterio-venous oxygen differences suggest that cerebral blood flow is increased relative to cerebral metabolic requirements. This relationship becomes unpredictable in patients with cerebral ischaemia following traumatic brain injury.[24] In this context, increased arterio-venous oxygen difference may be assumed to represent inadequate cerebral oxygen delivery for a given metabolic rate. By providing a continuous assessment of cerebral venous oxygenation, jugular venous oximetry acts primarily as a cerebral oximeter, much along the lines of pulse oximetry reflecting global systemic oxygenation. Jugular venous desaturation (< 55%) therefore represents cerebral hypoperfusion relative to global cerebral oxygen utilisation, as Gopinath *et al*, showed that sustained and repeated episodes of jugular venous desaturation were associated with adverse Glasgow outcome scores in a series of head injured patients.[25]

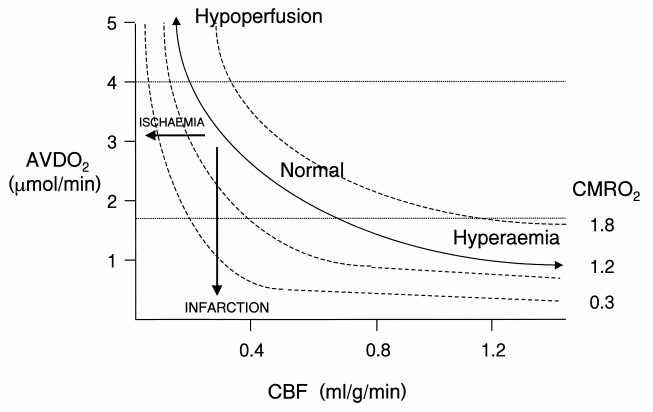

Figure 1. The relationship between cerebral blood flow (CBF) and cerebral metabolism in comatose patients. In the absence of cerebral ischaemia, the arterio-venous oxygen difference ($AVDO_2$) and CBF have the relationship illustrated by the solid curve with cerebral metabolic rate for oxygen ($CMRO_2$) relatively constant at an average of 0.9 μmol/g/min. In the presence of cerebral ischaemia/infarction (arrows), $AVDO_2$ and CBF have an unpredictable relationship.

Decreased values of arterio-venous oxygen difference are difficult to interpret, representing either cerebral hyperaemia or extremely low flow states where non-cerebral flow artefactually decreases the arteriovenous difference (e.g. during evolving brain death or severe cerebral infarction[23]). The usefulness and interpretation of high jugular venous saturation (> 80%) remains conjectural. Whether this reflects cerebral hyperaemia or decreased oxygen extraction or both has not been conclusively established. An uncontrolled study by Cruz *et al*, showed that the outcome of head injured patients managed aggressively with 'optimised hyperventilation' to maintain a normal cerebral oxygen extraction ratio was significantly better than a historical cohort of patients managed with cerebral perfusion pressure targeted therapy over a ten year period.[26] Despite these encouraging results, this study should be interpreted with some circumspection due to uncontrolled nature of the trial and significant intervention bias in the treatment group. Furthermore,

derived indices used to quantify cerebral oxygenation such as cerebral oxygen extraction ratio, cerebral haemodynamic reserve and lactate-oxygen index are calculated using the standard Fick principle and have not been validated in any animal or clinical trials.

The aggressive use of hyperventilation to induce cerebral oligaemia in face of suspected hyperaemia as suggested by high jugular venous saturations has not been substantiated in studies using more sensitive markers of cerebral blood flow and oxygenation.[23] These studies consistently show that hyperventilation remains a potent inducer of cerebral oligaemia and hypoxia, particularly in the first 48 hours following injury, even in the presence of raised jugular venous saturations.

Assessment of clinical management

Given the advances in neuromonitoring, accurate delineation of the extent of the primary injury and detection of secondary insults remains limited. Most of the information obtained reflects global change and may underestimate the pathophysiological processes at a regional or cellular level. However, it remains intuitive and somewhat engaging to hypothesise that if patients are maintained in a stable condition with assiduous attention at maintaining CPP and avoiding potentially compromising therapies, then outcome may be improved.

An insight into this question was obtained in a longitudinal study performed at the Royal Adelaide Hospital from 1992 to 1996. Over the initial two year period, an observational study outlining causes and associations of sustained jugular venous desaturation (< 55%) in patients with severe closed head injury (defined as a Glasgow Coma Score < 8 or with evidence of intracranial hypertension on initial CT scan) was performed.[27] Intracranial pressure was measured with intraparenchymal strain gauge monitors in addition to continuous transcranial Doppler insonation of the middle cerebral artery and continuous jugular venous oximetry. Clinically significant jugular venous desaturation was defined as a saturation of < 55% for more than 5 minutes duration in the presence of normal light intensity and calibration.

These parameters, in addition to routine haemodynamic measurements were sampled using a continuous computerised acquisition system for the duration of period of monitoring. During this period, therapy was directed at lowering sustained rises in intracranial pressure, using intermittent hyperventilation to a lower limit $PaCO_2$ of 28 mmHg, routine administration of mannitol to a maximum measured osmolality of 330 mosmol/l and modest fluid restriction.

Following the results of this observational study and in accordance with the AANS guidelines, a revised management algorithm was developed and implemented into clinical practice at the end of the two-year period. Therapy was then directed to maintain a right atrial pressure of 5 - 10 mmHg (in an attempt to achieve euvolaemia) and when attained, adrenaline or noradrenaline was titrated to achieve a CPP of at least 70 mmHg. Ventilation was tailored to achieve normocapnia ($PaCO_2$ > 35 mmHg) and fluids were administered so that measured osmolality did not exceed 300 mosmol/l. All sustained rises in intracranial pressure of > 20 mmHg, not responding to sedation and analgesia, mandated urgent CT scan to exclude intracranial mass lesions. During these episodes, mannitol was intermittently administered in boluses not exceeding 20 grams (within the confines of the prescribed venous pressure and osmolality). Sustained jugular venous desaturations mandated augmentation of CPP with adequate intravenous volume or augmentation with catecholamines and ensuring normocapnia. Incremental mannitol was only administered if the desaturation occurred in the context of raised intracranial pressure, and similarly, urgent CT scan were performed. An oligaemic pattern on transcranial Doppler in association with raised ICP and jugular venous desaturation indicated further augmentation of CPP with intravenous fluids and/or inotropes.

On the basis of this change in practice and continued monitoring and surveillance, a second interventional, non-randomised study was performed to determine the impact that this algorithm had on the incidence and causes of jugular venous desaturation.[28] Twenty patients each were studied before and after the institution of the algorithm. The patients were well matched with no difference in demographics or in the median presenting Glasgow Coma Score. Overall, the incidence and duration of episodes of sustained jugular venous desaturations were markedly different between the two groups (Figure 2).

There were significantly fewer episodes of sustained jugular venous desaturation in the intervention group compared with the observational group (42 vs 6 episodes, $p < 0.05$). The episodes of desaturation were also significantly shorter in the intervention group (mean duration 84 vs 38 minutes, $p < 0.05$). In the observational group, 46% of desaturations occurred in the first 24 hours, 38% in the second 24 hours and 16% after 48 hours, whilst in the intervention group, 85% occurred in the first 24 hours, none in the second 24 hours and 1 episode after 48 hours. No episodes occurred later than 72 hours in either group. Importantly, the change in clinical practice was most

markedly reflected in the difference in associations with sustained desaturation between the two groups (Figure 3).

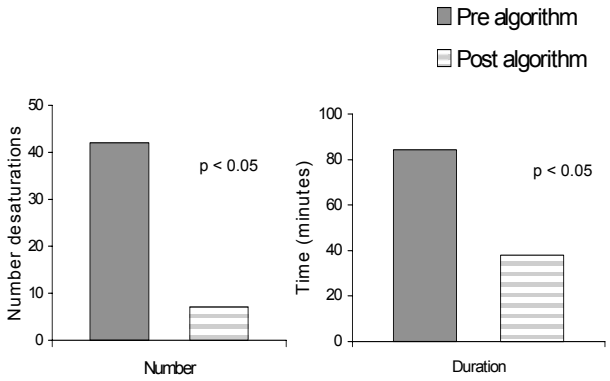

Figure 2. Comparison of the incidence (left-hand panel) and duration (right hand panel) of jugular venous desaturation prior to and after the institution of a cerebral perfusion pressure based management algorithm.

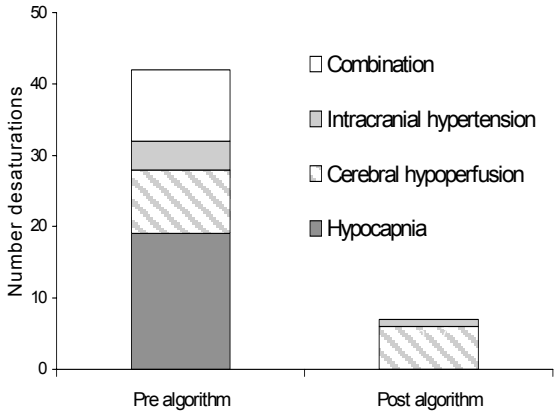

Figure 3. Comparison of the association of sustained jugular venous desaturations with hyperventilation induced hypocapnia, cerebral hypoperfusion (defined as CPP<60mmHg in the absence of intracranial hypertension) and intracranial hypertension as a sole entity prior to and after the institution of a cerebral perfusion pressure based management algorithm.

Before the algorithm, 45% of all episodes of sustained jugular venous desaturation were associated with hyperventilation induced hypocapnia. Cerebral hypoperfusion (defined as a CPP < 60 mmHg in the absence of intracranial hypertension) occurred in 22% of the episodes whilst intracranial hypertension as a sole entity occurred in 9%. A further 24% occurred as a result of combination of the other three.

In the intervention group, there were no episodes of hypocapnic induced desaturation. The majority (85%) occurred solely as a result of cerebral hypoperfusion: all of these occurred on presentation to the ICU, all responded to intravenous fluid resuscitation and probably represented inadequate volume resuscitation from the initial trauma. One patient developed a delayed haematoma which caused a marked rise in intracranial pressure in association with the jugular venous desaturation, which responded to evacuation of the haematoma. There were no differences in the incidence of patients with refractory intracranial hypertension. The six month Glasgow outcome scores between the two groups were obtained using independent assessors (Figure 4).

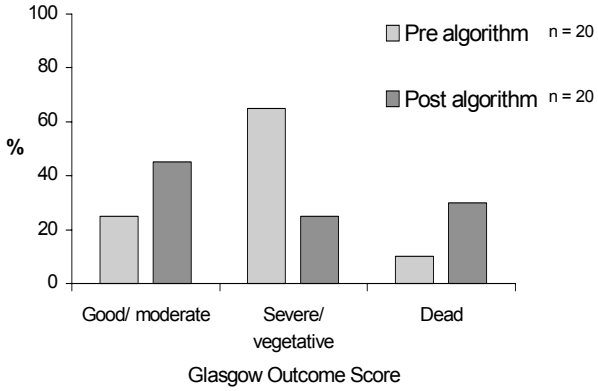

Figure 4. Comparison of 6 month Glasgow Outcome Scores on patients managed prior to and after the institution of a cerebral perfusion pressure based management algorithm.

As the numbers in this series are small, there is no significant difference observed between the groups in patients with good to moderate, severe to vegetative or fatal outcomes. However, there was a trend to more functional survivors and fewer severe or veget-ative survivors in the intervention group. The patients who died in both groups, all had severe primary brain injuries, which largely determined the fatal outcome.

Although it can be deduced that the number and severity of secondary ischaemic-hypoxic insults were significantly reduced in the intervention group, it is not possible to draw a firm conclusion that the significant reduction in episodes of jugular venous desaturation improved outcome (due to the crudeness of the Glasgow Outcome Score, the small sample size and potential for intervention bias). However, this study does lend credence to the theory that adhering to principles enunciated in the AANS guidelines may prevent potentially ischaemic or hypoxic cerebral insults.

Future role of multimodal monitoring and evolution of practice

As a result of this study and subsequent observations, the future role of multimodal monitoring in patients with traumatic brain injury can be considered.

Firstly, intracranial pressure monitoring is an insensitive monitor of the adequacy of cerebral metabolism. Only 9% of sustained episodes of jugular venous desaturation were associated with intracranial hypertension due to mass lesions as a sole entity, the majority of which were detectable by CT scanning.

In the acute scenario, intracranial pressure monitoring is frequently advocated as cerebral monitor in the polytraumatised patient As these patients frequently require prolonged operative interventions for surgical or orthopaedic procedures with the attendant risk of hypovolaemia and hypotension as a consequence, jugular venous oximetry may provide more reliable information about the adequacy of resuscitation and cerebral blood flow during the acute resuscitative period prior to admission to the Intensive Care Unit.

The majority of episodes of jugular venous desaturation occurred in the first 24 hours as a consequence of cerebral hypoperfusion in the absence of raised intracranial pressure. This not only highlights the recognition of cerebral oligaemia as a result of the primary injury,[24] but also the vulnerability of the injured brain to hypovolaemia in the acute phase. In this situation, the polytraumatised head injured patient should be considered for an early placement of a jugular venous catheter or use of transcranial Doppler. Mean arterial and CPP (if possible) should be targeted so that the SjO_2 is maintained >55%, irrespective of the cerebral perfusion pressure.

Secondly, as the majority of desaturations occurred within 36 hours following trauma and none were identified after 72 hours, the indication for jugular venous oximetry outside this time frame is questionable. As outlined above, the interpretation of 'hyperaemic patterns' on jugular venous oximetry remains controversial and probably reflects restoration of cerebral oligaemia following the initial insult or, in the case of a severe primary or secondary injury, true hyperaemia for which treatment options remain limited. There is no conclusive evidence to date that suggests that prolonged jugular venous oximetry monitoring in conjunction with 'anti-hyperaemic' therapies such as induced hypothermia, optimised hyperventilation, decompressive craniotomy or barbiturate therapy has any effect on reducing hyperaemia or improving outcome. However, if these modalities are considered, an argument can be made to use jugular venous oximetry, but purely in the context of detecting jugular venous desaturation and thereby preventing global oligaemia.

Finally, marked inter- and intra-individual variations in optimal CPP have been demonstrated.[29] These studies used jugular venous oximetry and transcranial Doppler to determine breakpoints where cerebral blood flow became pressure dependent and demonstrated a wide range of optimal cerebral perfusion pressures (40 to 90 mmHg) occurring both between patients and within patients monitored at subsequent intervals. Therefore, the aggressive defence of an arbitrary cerebral perfusion pressure of 70 mmHg may be difficult to attain without using high doses of catecholamines such as noradrenaline or adrenaline.

In a subgroup of euvolaemic patients, these infusions may rapidly approach rates of 40 - 80 μg/min of adrenaline or noradrenaline without a sustainable effect on cerebral perfusion pressure. This occurs in patients with normal and compromised cardiac function as a result of β-receptor downregulation induced by endogenous catecholamine release as a result of the traumatic brain injury (an effect which is potentially compounded by exogenous catecholamine infusions).

Catecholamine induced polyuria, and resultant hyperosmolal states are a frequent consequence of blindly targeting CPP. In patients with concomitant myocardial ischaemia or myocardial dysfunction, arrhythmias and exacerbation of myocardial ischaemia may result with obvious consequences. In patients who display 'catecholamine resistance', jugular venous oximetry may be used as a threshold indicator of adequate cerebral blood flow whilst a lower cerebral perfusion pressure is targeted to reduce catecholamine requirements. Provided SjO_2 is > 55%, it may be assumed that global cerebral blood flow is adequate for metabolic requirements at that point, irrespective of the current CPP. Additional assessment of global flow using transcranial Doppler is useful in ensuring that pulsatility index and diastolic flow velocities are maintained at non-oligaemic patterns. In these patients cerebral perfusion pressures of 50 - 70 mmHg may be adequate to meet metabolic requirements.

In conclusion, the impact of management guidelines in traumatic brain injury on qualitative and quantitative outcome has been difficult to determine. Despite technological advances in neuromonitoring, the current state of the art remains somewhat crude, as only global changes are reflected in these measurements which may underestimate the pathophysiological processes. There is however an increasing body of uncontrolled evidence to suggest that the close attention to the defence of systemic and therefore cerebral perfusion pressures prevents global cerebral ischaemia-hypoxic insults. In

this context, the reliance on complex multimodal monitoring may be reduced by effective strategies directed at maintaining a stable haemodynamic milieu. Perhaps the most effective neuromonitor is the pressure measured from a 20 gauge catheter in the brachial artery.

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