Changing trends in monitoring brain ischemia: from intracranial pressure to cerebral oximetry

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Purpose of review

Cerebral ischemia forms the pathophysiological basis of several acute neurological conditions. Successful management of these conditions depends on early and accurate identification of ischemia and prompt treatment. Several techniques of assessing ischemia have evolved over decades. But their importance in the management of neurological patients remains ambiguous.

Recent findings

Current trends in monitoring cerebral ischemia follow two pathways: (1) Indirect methods of assessing global and regional cerebral perfusion [intracranial pressure/ cerebral perfusion pressure (ICP/CPP), transcranial Doppler]; and (2) Assessment of adequacy of cerebral blood flow (CBF) at tissue level by monitoring global or regional oxygenation and metabolism ($SjvO_2$, rSO_2, $PbtO_2$, microdialysis).

Traditional approach to ICP/CPP monitoring has changed to more complex analysis of the ICP waveform to derive variables related to cerebral perfusion and vascular reactivity. Noninvasive techniques of cerebral perfusion pressure assessment are under investigation. Newer methods are being explored to derive indices of CBF autoregulation from various modalities of cerebral monitoring. Direct brain tissue oxygen tension monitoring and microdialysis facilitate regional monitoring of oxidative metabolism. However, there seems to be some complexity in interpreting the results from these monitors.

Summary

A wide range of options are available for monitoring adequacy of regional and global CBF. But no single monitor *per se* fulfils the requirements of all clinical situations. Impact of these monitors on clinical outcomes is equivocal. Also, at present, many of these monitors are invasive and not cost-effective.

Keywords

autoregulation, cerebral blood flow, cerebral ischemia, cerebral metabolism, cerebral oxygenation, intracranial pressure, microdialysis, transcranial Doppler

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Introduction

Inadequate cerebral perfusion and the consequent metabolic changes are the main causes of neurological deterioration in acute neurological conditions such as traumatic brain injury (TBI), subarchnoid hemorrhage (SAH), and so on. The outcome of cerebral ischemia is influenced by the balance between cerebral oxygen demand and oxygen delivery/utilization. Factors influencing this balance are shown in Table 1.

Intracranial pressure (ICP)/cerebral perfusion pressure (CPP) monitoring was started in the 1970s as a simplistic approach to assess adequacy of cerebral blood flow (CBF). This was later followed by some surrogate measures of global cerebral blood flow such as transcranial Doppler (TCD), jugular venous oxygen saturation ($SjvO_2$), and so on. Recent technology has paved the way for bedside monitoring of regional cerebral oxygenation and metabolism. The current review deals with the monitors for cerebral ischemia that have evolved over the past four decades and their current clinical status.

Intracranial pressure/cerebral perfusion pressure monitoring

Raised ICP with consequent low CPP is a major mechanism of cerebral ischemia [1,2] in TBI. Though neurosurgical centers in which ICP is usually monitored have reported low mortality [3,4••], there is no class I evidence supporting routine use of ICP monitoring in TBI. Acceptance of ICP monitoring increased after the publication of the Brain Trauma Foundation (BTF) recommendations [5], but the confidence in ICP monitoring among

physicians seems to be low [6]. The 2007 BTF guidelines, however, recommend the use of ICP monitoring in severe TBI patients at risk for intracranial hypertension as assessed by computed tomography and clinical features. The evidence also suggests that the ICP data are useful in guiding therapy, and there is an improvement in outcomes in those patients who respond to ICP-lowering therapies.

Advanced techniques of intracranial pressure waveform analysis

Traditionally, ICP monitoring has been used only for calculating CPP. Recent studies explored the potential to calculate the ischemic load on the brain from the ICP waveform. 'ICP-dose', which is calculated as the area under the ICP-time waveform, had a good correlation with patient outcome [7]. 'Pressure times dose' (PTDa) is another similar parameter; PTDa for ICP greater than 20 mmHg and CPP less than 60 mmHg had a high predictive power for functional outcome and in-hospital mortality in TBI [8]. Morphological clustering and analysis of ICP (MOCAIP) algorithm developed recently has the potential to forecast the ICP elevation before it actually occurs [9].

Assessment of cerebral blood flow autoregulation by using intracranial pressure waveform

A moving correlation coefficient between mean ICP and mean arterial blood pressure (MAP), called PRx, is used as a measure of CBF autoregulation. A positive PRx is associated with a nonreactive vascular bed. A negative PRx represents normally reactive vascular bed [10]. The U-shaped relationship between PRx and CPP provides a CPP value at which the pressure reactivity is maximal. This value of CPP may be used as the target in the treatment of TBI [11].

Effect of intracranial pressure monitoring on outcome

The outcome benefit of ICP/CPP-based management has never been proven convincingly. Several earlier studies in TBI showed lower mortality with ICP monitoring [12–17]. Ghajar [18] documented a mortality of 12% in the monitored group and 53% in the unmonitored group. In a recent review of all the trials reported after 1970, mortality rate was approximately 12% ($P < 0.001$) lower among patients in the intense ICP treatment group [4••]. Similar benefit could not be shown in many other studies; in some studies the mortality was, in fact, higher with ICP monitoring [19]. The lack of benefit with ICP monitoring suggests that refractory high ICP may simply be a marker of severity of brain injury. Inappropriate interventions, ineffectiveness of high CPP in improving blood flow to ischemic tissue [20], and complications associated with aggressive ICP therapy [21,22] are the other possible causes of futility of ICP monitoring. A recently attempted Cochrane database review could not find appropriate studies to assess the role of ICP monitoring on mortality or severe disability [23].

Key points

- Search for a simple bedside monitor for evaluation of cerebral ischemia continues.
- The emphasis is shifting from intracranial pressure (ICP)/cerebral perfusion pressure (CPP) and transcranial Doppler-CBFV monitoring to noninvasive assessment of CPP, direct measurement of local tissue oxygenation and metabolism (PbtO2 and microdialysis) and multimodality monitoring.
- Indices representing cerebral vascular reactivity are being developed from various neuro-monitors such as ICP, and PbtO2.
- NIRS promises to be a noninvasive cerebral oxygenation monitor for the future but the technology needs further refinement and clearer understanding.
- As of now the evidence for improvement in the clinical outcomes with any of the current monitoring techniques is not convincing.

The concept of effective cerebral perfusion pressure

Effective cerebral perfusion pressure (CPP_{eff}) is a recent concept based on an estimation of the arterial pressure at which CBF becomes zero [the critical closing pressure (CCP)]. The CCP is calculated as follows: middle cerebral artery (MCA) blood flow velocity waveform

Table 1 Factors affecting the cerebral oxygenation

	Factors favoring cerebral oxygenation	Factors interfering with cerebral oxygenation
Systemic factors	High/normal MAP/CPP	Low MAP/CPP
	Normal hemoglobin	Anemia
	Normal/high cardiac output	Low cardiac output
	Normoxia/hyperoxia	Systemic hypoxemia
	Normocapnia	Hypocapnia
Intracranial factors	Metabolic suppression (sedatives/hypothermia)	Hyperthermia
	Normal ICP/CPP	Seizures
	Cerebral vasodilatation	High ICP/low CPP
		Cerebral vasospasm

CPP, cerebral perfusion pressure; ICP, intracranial pressure, MAP, mean arterial blood pressure.

and arterial pressure waveform are concurrently recorded. A regression line drawn between the instantaneous values of MAP and MCA flow velocity is extrapolated to a point at which the flow velocity becomes zero. This MAP when the flow velocity becomes zero is referred to as CCP. CPP_{eff} is then calculated as the difference between MAP and CCP; CPP_{eff} has been found to be a better indicator of CBF changes than the conventional CPP [24].

Noninvasive cerebral perfusion pressure calculation

A transcranial color-coded duplex sonography (TCCS)-based equation has been developed recently for non-ivansive ICP monitoring. This helps to screen patients at risk of increased ICP for optimization of CPP [25•].

Cerebral blood flow monitors

Several direct and indirect measures are currently available for assessment of adequacy of both global and regional CBF.

Transcranial Doppler ultrasonography

Transcranial Doppler (TCD) ultrasonography provides a real-time noninvasive measurement of the blood flow velocity in the basal cerebral arteries, which correlates with CBF if the angle of insonation and the diameter of the insonated vessel remain constant. TCD is very useful in the diagnosis of high-velocity states caused by cerebral vasospasm or hyperemia. Distinction between the two conditions is made by calculating Lindegaard ratio, which is the ratio of MCA flow velocity to extracranial internal carotid artery (ICA) flow velocity. An increase in MCA flow velocity without a change in the Lindegaard ratio suggests hyperemia, whereas an increase in MCA flow velocity with an increase in the Lindgaard ratio suggests cerebral vasospasm. The pulsatility index calculated from the flow-velocity waveform reflects the cerebral vascular resistance (CVR). This parameter is calculated as the difference between the peak systolic velocity and end-diastolic velocity divided by the mean velocity. Several dynamic and static autoregulatory tests have been developed to assess the reactivity of the cerebral circulation [26,27]. The autoregulatory 'threshold' for CPP has been determined by using TCD [28].

A recent development in TCD technology – the transcranial color-coded duplex sonography (TCCS) – helps visualization of the arteries in color, and measurement of angle-corrected blood flow velocities at a specific site of the artery.

Clinical uses of transcranial Doppler ultrasonography

TCD ultrasonography is routinely used for the diagnosis of vasospasm and evaluation of its therapy in SAH [29]. The severity of vasospasm correlates with the degree of acceleration of the flow velocities [30]. The accuracy of TCD to detect vasospasm is good only for MCA, terminal ICA and basilar artery. Its sensitivity is low and specificity only moderate for ACA [31]. TCD is not very sensitive for the detection of distal vasospasm.

TCD flow velocities are used as surrogate markers of CBF changes in TBI. They are also used to test autoregulation, vascular response to CO_2 and traumatic vasospasm. An admission flow velocity of less than 28 cm/s predicts early mortality in patients with TBI [32]. Patterns of TCD flow velocity consistent with a progressive reduction in CPP have been described – an initial increase in systolic velocity and decrease in diastolic velocity occurs, followed by an oscillatory pattern and finally total obliteration of the waveform [33]. Though pulsatility index can be used as an approximate pointer of ICP level, it cannot replace ICP monitoring [34]. TCD is also used as an ancillary tool to demonstrate intracranial circulatory arrest for the diagnosis of brain death.

Recently, TCD has been assuming a greater role in the management of stroke. It provides a rapid, bedside assessment of the vascular territory involved. In MCA stroke, its sensitivity, in comparison with angiograpy is 91% and its specificity, 93% [35]. Fast insonation protocols have been developed for rapid diagnosis and early thrombolytic therapy [36,37]. After thrombolysis, TCD facilitates continuous monitoring for reocclusion, distal occlusion, restenosis and recanalization and also to identify hyperemia. In CLOTBUST II trial, ultrasound *per se* facilitated breaking down the thrombus and assessment of recanalization during tissue plasminogen activator (t-PA) therapy [38]. Consensus recommendations based on TCCS for the assessment of intracranial arteries in clinical trials on acute stroke have been published in 2009 [39].

Jugular venous oxygen saturation

$SjvO_2$ is a measure of global balance between cerebral oxygen delivery and utilization. Measurement of $SjvO_2$ can be made continuously by using fiber-optic catheters or intermittently, by analyzing the blood sample using a co-oximeter. The normal range for $SjvO_2$ is 60–75%, and desaturation to less than 50% is regarded as indicative of cerebral ischemia. $SjvO_2$ also decreases when there is disproportionately high metabolism compared to CBF (e.g. seizure or hyperthermia). However, some recent studies claim that up to half of the measured desaturations in $SjvO_2$ below 50% may be false positives [40]. High $SjvO_2$ is seen when oxygen demand decreases secondary to mitochondrial dysfunction or cell death.

Clinical utility of jugular venous oxygen saturation monitoring

In TBI, $SjvO_2$ monitoring provides an early diagnosis of ischemia resulting from either intracranial or systemic

causes [41,42]. $SjvO_2$ monitoring is used for optimizing hyperventilation, and CPP. Used along with TCD, $SjvO_2$ helps to distinguish cerebral hyperemia from vasospasm. Cruz [43] identified a group of head-injured patients who responded to pentobarbital with a decrease in $SjvO_2$. Similar observations were made with propofol too in elective craniotomy patients during hyperventilation and hypothermia [44]. The vasoconstrictive effects of the agents probably caused the oligemic cerebral hypoxia. Small series have shown that $SjvO_2$ monitoring may improve outcome after TBI [45–47]. Level III evidence of BTF guidelines advocates maintenance of an $SjvO_2$ greater than 50%. In patients undergoing cardiopulmonary bypass (CPB) procedures, $SjvO_2$ was higher among those who had postoperative cognitive decline [48].

Jugular venous oxygen saturation monitoring is a global measure; it has a poor correlation with regional tissue oxygenation in the areas of focal pathology [49]. Positron emission tomography (PET) and microdialysis studies showed that $SjvO_2$ does not decrease to below 50% until 13% of the brain becomes ischemic [50].

Arterio-jugular venous difference of plasma lactate is used in the diagnosis of cerebral ischemia with a sensitivity and specificity of 3.3 and 97.7%, respectively, and a false-negative rate of 96.7% and a false-positive rate of 2.3% [51].

Near-infrared spectroscopy

When a light beam in the near-infrared red range (700–1000 nm) is passed through brain tissue, it is both scattered and absorbed. The absorption is proportional to the concentration of certain chromophores, mainly iron in hemoglobin and copper in cytochrome aa3. Changes in the concentration of near-infrared light as it passes through these compounds can be quantified using a modified Beer-Lambert law [52]. The system uses two sensors. The proximal sensor records infrared light reflected from superficial tissues, whereas the distal signal represents the brain tissue saturation. The subtraction between these two signals represents a venous weighted estimate of the regional cerebral oxygen saturation (rSO_2).

Clinical use of near-infrared spectroscopy

Significant changes in cerebral oxygenation were detected by near-infrared spectroscopy (NIRS) in patients undergoing deep hypothermic circulatory arrest (DHCA). NIRS has been used to test for adequate brain protection during aortic arch surgery under DHCA [53]. NIRS changes precede changes in ICP in patients having delayed traumatic hematomas [54]. In patients with carotid artery occlusion, oxyhemoglobin saturation at rest measured by NIRS could discriminate symptomatic from asymptomatic patients [55].

Near-infrared spectroscopy has been compared with jugular venous oximetry and brain oxygen tension [56]. rSO_2 had low accuracy for detecting moderate cerebral hypoxia ($PbtO_2 \leq 15$ mmHg) and was moderately accurate for detecting severe cerebral hypoxemia ($PbtO_2 \leq 12$ mmHg).

Preoperative risk stratification for long-term morbidity and mortality in cardiac surgical patients has been done with NIRS. Preoperative values are reflective of the severity of cardiopulmonary dysfunction [57].

Near-infrared spectroscopy has been used to test CBF autoregulation [58]. An NIRS-based index called total hemoglobin reactivity (THx), was correlated with pressure reactivity index (PRx) derived from ICP and blood pressure waveforms [59]. The NIRS-based autoregulatory index was also compared with a similar index derived form TCD called Mx in patients undergoing CPB [60].

Brain tissue oxygen tension

Given the metabolic heterogeneity of brain areas, particularly after injury, cerebral oxygenation may vary between various regions of the brain. $PbtO_2$ monitoring provides a highly focal measure of cerebral oxygenation. This monitoring is more useful and the therapy better directed, if the probe is placed in the 'penumbra zone'. The physiology and practical aspects of $PbtO_2$ monitoring have been reviewed recently [61].

There is an ongoing debate on what the measured $PbtO_2$ represents. Rosenthal *et al.* [62] found a significant relationship between $PbtO_2$ and the product of CBF and cerebral arterio-venous oxygen tension difference, which suggests a strong association between $PbtO_2$ and diffusion of dissolved plasma oxygen across the blood–brain barrier.

$PbtO_2$ value in patients with normal ICP and CPP is 25–30 mmHg [63] and the critical threshold for ischemic damage is around 10–15 mmHg [64].

Clinical role of brain tissue oxygen tension

In TBI, hypoxic episodes are common even when CPP and MAP are within normal range [65] and cerebral oxygenation is poorly predicted by usual clinical and physiological factors [66].

$PbtO_2$ has been monitored in clinical studies involving osmotherapy, diagnosis of vasospasm, benefits of decompressive craniotomy and the adverse effect of spontaneous hyperventilation in TBI [67–70,71•,72]. A $PbtO_2$

value of 0 mmHg has been shown to correlate with clinical diagnosis of brain death in children with TBI [73].

Evaluation of the autoregulatory status of cerebral circulation by brain tissue oxygen tension

The index of tissue oxygen reactivity (ORx), calculated as the correlation coefficient between $PbtO_2$ and CPP over a period of time, can be used as an indicator of CBF autoregulation. This parameter was compared with PRx index [74]. A greater increase in $PbtO_2/PaO_2$ in response to an oxygen challenge is associated with poorer outcome [75••]. This probably is a pointer to the loss of cerebral vascular reactivity and a consequent passive increase in $PbtO_2$ during oxygen challenge.

Brain tissue oxygen tension and outcome

Although low $PbtO_2$ is associated with poor outcome, it is not clear if manipulation of this variable can positively influence the outcome. Several studies compared $PbtO_2$-based therapy with ICP/CPP-based therapy in TBI [76–78]. In one study, among patients with similar ICP and CPP levels, mortality rate in patients treated using conventional ICP and CPP management was 44%, whereas addition of $PbtO_2$ monitoring decreased it to 25% ($P < 0.05$) [78]. Overall, 40% of patients receiving ICP/CPP-guided management and 64.3% of those receiving $PbtO_2$-guided management had a favorable short-term outcome ($P = 0.01$). In a study of 139 patients treated by a $PbtO_2$-guided protocol, elevated ICP and persistent low $PbtO_2$ at 2 h (16.23±14.75 mmHg in patients who died vs. 25.97 ± 13.47 mmHg in the survivors, $P < 0.001$) represented increasing odds of death [odds ratio (OR) 14.3 at 48 h]. Patients with favorable outcomes had significantly higher mean daily $PbtO_2$ and CPP values compared to nonsurvivors (day 0: 14.24 ± 17.19 vs. 21.33 ± 18.05, $P < 0.05$; day 4: 19.51 ± 10.73 vs. 27.99 ± 4.07, $P < 0.0001$) [76].

The outcome benefit seen in the above studies could not be reproduced in other studies. Though $PbtO_2$-guided therapy was associated with a decreased duration of episodes of cerebral hypoxia, there was no significant improvement in the outcome [79]. In the largest reported study comprising 629 patients of severe TBI, $PbtO_2$ monitoring did not reduce mortality; on the contrary, it was associated with poorer neurological outcome and increased hospital resource utilization [80].

Cerebral microdialysis

Cerebral microdialysis allows continuous monitoring of changes in brain tissue chemistry. The underlying principle of this monitor is that biochemical changes occur before low CPP is detectable [81]. The key substances that can be analyzed from the dialysate are: glucose, lactate, pyruvate, adenosine, xanthine, glutamate, aspartate, gamma amino butyric acid, glycerol, potassium, cytokines and administered drugs (e.g. antibiotics, temazolamide).

Clinical utility

Lactate and the lactate pyruvate index (LPI) are the two markers that are quite frequently used to detect brain tissue hypoxia. However, $PbtO_2$ and lactate or lactate pyruvate ratio seem to have a complex relationship; in many cases, lactate or LPI might have increased, whereas $PbtO_2$ values are within the normal range [82].

In TBI, cerebral microdialysis has been used to guide CPP targets, and hyperventilation [83]. Derangement of metabolism during periods of intracranial hypertension has been associated with a reduction in brain glucose and elevation of the lactate pyruvate ratio. The concentrations of excitatory amino acids – glutamate and aspartate – had a wide variation. Energy metabolism may be impaired in severe TBI even in the presence of adequate cerebral oxygen transport.

In patients with SAH, an increased risk of metabolic derangement was noted at hemoglobin concentrations below 10 g/dl [84]. Recently, microdialysis has been used to identify new biomarkers of cellular injury [85]. Some authors claim that the local chemistry is weakly correlated to ICP and CPP and no significant correlation was found between clinical outcomes and microdialysis [86].

Other techniques of cerebral blood flow assessment

Of the several other techniques that are under trial, some provide continuous measurement, whereas the others offer only snapshot values.

Ultrasonic perivascular flow probe

An ultrasonic perivascular flow probe has recently been developed for direct intraoperative CBF measurement [87,88]. Using this technique, it has been noted that re-application of the clip was required in about one-third of the patients undergoing intracranial aneurysm surgery [88].

Thermal diffusion technique

Thermal diffusion flow measurement is a technique of real-time continuous measurement of CBF. The probe has two gold plates, one heated and one nonheated. The temperature difference between these plates is converted to a CBF value. This technique measures blood flow in small volumes of tissue, hence there is possibility of inaccuracy, as brain blood flow distribution is heterogeneous. Studies have shown that CBF estimated by thermal diffusion correlated with $PbtO_2$ in 90% of episodes [89]. Cerebral vasoreactivity has been assessed in

severe TBI patients using the CBF probe by calculating changes in the local CVR in response to changes in MAP and hyperventilation. Response to CO_2 changes was more consistent while response to MAP changes was variable [90].

Radiological techniques

Imaging techniques such as perfusion CT, stable-xenon-enhanced computed tomography (XeCT), perfusion MRI, single photon emission computed tomography (SPECT) and PET provide information on regional CBF. The limitation of these techniques is that they are single shot measurements, and require the patients to be transferred to the facilities.

Conclusion

In conclusion, technology and concepts of monitoring cerebral ischemia have come a long way from indirect measures like ICP and CPP to direct $PbtO_2$ and microdialysis. With some of the current devices, it is possible to monitor changes in cellular physiology. The newer challenges are to comprehend the physiological basis and clinical implications of the monitored parameters and to identify an ideal combination of global and regional monitors that meet the requirements of given clinical situations. Multimodal monitoring with ICP, TCD, $PbtO_2$, microdialysis appears to be the future of monitoring and managing cerebral ischemia.

Acknowledgements

Conflicts of interest

None declared.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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