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The Utility of Cerebral Blood Flow Assessment in TBI

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Abstract Over the past few decades, intracranial monitoring technologies focused on treating and preempting secondary injury after traumatic brain injury (TBI) have experienced considerable growth. A physiological measure fundamental to the management of these patients is cerebral blood flow (CBF), which may be determined directly or indirectly. Direct measurement has proven difficult previously; however, invasive and non-invasive CBF monitors are now available. This article reviews the history of CBF measurements in TBI as well as the role of CBF in pathologies associated with TBI, such as cerebral autoregulation, hyperemia, and cortical spreading depression. The limitations of various CBF monitors are reviewed in order to better understand their role in TBI management.

Keywords Cerebral blood flow · Traumatic brain injury · Intracranial monitoring · Cerebral autoregulation · Hyperemia · Cortical spreading depression

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Introduction

With improved access to medical care and better treatments for traumatic brain injury (TBI), hospitals will likely observe an increase in encounters and patients will experience a decline in mortality over the next decade. This trend makes neurocritical care increasingly pertinent and the related technologies increasingly relevant to the management and understanding of TBI [1–3].

TBI is classified into two components: primary and secondary injury. While primary injuries are the result of mechanical forces causing compressive and shearing injuries, secondary injuries are believed to be the consequence of subsequent physiologic insults including ischemia, hypoxia, and metabolic disturbances [4]. Secondary injuries, especially hypotension, significantly impact outcome after TBI [5–7]. Hypotension worsens outcome by permitting cerebral ischemia. Therefore, ensuring adequate blood flow to and perfusion of cerebral tissue is a mainstay of TBI management.

Cerebral blood flow (CBF) can be measured both directly and indirectly; however, direct measurement has long proven challenging. Therefore, surrogate variables have been used to monitor and treat patients with TBI. Cerebral perfusion pressure, which is the difference between mean arterial pressure (MAP) and intracranial pressure (ICP) (CPP = MAP-ICP), can be easily calculated based on direct ICP measurement. Although the ideal CPP threshold to optimize CBF has not been clearly defined, most authors suggest that values of 60–70 should be adequate [8]. Given the heterogeneity of physiologic dysfunction in TBI, understanding the patterns of CBF dysfunction affords the clinician better management strategies aimed at preventing ischemia in the head-injured patient.

History of Cerebral Blood Flow Measurements in Traumatic Brain Injury

The measurement of CBF is predicated on the Fick principle which states that the quantity of a substance taken up by an organ is equal to the blood flow through that organ multiplied by the difference of the arterial and venous concentrations [9]. Kety et al. demonstrated that CBF could be quantified by measuring concentrations of inert gas within tissue [10]. Subsequently, radioisotopes, specifically Xe-133, have been used to document cerebral uptake and to calculate CBF [11]. Computer tomography using stable Xenon (Xe/CT), rather than the isotope form, has since became the most validated method for measuring CBF, likely owing to its radio-opacity similar to iodine [12]. Xe/CT as a measure of CBF has undergone rigorous cross-correlation assessment with destructive (microspheres [13], iodoantipyrine [14]) and in vivo (xenon133 [15], PET [16], thermal dilution flow probes [17]) CBF technologies.

Analysis of CBF plays a key role in the management of TBI. Historically, aggressive hyperventilation, with resultant vasoconstriction, was the mainstay of therapy in order to treat elevated ICP. However, this intervention could prove injurious to patients with cerebral ischemia. Early work utilizing Xe/CT in the assessment of TBI patients showed that ischemia was common in the acute phase of TBI [18]. Using quantitative CBF, a safe level of hyperventilation in the head-injured patient could be defined to avoid secondary iatrogenic ischemia [19].

Transcranial Doppler Ultrasound

Transcranial Doppler (TCD) ultrasound is a well-studied tool that offers a non-invasive and easily reproducible method for calculating CBF. TCD is based upon measurements of flow velocity, FV, through a cerebral vessel. A linear relationship is described between CBF and FV assuming a stable cross-sectional area and angle of insonation:

$$\mathrm{CBF} = \mathrm{FV} \times (\text{area of the insonated vessel}) \times (\text{cosine of angle of insonation})$$

TCD-based studies represent flow velocity rather than actual blood flow, and increases in velocity measurements may be secondary to increased blood volume or decreased vessel caliber with no effect on local CBF [20]. The Lindegaard ratio (LR), the ratio of the middle cerebral artery velocity to the internal carotid velocity, may help to determine whether vascular narrowing is the cause [21, 22] but remains an indirect technique for the measurement of CBF.

Blood flow assessments may also be useful in the management of TBI in order to determine the response to an intervention. This may be related to hyperventilation as described above or other physiologic variables such as blood pressure management. In addition to induced hyperventilation, patients with severe TBI may hyperventilate to very low levels and the clinical significance of this is difficult to assess without measurement of CBF. In some patients with brain injury, hyperventilation may induce ischemia and, therefore, CBF monitoring may guide sedative therapy and mechanical ventilation.

The use of Xe/CT in the first few hours after TBI has revealed CBF values below the ischemic thresholds of 18 mL per 100 g of tissue per minute in 31 % of TBI patients [18]. Ischemia defined by Xe/CT studies in TBI patients has also been found to be predictors of long-term outcome [23]. This observation raises the concern for the routine use of hyperventilation in the acute phase of TBI management [24, 25]. After the initial hypoperfusional phase recognized in TBI patients, two additional phases of CBF response have been identified [26–28]:

1. Hypoperfused phase (day 0) defined by low CBF and relatively normal MCA velocity
2. Hyperperfused phase (days 1–3) defined by raised CBF, high MCA velocity, and normal LR
3. Vasospasm phase (days 4–14) defined by a lower CBF, high MCA velocity, and high LR

It is clear that significant variation in this response is observed within subgroups of patients depending on age, severity of primary and secondary injury, etc. In addition, the vascular response following TBI not only varies from patient to patient but also varies within a single patient at different time points necessitating individualized care. This concept represents a departure from the standard ICP- or CPP-targeted therapies. Although generalized trends have been observed, as mentioned before, significant variations can occur in subgroups depending on a variety of variables making it desirable to ensure CBF monitoring to identify each patient's CBF profile and to guide therapeutic interventions.

Disturbances of Cerebral Blood Flow in Traumatic Brain Injury

Cerebral Autoregulation

In 1938, Fog demonstrated that an increase in blood pressure led to vasoconstriction in surface vessels of the brain and vice versa for a decrease in blood pressure [29]. Lassen then established that CBF is independent of changes in MAP within a range, creating the well-known autoregulatory curve [30].

Cerebral autoregulation (CA) is a protective hemodynamic mechanism evolved to protect the brain from fluctuations in

CPP causing either hypoperfusion or hyperperfusion (Fig. 1). The mechanism of autoregulation is an intrinsic property of the cerebral vasculature not related to chemical feedback and shown to occur in sympathetically and parasympathetically denervated animals [31]. Vasodilation and vasoconstriction represents the "first-line" immediate response to falling and rising perfusion pressure, respectively, which are secondary to a "myogenic response" [32]. Changes in precapillary resistance (R) which underlie cerebral autoregulation can be calculated with the below equation [33]:

$$R = (\text{Pa–ICP}) \Big/ F$$

R	Precapillary resistance
Pa	Arterial blood pressure
ICP	Intracranial pressure
CPP	Cerebral perfusion pressure = Pa − ICP
F	Cerebral blood flow

The state of cerebral autoregulatory dilation can be assessed by measuring CBF before and after a vasodilatory challenge [34, 35]. If the vasculature is already maximally vasodilated, giving a vasodilatory agent such as acetazolamide or CO2 will demonstrate that the area in question cannot adequately vasodilate further and may in fact demonstrate a paradoxical decrease in flow (steal) due to vasodilation of surrounding beds. In a diffuse problem such as TBI, it is critically important to have a quantitative assessment since such changes may occur symmetrically [36].

Measurement of ICP, when coupled with TCD or provocative hemodynamic maneuver, may provide a surrogate measure of vascular reactivity in TBI [37]. For example, if ICP remains stable with changes in arterial blood pressure, then CA is thought to be preserved, whereas if vessels have reached maximum vasodilation, then an increase in arterial pressure will result in an elevation in ICP [38].

In TBI, various indices have been calculated as surrogate markers for CA based upon the aforementioned suppositions. The mean velocity index (Mx) is the correlation coefficient between flow velocity (FV) and CPP and can be calculated continuously with TCD and CPP waveforms. A positive Mx indicates disturbed reactivity, which is significantly associated with unfavorable outcomes in the first 2 days after TBI [39]. While Mx assesses the response of one individual artery, the cerebrovascular pressure reactivity (PRx), which is calculated by determining the correlation coefficient of time-averaged data points of ICP and arterial blood pressure, attempts to reflect a more global response [40].

In a validation study, significant correlations were found between positron emission tomography (PET)- and TCD-based autoregulation calculations defined as the static rate of regulation (SROR), which measures the percentage change of cerebrovascular reactivity divided by the percentage change in CPP [41]. More specifically, significant correlations were found between PET-based SROR calculations and TCD-based PRx index [42]. Using TCD-based indices, another study found that TBI patients experienced disruption of CA illustrated by a positive correlation of both indices. Furthermore, this study demonstrated that PRx and Mx values correlated significantly with 3-month clinical outcomes [43]. PRx was more strongly associated with in-hospital mortality, and a PRx greater than 0.3 was associated with an increase in mortality rate from 20 to 70 % [44]. Patients with advanced age had significantly disturbed cerebrovascular reactivity as

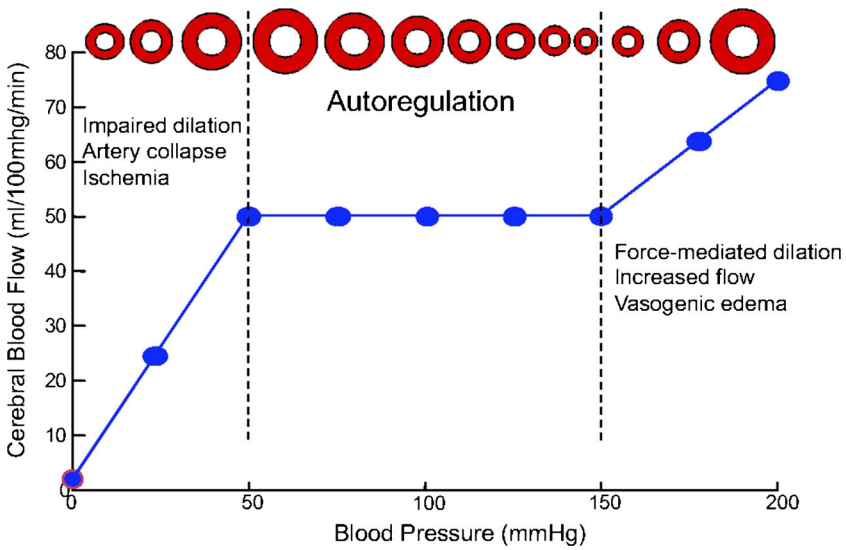

Fig. 1 Cerebral blood flow in relation to artery lumen diameter. *Dotted lines* represent the lower and upper limits of cerebral blood flow autoregulation. *Red circles* represent the cerebral arteries, and *blue line* represents the cerebral blood flow. Modified from Mangat (129); used with permission. AJP-Heart Circ Physiol • doi:10.1152/ajpheart.00490.2012 • www.ajpheart.org

measured by PRx possibly providing some rationale for their worse outcomes [45].

Steiner et al. described "autoregulation"-guided therapy, which targets an optimal CPP (CPP_{opt}), defined as the CPP that correlates to the lowest PRx value indicating intact cerebrovascular reactivity [46]. In a retrospective study of 327 TBI patients, a CPP below CPP_{opt} (e.g., hypoperfusion) was associated with increased mortality, a CPP above CPP_{opt} (e.g., hyperperfusion) was associated with severe disability, and a CPP closely aligned with CPP_{opt} was associated with a favorable outcome [47]. There have been no prospective studies to date investigating autoregulation-guided therapy [48••].

While surrogate markers like Mx and PRx provide some measure of cerebrovascular reactivity, their calculations are not based upon direct measures of CBF. After TBI, cerebral metabolism is significantly affected by fever, pain, stimulation, local neuronal excitation causing variations in perfusion, and metabolism that may not be related to blood pressure and therefore not be apparent by indices such as Mx and PRx [49]. In addition, ICP may be affected by many other variables including mass lesions and edema so may or may not be a reliable foundation for assessing cerebral vascular reactivity.

Recently at the University of New Mexico Hospital, a 5-year experience with multimodality monitoring was published detailing usage of the Hummingbird Monitoring System (InnerSpace Neurosolutions, Tustin, CA). This system allows for placement of an external ventricular drain, parenchymal ICP monitor, as well as two side ports which are commonly used for a Licox (Integra Lifesciences Corp., Plainsboro, NJ) and Hemedex (Hemedex Inc, Cambridge, MA) probe at our institution but may be used for a depth electrode or microdialysis catheter [50]. After detailed synchronization of data streams, CBF and MAP were directly compared. In the case example in Fig. 2a, the plots are highly correlated, indicating that CBF was clearly dependent on fluctuations in MAP, which defines loss of CA. This suggests a direct method of measurement of the degree of autoregulatory function. Figure 2b demonstrates the ability to track the degree of correlation using a correlation coefficient. The closer the value is to 1, the more there is loss of autoregulation. Notably, there were significant changes in this profile with loss of autoregulation on post-injury days 1–3 and subsequent re-establishment of autoregulatory processes after day 4.

These preliminary observations may represent a new method for ongoing assessment of the state of autoregulatory balance by using intrinsic fluctuations in arterial pressure. Recently, Tackla et al. report on 7 TBI patients, where an optimal CPP derived from PRx values is compared to an ideal CPP range based upon regional CBF (rCBF) measurements collected using a Hemedex rCBF probe. Results suggest that there is considerable heterogeneity in the ideal versus optimal CPP values with rCBF-based CPP values being higher in 6 out of the 7 cases than the PRx-based CPP values [52•].

These observations will need to be applied to larger data sets and determine how this direct measurement of CBF and autoregulatory state relates to clinical outcome. In addition, it will be key to attempt to understand how these direct measurements relate to the more widely used indirect Mx and PRx variables.

Hyperemia

As early as 1966, Lassen described a phenomenon of "luxury perfusion" in a traumatic brain-injured patient who appeared to have a normal CBF measurement yet a reduced arteriovenous difference indicating a subnormal cerebral metabolic rate and hence the description of "luxury perfusion" [53]. Xe/CT studies of TBI patients compared to a non-injured control group revealed a transient episode of hyperemia in some patients, subcategorized as either absolute hyperemia defined as a CBF greater than 55.3 mL/100 g/min or relative hyperemia defined as CBF between 32.9 and 55.3 mL/100 g/min with relative hyperemia found in conjunction with a depressed cerebral metabolic rate [54].

Further work investigating TBI in children yielded a common finding of bilateral diffuse cerebral swelling termed "malignant brain edema," which may in fact be age-related hyperemia [55]. Quantitative CBF data with Xe/CT showed that head-injured children had an increase in CBF to 55 ml/100 g/min on post-injury days 1–2 from a mean CBF of 45 ml/100 g/min on post-injury day 0. Also, head-injured children with a favorable outcome had more pronounced increase in CBF on post-injury days 1 to 2 indicating that a hyperemic phase seen during the 1st to 2nd day post-injury may be a normal physiologic response or target goal of therapy [56, 57].

TCD-based studies evaluating the Lindegaard ratio in adult TBI patients reveal a suspected hyperperfusion phase within days 1–5 after the head injury [27, 28]. Kelly et al. demonstrated elevated CBF (>55 ml/100 g/min) by Xe/CT measurements and significantly decreased AVDO2 by jugular bulb catheters during these hyperemic episodes. It was also shown that patients exhibiting hyperemia were younger, on average. Although no statistically significant relationship could be made between high ICP and hyperemia, a subset of patients with elevated ICP and hyperemia were identified to have longer durations of elevated blood flow and worse outcomes [58]. In this group, the hyperemic response may be a negative factor being a covariate with more severe injury.

Turek et al. further evaluated TBI patients with transcranial color-coded sonography (TCCS) and ICP monitoring and demonstrated significant hemodynamic changes in 50 % of patients as defined by increased TCCS flow velocities. Further filtering using Lindegaard ratios defined 31 % of those episodes as hyperemic with increased FV and LR less than 3. A higher proportion of hemodynamic changes as defined above

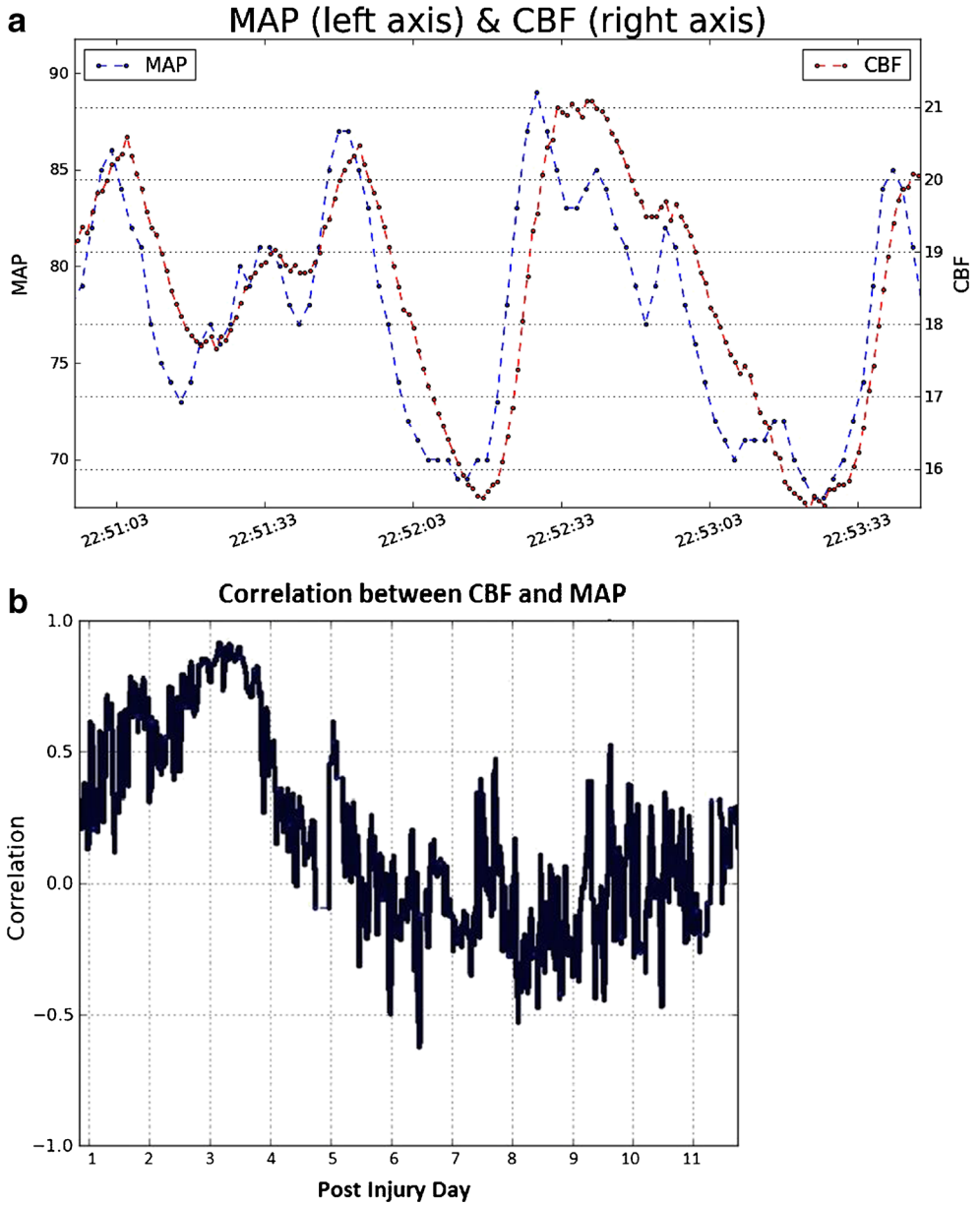

Fig. 2 Data from the Hummingbird Intracranial Monitoring System (InnerSpace Neurosolutions, Tustin, CA) with ventricular and parenchymal ICP monitoring as well as local PbtO2 and CBF monitoring. All data is captured by the Component Neuromonitoring System (CNS, Moberg Technologies) and displayed at bedside. **a** 2–3 min of continuous MAP (*blue dashed line*) and CBF (*red dashed line*) data recorded on an aneurysmal subarachnoid hemorrhage patient with each tracing overlapped over another showing a strong correlation and loss of autoregulation. **b** Correlation values between MAP and CBF recorded over the course of intracranial monitors in an aneurysmal subarachnoid hemorrhage patient, which displays high correlation values initially followed by lower values post-injury day 3 indicating initial dysfunction of autoregulation with subsequent re-establishment of autoregulatory processes [51]

were due to hyperemia when stratified along the lines of elevated ICP versus non-elevated ICP, perhaps identifying useful markers for therapeutic interventions [59].

Figure 3 shows multimodal monitoring data from a 16-year-old traumatic brain-injured patient who had surges in MAP followed by sudden increases in CBF and brain tissue oxygenation ($PbtO_2$) values. Sudden surges in MAP appeared to be linked to sudden increases in ICP as well, which resolved with treatment of MAP back to baseline values.

Cortical Spreading Depression

Described by Leao in 1944, cortical spreading depressions (CSD) are slow, propagating waves of neuronal and glial depolarization [60]. CSDs are found to occur spontaneously in pathologic states such as hypoxic, ischemic, or hyperglycemic brain tissue, and recovery occurs over a prolonged time course [61]. During CSD in a relatively normal tissue (such as experimental conditions or migraine), oxygen consumption increases with an

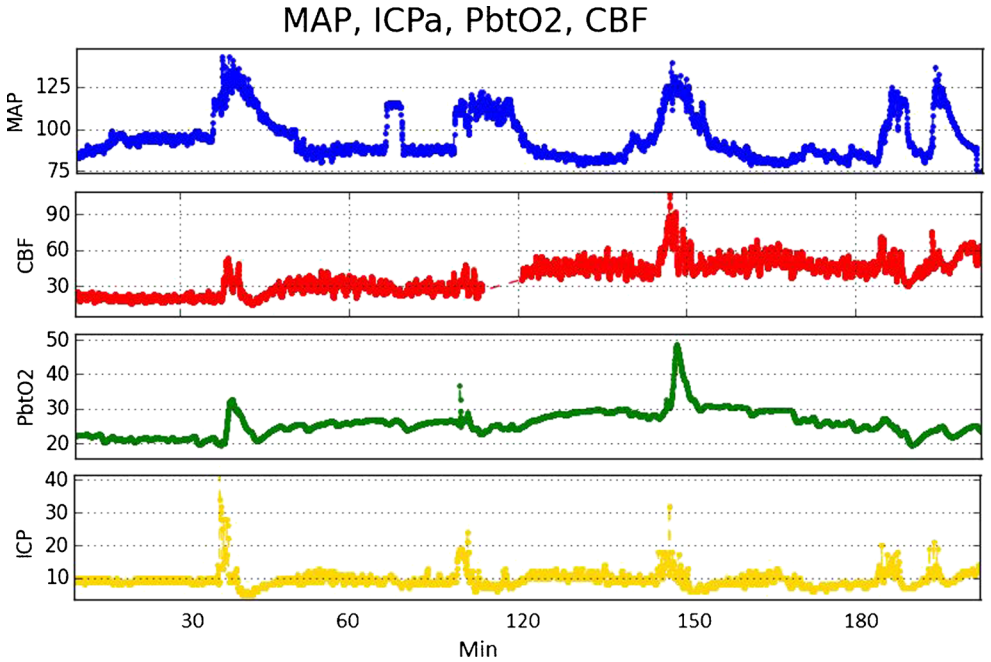

Fig. 3 Data from the Hummingbird Intracranial Monitoring System (InnerSpace Neurosolutions: Tustin, CA) with ventricular and parenchymal ICP monitoring and local PbtO2 and CBF monitoring. All data is captured by the Component Neuromonitoring System (CNS, Moberg Technologies) and displayed at bedside. Strip data above is for a 16-year-old female involved in a motor vehicle collision, who was air transferred to the University of New Mexico Hospital. On arrival, patient had a GCS of 7T and had intracranial monitors placed approximately 24 h after injury. The four rows display MAP, CBF, PbtO2, and parenchymal ICP, respectively. Interval surges in MAP can be correlated to rises in CBF and $PbtO_2$ with associated rises in ICP with downtrending values of all variables as MAP returns back to baseline

initial decrease in CBF [62, 63]. Subsequently, CBF increases by up to 100–200 % [64] to match the metabolic demand of recovery from the depolarization, termed neurovascular coupling.

To test the CBF response to CSD in the human brain, Dreier et al. placed novel subdural opto-electrodes on the cortical surface at the time of surgery in 13 aneurysmal subarachnoid hemorrhage patients. This device allowed for laser Doppler flowmetry and direct current electrocorticography measurements to detect CSDs and simultaneously record regional CBF data. A spectrum of responses to CSD was observed ranging from a "physiologic" increase in CBF to an "inverse" hemodynamic response associated with prolonged episodes of hypoperfusion [65, 66]. In animal models, products of hemolysis within the subarachnoid space have been shown to blunt the increased CBF response associated with CSDs, which may be reflective of the inverse hemodynamic response observed in SAH [67, 68].

Traumatic subarachnoid hemorrhage, cortical contusions, and extra-axial hemorrhage may incite CSDs in TBI. Additionally, complications of TBI, including hypotension, hypoxia, elevated ICP, as well as disturbances in cerebral autoregulation, may contribute to poor brain tissue perfusion and oxygenation, potentially inducing an inverse hemodynamic response to CSD [69].

The incidence of CSD in TBI has been reported to be as high as 50–60 % of patients undergoing craniotomy. A temporal trend was identified with CSDs occurring in greater frequency within the first 36 h and with a second peak occurring days 6–7 post-head injury [70]. The timing of CSDs in TBI patients coincides with the time course of CBF alterations in TBI patients with the greatest risk for hypoperfusion occurring within the first 24 h and a secondary phase of decreased CBF occurring during the proposed "vasospasm" phase, typically seen within days 4–14 post-head injury.

Hinzman et al. demonstrated the role of vascular coupling of CSDs and CBF in TBI patients with an implanted thermal diffusion microprobe adjacent to the electrode strip. An inverse response was recorded in 32 % of CSDs, causing regional hypoperfusion leading to further secondary ischemic insults. Preliminary data suggests that worsening cerebral autoregulation appears to be correlated with an inverse hemodynamic response to CSDs [71••].

There is a consistent association of CSD, particularly clusters of CSD in recovering tissue as well as in severely damaged brain with poor outcome [72]. The inverse hemodynamic response and resultant lower average CBF levels have also been associated with worse outcome [71••]. The evidence is mounting that CSDs in certain TBI patients cause worsening of ischemic injury. Monitoring of CSDs and CBF and the

subsequent neurovascular response may help in targeted therapy aimed at either reducing CSD or mitigating the inverse hemodynamic response. This area of study may represent a novel target for preventing delayed ischemic injury in TBI.

Measuring of CBF in Traumatic Brain Injury

Numerous technologies currently exist that provide either direct CBF measurements or provide a marker of cerebral perfusion, and each has inherent limitations. Technologies provide data that is either continuous vs intermittent, regional vs global, quantitative vs non-quantitative, or invasive vs non-invasive in design. A number of factors including expertise in the aforementioned technologies as well as the capability of an institution will dictate what type of monitoring can be used; however, ideally, coupling continuous, regional CBF data monitoring with intermittent global CBF measures should be an ideal monitoring platform.

Continuous CBF Monitoring

Continuous CBF data is primarily acquired with the use of implanted probes. The thermal diffusion probe consists of two thermistors embedded in a catheter and provides continuous, quantitative, regional CBF measurements. Good agreement is reported between TD microprobe measurements and Xe/CT findings within a 5-cm^3 volume around the probe [73]. Since the design of the TD microprobe is based up on the dissipation of heat from a thermal field created by the distal portion of the catheter, placement of the catheter near a thermally significant vessel can limit data collection. Other limitations of data acquisition include a safety mechanism for not overheating tissue when the patient's temperature reaches 39.5 as well as recalibration occurring every 2 h. In one study, placement of a TD microprobe yielded reliable regional CBF only 39 % of time [71••]. In our experience, the TD microprobe provides reliable data about 30–40 % of the time taking into account dysfunction secondary to placement errors and missing data secondary to recalibrations.

Brain tissue oxygenation (PbtO2) is thought to represent a surrogate measure of CBF and can also be measured using an implanted probe, Licox (Integra Lifesciences Corp.: Plainsboro, NJ). In a PET validated study, absolute values of PbtO2 did not correlate to absolute values of oxygen tension within end capillaries, PvO2; however, there was a significant relationship in changes between the two variables when the probe was placed within non-lesioned brain tissue [74]. Comparing regional CBF values to PbtO2 measurements in TBI patients within the least injured brain parenchyma indicates that low PbtO2 values are most likely a combination of low CBF and/or low PaO2 values [75]. Several studies, utilizing PbtO2-guided therapy, report improved outcomes as compared to historical controls [76–78]. In our experience at UNMH, there was no significant correlation between PbtO2 values and regional CBF data collected from the TD microprobe. We did, however, find a statistically significant difference in PbtO2 values of 22 vs 16 mmHg in patients who survived as compared to those who died, respectively. Interestingly, ICP was not associated with mortality, which is logical given that much of TBI management is aimed at lowering ICP. These data suggest that PbtO2 monitoring may be valuable in prognostication after TBI [79].

Jugular venous bulb oximetry (SjvO2) is an alternative surrogate marker of CBF providing continuous global data on the balance between cerebral perfusion and metabolism. There are technical considerations with laterality of cannulation with most investigators selecting the right internal jugular vein, which typically is the dominant vessel. Variations in CNS venous drainage affect one-sided sampling techniques and have led to bilateral cannulation in some investigations. And while providing a global picture, SjvO2 is limited on providing insight on areas of regional ischemia [80]. The literature is mixed on studies comparing SjvO2 monitoring with regional PbtO2 values with some reporting good correlation [81, 82] and other studies finding no significant correlation in change of each variable [83]. At least 13 % of the brain volume needs to be ischemic for the SjvO2 to be abnormal, and as such, regional ischemic events can be masked by global SjvO2 data [84]. Furthermore, standard practices of hyperventilation as a part of ICP management for traumatic brain injury revealed significant regional ischemia with PET studies undetected by SjvO2 measurements [85]. Nonetheless, the occurrences of desaturations in TBI patients, defined as SvjO2 <50 % for more than 10 min, was found to correlate with worse outcomes [86, 87].

Near-infrared spectroscopy offers a non-invasive method of continuous non-quantitative blood flow measurements; however, this technology has been met with mixed results. Utilizing an optical monitoring technique, changes in oxy- and deoxy-hemoglobin are derived via optodes that are attached to the frontal scalp bilaterally [88]. The targeted region of the brain is the frontal lobes due to the ability to place the pads on the scalp free of hair. However, contusions occurring in the frontal lobes can often confound these measurements. In a validation study, a linear correlation was demonstrated between frontal NIRS cerebral oxygenation measurements and regional CBF on CT perfusion imaging [89]. However, the results have been mixed when comparing the relationship of NIRS cerebral oxygenation with Xe/CT, a quantitative CBF study [90, 91]. Similarly, NIRS cerebral oxygenation does not appear to correlate with jugular venous bulb oximetry [92], although it may correlate with SjvO2 measured on the ipsilateral, but not contralateral, side [93]. In a recent study of 22 TBI patients with approx. 42,000 paired records of regional PbtO2 and NRIS cerebral oxygenation, NIRS was poor at

detecting moderate intracerebral hypoxia defined as PbtO2 <15 but improved to statistical significance with severe intracerebral hypoxia defined as PbtO2 <12 [94]. While it is very appealing to have a non-invasive continuous monitor of cerebral perfusion, further investigations are needed to validate this technology in clinical practice and currently serve best as a complimentary tool in neuromonitoring.

While the above-mentioned technologies offer an advantage of continuous data allowing for potential real-time therapeutic interventions, the major limitation of regional data collection is the inability to generalize that information to the rest of the brain, which can represent a heterogeneous mixture of pathology in traumatic brain injury. This requires more global measures of cerebral blood flow.

Intermittent CBF Monitoring

Imaging modalities such as PET, SPECT, and Xe/CT give more global CBF data and can be used to validate how reflective focal, continuous measurements are to the remainder of the brain. The ability to quickly repeat imaging studies at bedside has made Xe/CT a more desirable tool in evaluating CBF in the head-injured patient in order to determine the optimal management strategy for various parameters. While this non-invasive measurement gives a rather whole brain picture, the main limitation is in its ability to give continuous and immediate CBF data that may change before the next interval scan or changes in other markers like ICP, missing an opportunity for therapeutic intervention [95].

Brain perfusion studies are an alternative imaging modality that utilize an intravascular tracer such as iodine or gadolinium, depending on whether a CT or MRI is used. In contrast to Xe/CT studies that utilize a diffusible gas which is lipid soluble and able to cross the blood-brain barrier, brain perfusion studies detect signal changes secondary to a tracer as it travels through the cerebral vasculature. Brain perfusion studies provide a color-coded map with CBF, cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP) measurements.

Data derived from admission CT perfusion scans as well as Xenon/CT scans are significantly associated with outcome after TBI [23, 96]. Good correlations have been found with CT perfusion and Xe/CT studies [97] as well as CT perfusion and PET-based CBF values [98]; however, the inclusion of large vessels in CT perfusion-based calculations tends to overestimate CBF values [99]. There are technical assumptions inherent in CT perfusion that must be recognized. The enhancement curve from which CBF is calculated is based upon an input artery assumed to be normal, which may or may not be correct in a diffuse injury. These issues allow for variations in calculated CBF values and issues with reproducibility from one investigator to another [100, 101]. Also, there is difficulty with applying the normal CBF and CBF threshold values to those obtained by CT perfusion studies as CT perfusion utilizes an intravascular tracer and reports on intravascular CBF as opposed to Xe/CT and PET studies which utilize a diffusible tracer that passes the blood-brain barrier most likely indicating a related but slightly different physiologic parameter [102••].

TCD assesses flow velocities only for large vessels, and may miss regional areas of impairment. A number of assumptions are made with TCD-based measurements limiting its utility. It is assumed that the diameter of the insonated vessel does not change; this may be problematic in pathologies that exhibit vasospasm, possibly including TBI patients. Also, heterogeneity in collateral circulation may account for a weaker correlation between CBF and FV [103, 104]. Technical issues exist with prolonged data collection specifically with dislocation of the probe especially during routine nursing care changing the angle of insonation and violating the assumed relationship between CBF and FV [105], and while long-term probe fixation devices exist, results have been mixed [106]. Extensive literature is published on various TCD-based indices like pulsatility index (PI) [107], non-invasive ICP [108], pressure reactivity index (PRx) [38, 46], Mx [108], and Sx [109] and their ability to predict ICP, disturbances in autoregulation, and/or TBI outcomes data.

Conclusion

The management of TBI has been guided by the principle of preventing secondary injury. Numerous markers such as ICP and CPP have been monitored in an attempt to guide TBI management but cannot act as a replacement for quantitative markers of CBF. It is important to remember that the various CBF technologies have inherent limitations in their design as well as measurements, and the ideal combination of regional and global data with other well-established markers, such as ICP, has yet to be determined. However, ongoing studies of CBF and other multimodal neuromonitoring are asking more sophisticated questions addressing the underlying pathophysiological processes underlying TBI. Understanding the associations between those pathologic mechanisms and CBF will improve our ability to prevent and/or treat secondary insults. Most importantly, better monitoring technologies will improve our ability to prognosticate outcomes following severe TBI.

Compliance with Ethical Standards

Conflict of Interest Omar S. Akbik, Andrew P. Carlson, Mark Krasberg, and Howard Yonas declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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