Neurocritical Care

ISSN 1541-6933/06/4:83–92
DOI: 10.1385/Neurocrit. Care 2006;04:83–92

Perspectives in Brain Physiology

Neuromonitoring in Neurological Critical Care

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Abstract

In this article, we review technologies available for direct monitoring of cerebral oxygenation and metabolic status, including jugular venous oxygen saturation, brain tissue oxygen tension, transcranial cerebral oximetry with near-infrared spectroscopy, Positron emission tomography oxidative metabolism, single-photon emission computed tomography/computed tomography perfusion and functional imaging, and cerebral metabolite measurement using microdialysis. We also introduce a novel method of monitoring cerebral perfusion that may substitute for direct monitoring of oxygenation in the future.

Key Words: Neuromonitoring; ICP; SPECT; PET; ventriculostomy; cerebral oximetry.

(Neurocrit. Care 2006;04:83–92)

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Neurological Intensive Care Monitoring

Injuries to the central nervous system are characterized by a primary insult followed by secondary or associated injuries. Primary injuries most commonly followed with cerebral monitoring can be broadly categorized into cerebrovascular accidents (ischemic or hemorrhagic) or traumatic (blunt or penetrating). Regardless of the initial insult, a cascade of responses at the molecular, cellular, tissue, and organ level are set into motion in the moments after injury. This response to injury, and impact of injuries to interdependent systems (cardiac, pulmonary, renal, etc.) is more often associated with secondary injury *(8,18–20,55,58,75,91)*. Although some efforts are currently being made to affect primary injury, the main focus of neurological critical care remains prevention of secondary injury *(75,110)*. Epidemiological efforts, such as those made by the Traumatic Coma Data Bank (TCDB) and the International Data Bank, have revealed the impact of secondary insults such as hypotension, hypoxia, and increased intracranial pressure (ICP) *(18–20,49–53,74,76,95)*. For example, Chesnut's analysis of the TCDB concluded that one or more episodes of hypotension, defined as a systolic blood pressure (SBP) less than 90 mmHg, was associated with a doubling of the mortality rate and a dramatic increase in morbidity *(18–20)*. Both of these rates were further exacerbated by concomitant episodes of hypoxia. The significance of these findings and similar epidemiological results is that they identify prognostic variables that are amenable to therapeutic interventions and define the targets for goal-based therapy of neurological injury *(15)*.

Although the processes contributing to secondary brain injury are widely varied, they share a final common pathological pathway characterized by compromise of cerebral tissue perfusion, oxygenation, and metabolism *(18,19,80,91)*. It has been the goal of neuromonitoring to provide for the early detection of these insults so that appropriate interventions can be instituted. There is a rapidly advancing front of technologies offering

Table 1
Devices Both Proven and Experimentally Available to the Neurointensivist for Both Invasive and Noninvasive Neuromonitoring

Neuromonitoring Options
Jugular venous oxygen saturation
Brain tissue oximetry
Near infrared spectroscopy
Microdialysis
Intracranial pressure monitoring
Positron emission tomography
Single-photon emission computed tomography
Computed tomography perfusion
Transcranial Doppler ultrasonography
Quantitative cerebral blood flow
Contrast-enhanced ultrasound

continuous, quantitative, and sensitive assessment of clinically relevant parameters in global and direct indices of cerebral tissue oxygenation and metabolism *(40,54,60,87,99,105)*.

In this article, we review proven techniques and recent advances in the monitoring of critical neurological injury (Table 1). We will first discuss invasive measurements of ICP and cerebral oxygenation, global indices such as jugular venous oxygen saturation ($SjvO_2$), and local indices such as tissue pO_2 monitoring. We then discuss measurements of cerebral perfusion, pressure and metabolism with microdialysis, and positron emission tomography (PET) oxidative metabolism and single-photon emission computed tomography (SPECT)/CT perfusion. We will briefly review continuous quantitate measurement of cerebral blood flow (CBF) and highlight a novel minimally invasive approach for assessing real-time cerebral perfusion as an adjunct measure of cerebral oxygenation in the intensive care unit (ICU).

External Ventricular Drainage/ICP Monitoring

Since its introduction in the 1960s, no single neuromonitoring technique has been as universally accepted by neurosurgeons and critical care physicians as ICP monitoring *(69)*.

Review of the TCDB demonstrates that ICP elevations greater than 20 mmHg and depressions of cerebral perfusion pressure (CPP) were associated with poor outcomes *(35,94)*. Though many "minimally invasive" fiber-optic based pressure monitors are available, the gold standard remains external ventriculostomy. In the accepted technique, a frontal or occipital burr hole is placed over the non-dominant hemisphere, and a silastic catheter is passed into a ventricle. This is then attached to a closed system capable of pressure transduction, with side ports for sampling or instillation.

The major benefit of ventriculostomy is that it is both a diagnostic and therapeutic intervention, and is the neurocritical care equivalent of a central line. Aside from passive pressure monitoring, it affords the clinician the ability to sample cerebrospinal fluid (CSF), not only for infection control, but also for laboratory analysis of metabolites. Novel theraupeutic agents may be instilled into the intrathecal space, bypassing the blood–brain barrier. Ventriculostomies can be more difficult to place than subdural or parenchymal bolts. However, other techniques for ICP monitoring are subject to drift, as much as 3 mmHg/day, and are not subject to recalibration *in situ (11–13,35,85,90)*. Furthermore, multiple head-to-head trials have demonstrated that the complication rate for ventriculostomies performed by neurosurgeons are the same as "less-invasive" pressure monitors *(3,11,12,35,84)*.

The use of ventriculostomy was initially empiric, with no published norms or goals. Review of early trauma patients has shown that patients arriving with a Glasgow Coma Scale (GCS) score of 3–8 and an abnormal computed tomography (CT) are most likely to develop intracranial hypertension *(82)*. Those with altered levels of consciousness with a normal CT but associated age, hypotension, or reproducible posturing are also at risk for elevated ICPs. These patients are most likely to benefit from ICP monitoring. Several studies with such entry criteria have then examined the impact of ICP management on outcome *(2,14,52,82)*. Without ICP monitoring, the published mortality rates for severe head injury (GCS < 8) patients range from 30 to 50% *(2,14,52,82)*. One series reported more than halving the mortality by ICP monitoring and aggressive treatment *(30)*. Currently, there is only class II literature supporting the monitoring of ICP. We will never be able to obtain class-I evidence to support ventriculostomy and ICP monitoring. The ethical and financial hurdles loom too large *(35)*. Despite this limitation, if one were to choose a single invasive monitor to place, ventriculostomy is clearly the answer. Its ability to monitor and treat elevated ICP, along with providing a viaduct for any laboratory study desired on CSF, gives it the greatest benefit to risk ratio, and largest proven impact on outcome.

Jugular Venous Oxygen Saturation ($SjvO_2$)

One of the first technologies developed for examining metabolic demands of the brain during injury was the measurement of jugular venous oxygen saturation ($SjvO_2$) *(7,60,91,99,105)*. Measurements are taken from an internal jugular vein catheter directed to the jugular bulb; if the injury is more global than focal, the dominant jugular vein may be sampled, whereas the jugular vein ipsilateral to focal brain injury may be catheterized in more local injury.

$SjvO_2$ is an indicator of the balance between global cerebral oxygen delivery and metabolic demand *(61,62,91)*. Direct measurement allows for calculation of the aterio-venous O_2 difference, or oxygen extraction by the cerebral tissues. Under normal physiological circumstances, cerebral autoregulation allows for increases in CBF to match increased cerebral metabolic requirements, keeping the arterio-venous difference at a near constant 6.3 ± 2.4 mL O_2/dL blood *(60,91,70)*.

Interpretation of the $SjvO_2$, and its usefulness in directing therapy, requires concomitant measurement of the blood hemoglobin concentration and estimation or calculation of the $AVDO_2$. Given the oxygenation of arterial and venous blood are both governed by $caO_2 = 1.34 \times Hgb(SpO_2) + 0.003(pO_2)$, the $AVDO_2 = 1.39 \times Hgb(SaO_2 - SjvO_2) + 0.003(PaO_2 - PjvO_2)$ *(116)*. If the clinician maintains a critical patient near 100% saturation, and there is no lung injury (i.e., acute respiratory distress syndrome) affecting the partial pressure of O_2 in the blood, then the only variables affecting the A-V difference across the intracranial circulation are hemoglobin and oxygen extraction by the tissues as measured by $SjvO_2$.

During times of injury or stress, there may be perturbations in cerebral autoregulation and/or oxygen extraction that impact the $SjvO_2$. As stated previously, under normal circumstances, the A-V gradient is kept constant by adjusting blood flow to match metabolic requirements. If autoregulation is lost, then $SjvO_2$ may rise or fall depending on the metabolic demand as CBF is kept constant. Additionally, injury pathways in the brain drive the tissues toward nonoxidative phopshorylation, decreasing the metabolic requirements, even if autoregulation is maintained. This absolute drop in cerebral metabolic rate of oxygen consumption ($CMRO_2$) is reflected in an abnormally elevated $SjvO_2$ *(91,105)*.

Based on some of the above assumptions of the cardiopulmonary status of a critically ill patient, normal values and ischemic thresholds have been empirically determined and offered as guidelines for the clinical interpretation of jugular venous oxygenation *(91,105)*. Normal values of jugular venous oxygenation for healthy men, for example, have been found to range from 55 to 71%, with a mean of 61.8%, whereas in patients with head injuries, the range was found to be considerably wider (32 to 96%) and the mean modestly higher (68.1% ± 9.7%) *(32,36,91,92)*. Although ischemic thresholds may differ for individuals with and without cerebral injury, in general, jugular venous oxygenation levels falling less than 50% have been associated with progressive cerebral hypoxia, whereas levels less than 20% typically signal irreversible ischemic injury *(91,105)*. Values greater than 75%, on the other hand, may suggest cerebral hyperemia and portends worse outcome in patients with severe head injury *(21)*.

Although still controversial, jugular venous oxygenation may be used to titrate ventilation rates to maximize reduction in CBF, and therefore ICP by removal of CO_2, while maintaining adequate oxygen delivery *(122)*. As the CBF drops, there is an initial small compensatory drop in $SjvO_2$ prior to a precipitous fall when safe limits of reduced CBF are reached *(1)*. It is additionally useful in the detection of increasing intracranial hypertension, A-V fistulas, and progression to brain death. Note that a single $SjvO_2$ value is not indicative of a clinical diagnosis of brain death—the timecourse of very low $SjvO_2$ progressing to a high, near arterial level as O_2 extraction ceases is merely suggestive. Jugular venous measurements are not, and should not be used as, adjuncts in the legal diagnosis of brain death *(23)*.

There are many problems with jugular venous oxygen measurement that limit its practical application. The main problem is that it is insensitive to the regional hypoxic or ischemic changes that might occur in cases of focal primary traumatic injury or stroke occurring in the periphery of a cerebrovascular distribution *(39,60,105)*. Because of the mixing of venous blood that occurs, there can be wide variation in values obtained; moreover, changes in oxygenation often do not correlate with clinical status. In these latter instances, either invasive or noninvasive neuromonitoring technologies more sensitive to local changes in cerebral oxygenation might be more appropriate. Next, we will consider each of these possibilities in turn.

Brain Tissue Oximetry

Developed as a modification of electrodes originally designed for continuous intra-arterial monitoring in critical care patients, cerebral oxygen tension probes are sensitive to focal cerebral ischemic changes that might otherwise go undetected with a more global measure such as jugular bulb oximetry *(25,60,63,78,99,105,114,115)*. Currently, there are two types of oxygen tension monitors available for clinical use: the Licox (GMS, Kiel-Mielkendorf, Germany) and the Neurotrend systems (Diometrics Medical, St. Paul, MN).

The Licox probe relies on a polarographic Clark-type electrode, consisting of an anode and a cathode in contact with an electrolyte solution. The tip of the electrode is covered by a semi-permeable membrane, such as polypropylene, through which gasses such as oxygen but not other ions or contaminants can diffuse. The electrode then measures the oxygen tension amperometrically, producing a current that is directly proportional to the partial pressure of oxygen reaching the surface of the platinum cathode. With a diameter of 0.8 mm and an overall length of 150 mm, the Licox catheter is sensitive to oxygen tensions over a surface area of 13 mm^2 and may be used in conjunction with a thermocouple temperature sensor.

The second monitor currently available for clinical use is the Neurotrend system, which is a multiparameter sensor using optical fluorescence in combination with fiber optics to offer continuous measurement not only of brain tissue oxygenation and temperature but also of cerebral carbon dioxide and pH levels. Neurotrend's sensors employ a fluorescence-quenching technique in which changes in the wavelength of light reflect changes in the local concentrations of oxygen, carbon dioxide and hydrogen ions. With a diameter of 0.5 mm, the Neurotrend catheter has a sensor membrane length of 25 mm, of which approximately 2 mm is sensitive to each of the parameters recorded in its four internally staggered probes. Because of differences in the required insertion depths (the Neurotrend oxygen sensor lies about 2.5 mm from its tip, necessitating placement at a greater depth in the brain parenchyma than the Licox catheter) and technical specifications, the Licox and Neurotrend systems are difficult to compare, although Sarrafzadeh et al. evaluated the two monitors in seven patients with severe head injuries and found a close correlation of readings between the probes when they were placed in similar areas of brain tissue *(97,105)*.

As oxygen reaches the cerebral capillaries, it relies on passive diffusion down its concentration gradient to traverse the distance from the red blood cells to the parenchymal mitochondria. In addition, because parenchymal oxygen tension reflects regional blood flow and vascularity, partial pressures will vary according to the relative proportions of gray and white matter in the volume sampled, being slightly higher in the former than in the latter (Although CBF normally averages between 50 and 60 mL/100 g/minute, as discussed previously, it varies significantly between gray and white matter, being approximately 70 mL/100 g/minute in the former versus 20 mL/100 g/minute in the latter *[62,119]*).

Despite this variability and the fact that much of the cerebral oxygenation data for so-called "normal" subjects has come from recordings in patients undergoing cerebrovascular surgery or being monitored following severe traumatic brain injury, investigators nonetheless have been able to propose empirically determined ischemic thresholds for cerebral oxygen tension, which they have correlated with similar values obtained for more established neuromonitoring technologies such as jugular bulb oximetry *(26,27,37,60,64,121)*. Although

the methodology employed and the clinical questions addressed have varied among studies, most investigators have found that cerebral oxygen tension levels falling below approximately 20 ± 2 mmHg are indicative of increased risk of cerebral ischemia *(9,105,113,115)*. Consistent with these findings, Kiening et al. and Gopinath et al. determined that the generally accepted threshold for ischemia according to $SjvO_2$ of 50% corresponded to a parenchymal oxygen tension level of approximately 8 to 8.5 mmHg *(37,64)*.

Since its introduction to neurological research and clinical practice, cerebral oximetry has demonstrated that many of the secondary processes complicating primary brain injury can lower parenchymal oxygenation levels *(24,60,99,111)*. Hypotension, hypoxia, intracranial hypertension, and vasoconstriction secondary to hyperventilation have all been shown to lower cerebral oxygen tension *(15,46,121)*. In the case of the latter findings, for example, Manley et al. have used a swine model to demonstrate that an episode of hyperventilation lasting 10 minutes was sufficient to effect a 40% decrease in brain tissue oxygenation, and that this effect was further exacerbated in the context of hemorrhagic shock, in which cerebral oxygenation levels fell 56% from baseline *(71,72)*. Human studies, such as those cited in the evidentiary tables of the guidelines for the Management and Prognosis of Severe Traumatic Brain Injury, which now recommend against the routine use of prophylactic or prolonged hyperventilation, offer concordant findings *(15,24,63,115)*.

Although current cerebral oxygen probes are sensitive to regional hypoxic and ischemic changes that a more global instrument such as $SjvO_2$ might miss, their relative virtue is perhaps their chief limitation as well. Because they can capture data from only a small volume of brain tissue, such devices are susceptible to sampling bias, and changes recorded in the volume measured may not be representative of those occurring in the entire region affected by the insult *(99,105)*. In addition, because the probes are invasive, requiring placement in the brain parenchyma and fixation in the calvarium, they cannot be readily shifted to sample other areas, as a noninvasive measure, such as transcranial cerebral oximetry might.

Transcranial Cerebral Oximetry: Near-Infrared Spectroscopy

Whereas much is known about the biochemistry and biophysics of near-infrared spectroscopy, translating that knowledge into clinical practice has proven considerably more difficult, so much so that only one noninvasive patient monitoring system based on its principles is currently available for commercial use in the United States (the INVOS cerebral oximeter system, Somanetics, Troy, MI). Furthermore, because of a lack of standardization of the technology, the algorithms used to assess cerebral oxygenation and even the parameters actually measured vary among studies *(86,105)*. In short, this once-promising technology has not translated into a useful clinical monitoring device.

In spite of these limitations, investigators have been able to conduct a number of studies in humans using cerebral oximetry to evaluate oxygenation status and sufficiency *(105)*. These studies have been unable to determine reference ranges of parameters for "normal" subjects or ischemic thresholds. There is some suggestion, however, that trends over time may have clinical value.

Invasive Metabolite Measurement: Microdialysis

Deprived of oxygen and glucose, increasing anaerobic metabolism leads to a complicated constellation of events as stores of adenosine-5′-trisphosphate (ATP) fall: there is accumulation of lactate and hydrogen ions leading to cellular acidosis; there is progressive mitochondrial failure; increasing intracellular calcium levels, excitatory neurotransmitter release, proteolysis, lipolysis, free-radical formation, cytoskeletal dissolution, DNA fragmentation, cellular necrosis, and progressive inflammation *(22,102–104)*. It is possible that cerebral microdialysis can detect such metabolic changes prior to irreversible injury *(57,60,87,99)*. In addition, cerebral microdialysis catheters can be used for administration of therapeutic agents *(16,56,81)*.

The principles of microdialysis where articulated by Fick in the mid-19th century when he experimentally determined that the rate of diffusion of a substance is directly proportional to its change in concentration per unit distance (i.e., its concentration gradient) and to the cross-sectional area through which it is diffusing *(31)*. The proportionality or diffusion constant of this relation depends both on the intrinsic properties of the substances and media involved (i.e., their molecular weight and charge) and on extrinsic variables such as temperature and external pressure.

In clinical practice, a microdialysis catheter acts much like a vascular capillary, sampling the extracellular space of the brain and recording its composition as a function of time *(60,87,99)*. Typically, a small diameter probe with a semi-permeable polycarbonate (polyamide) membrane at its tip is placed directly into the cerebral parenchyma and perfused with a carrier medium, the perfusate (e.g., Lactated Ringer's solution), at a constant, ultra-low flow rate using a microinfusion pump (e.g., 0.3 μL/minute, CMA Microdialysis pump, CMA, Solna, Sweden). Substances from the extracellular parenchymal space then diffuse across the membrane into the perfusate, which can subsequently be collected in microvials and analyzed at bedside using a portable kinetic enzymatic analyzer, capable of detecting, quantifying, and displaying graphically as trends over time the concentrations of metabolites such as glucose, lactate and pyruvate. Depending on the permeability of the microdialysis membrane, substances with molecular weights up to 20 kDa, or even 100 kDa, can now be collected for clinical assessment.

Although the microdialysis analyzer is able to quantitate the presence of multiple metabolites, the concentrations determined for the microdialysate do not typically correspond to their true extracellular concentrations *(45,60,87,99)*. In other words, recovery of substances in the perfusate, expressed as the ratio of the concentration of the substance in the perfusate to its concentration in the extracellular fluid, is incomplete or relative rather than absolute, and varies according to multiple factors, including the length, diameter, and type of membrane used, the chemical composition of the perfusate and its flow rate, and the molecular characteristics (mass, shape, charge) of the analyte being collected. In general, larger membranes and lower flow rates permit greater relative recovery, though the fact that recovery and thus the concentration determined for the analyte depend on the techniques employed makes direct

comparison of absolute values difficult when different collection methods are used.

Cerebral microdialysis has been proposed for use in patients with epilepsy, stroke, subarachnoid hemorrhage, and traumatic brain injury, among others *(34,44,60,67,68,78,79,88,98,100,112)*. There has been some experience and data collected: for example, episodes of secondary insults such as intracranial hypertension and cerebral ischemia were correlated with decreased glucose and increased lactate concentrations (or increased lactate/pyruvate ratios) *(28,33,34,59,60,78,87,89,96,98–100)*. Findings of increased levels of excitatory amino acids, markers of cellular destruction such as glycerol or glycine, and potential indicators of free-radical formation such as allantoin and parabanic acid (both oxidation products of free-radical scavengers) may also predict metabolic catastrophes in the setting of protracted secondary pathophysiologic processes *(17,29,33,41,42,60,66,73,87,89)*.

Although microdialysis has great potential, the technology is not without its limitations *(67)*. The dependence of the recovery of substances on the technique of collection employed makes direct comparison across subjects or among studies and determination of absolute ischemic or anaerobic thresholds difficult if not impossible *(45,87,99)*. As was the case with near-infrared spectroscopy, relative intrasubject changes from baseline may prove to be the most useful clinical parameters to monitor, although, again, diagnostic and prognostic values for such changes remain to be established. Furthermore, as was the case with brain tissue oximetry, microdialysis probes capture data from only a small volume of brain tissue and so suffer from a similar susceptibility to sampling bias. Finally, because the microdialysis catheters, like the oxygen tension probes, are invasive, the question has been raised as to whether they are, in effect, "monitoring their own lesions," in that their insertion effects an inevitable degree of local inflammation and hemorrhage *(60,87)*.

Functional Neuroimaging

One of the most important advances in the management of critical patients has been the emergence of functional imaging. Initially, radiography was focused on ever more detailed, but *static* anatomic imaging. With the advent of PET and magnetic resonance imaging (MRI), radiology underwent a paradigm shift toward providing information about the metabolism of tissues. In spite of faster scanners, higher resolution detectors, and more powerful computers, all of these techniques are limited by providing information during a fixed window—they are not continuous monitoring techniques. Nonetheless, important information about the diagnosis, management, and prognosis of critically injured patients should be obtained as it provides a context for interpreting data from continuous monitors.

PET

PET is an imaging technique that takes advantage of the elimination reaction of positron collisions with electrons. Positrons are antimatter—the positively charged equivalent of an electron. When emitted, a positron will collide with a nearby electron, yielding two photons. In clinical PET, these positron emmiters are attached to a bioactive molecule. In theory, any molecule can be tagged, but most often, deoxyglucose is attached to the fluoride isotope ^{18}F, yielding ^{18}Fluoro-Deoxy-Glucose (FDG). Deoxyglucose is trapped in cells because of the inability of glucose-6-phosphatase to metabolize ^{18}FDG-P. Once trapped, the positron emissions are detected, and relative consumption of the metabolite by metabolically active tissues can be mapped *(109)*. These photons are detected over time and space, and through a significant amount of preprocessing, functional maps in individual (by fusion with patient CT data) or standard (e.g., Taliarach) space are obtained *(65,107)*.

PET has been extensively studied in intracranial disease, and has been shown to be sensitive and specific for changes in relative cerebral blood flow (rCBF), relative blood volume (rCBV), and relative metabolic O_2 and glucose requirements ($rCMRO_2$/rCMRGlu). A variation on PET, single photon emission tomography (SPET) utilizing a single detector setup is capable of less indirect measurements of CBF. SPET has been examined in the setting of traumatic brain injury, and often revealed perfusion abnormalities not detected by CT or MR *(65)*. As sensitive as it is, PET is unable to distinguish metabolic changes because of functional changes and those caused by structural damage *(83)*.

FDG-PET has been used to identify some traumatic injuries not associated with overt anatomic abnormalities. For example, diffuse axonal injury is associated with diffuse cortical hypometabolism and marked decrease in $CMRO_2$ in visual cortex *(6,83)*. Studies of patients with epidural and subdural hematomas have demonstrated that not only is adjacent cortex affected, but that there are contralateral changes in CBF. And for focal lesions, a repeated pattern of associated contralateral cerebellar diminished metabolism has been seen in multiple studies. This so-called "crossed cerebellar diaschisis" is thought to be the result of coritco-ponto-cerebellar pathway signaling. Finally, the "post-concussive syndrome," (characterized by altered personality and memory and attention deficits) is associated with rCBF and rCMRGlu abnormalities in the mesial frontal lobes *(65,107)*.

In spite of the sensitivity of PET, very little evidence exists that routine use for patients with traumatic brain injury has a positive impact on outcomes. Instead, most studies serve to emphasize the importance of treating "the whole brain," even for a focal lesion. The promise of PET in the setting of neurotrauma is a better understanding of underlying molecular pathways of secondary injury and recovery. PET may also be used, similar to MR, to identify areas of permanent damage vs cortical stunning.

SPECT /CT Perfusion

Single-photon emission computed tomography (SPECT) shares the same basic principles as PET scanning. In this technique, a radioactive tracer is administered, and emission of γ rays are detected using a standard CT multidetector array. Unlike PET, the tracers are not linked to bioactive metabolites, do not leave the circulation, and therefore only measurements of blood flow are made. Common tracers include ^{133}Xe and ^{99}Tc-HMPAO (Hydroxymethylpropylene amine oxime). The spatial resolution of SPECT tends to be less than that of PET. However, SPECT does not require any more hardware than a standard CT scanner, and does not require preparation of

radiolabeled glucose, or other metabolites. SPECT directly measures CBV and mean transit time (MTT). CBF is then calculated via CBF = CBV/MTT. XeCT has largely been replaced with Tc-SPECT or CT Perfusion caused by Xenon's re-categorization as a pharmacologic agent with sedative and anesthetic properties *(118)*.

The findings of SPECT in the setting of neurotrauma are equivalent to PET. Multiple studies have demonstrated global alterations in CBF in DAI, hypoperfusion in the thalami, basal ganglia, calcarine cortex, and so on, and focal frontal alterations relatable to symptoms of the concussive syndrome *(4,5)*. Abnormalities detected on early (<24 hours post injury) SPECT, along with "negative" initial SPECT scans have been shown to correlate well with patient outcome *(47,48,101)*. Furthermore, HMPAO-SPECT has been shown to increase the sensitivity of CT 125% in the detection of abnormalities on the initial post trauma scan *(38,83)*. SPECT combined with an abnormal CT, or data from invasive monitors, can demonstrate areas of "misery" and "luxury perfusion"—representing uncoupling of perfusion and metabolic requirements. PET is able to do this within a single modality, but scanning times are much longer *(93)*.

CT perfusion is a newer modality that yields the same information as SPECT (rCBV, rMTT, rCBF), utilizing a normal contrast bolus. The CT is set to acquire in "cine-mode," continuous scanning without gantry movement, and the injected bolus flows within the cerebral vascular. This causes the bolus to wash in, and wash out of the field of view. With post-processing, CBV and MTT can be measured *(43)*. Unlike MR-perfusion (not discussed), CT perfusion allows calculation of absolute CBF, rather than relative CBF between the two hemispheres *(106,117)*.

A recently published *(117)* prospective trial of CT perfusion in patients with ICP monitors in place demonstrated the ability of CT perfusion to accurately detect preservation or impairment of cerebral autoregulation. Unlike many other non-invasive imaging modalities, this has significant clinical relevance. For patients with normal autoregulation, alterations of mean arterial pressure (MAP) are unlikely to affect CPP, whereas for those without autoregulation, elevations of the MAP are more likely to result in elevated ICP rather than CPP.

The functional imaging modalities provide important contextual information for treatment of neurocritical patients. Data gathered from initial CTs and MRIs aid in the diagnosis and heavily weigh in the decision to apply invasive monitoring. Perfusion abnormalities seen on CT/MR can help guide the placement of oximeters and microdialysis catheters. MR and PET can help to confirm infarction of tissue suspected from microdialysis data. However, all of these modalities require heavy expenditures: (1) Not all facilities are equipped with the special equipment to prepare radiolabeled metabolites for PET; (2) Although most scanners can theoretically provide functional information, it requires heavy computational analysis and a radiologist experienced in their interpretation; and (3) The critical patient must be transported from the ICU to the scanner, and must be stable enough to undergo prolonged scans. With this in mind, a modification to ultrasound has been developed to provide bedside functional imaging.

Continuous Quantitative Cerebral Blood Flow Monitoring

Although surrogates for the direct measurement of CBF are in use, the recent introduction of bedside continuous quantitative CBF monitoring with such techniques as laser Doppler flowmetry (LDF) and thermal diffusion flowmetry (TDF) offer intriguing options in this regard. LDF measures erythrocyte flux and relative changes in CBF, whereas TDF measures nutritive perfusion and is thus provides a more direct measure of CBF. Both are available as intraparencyhmal probes placed through a small craniotomy and held in place by skull bolt and offer the advantage over conventional flow velocity devices such as transcranial Doppler in assessing tissue perfusion in the microcirculation rather than in major vessels.

Thermal diffusion flowmetry differs from LDF in offering a quantitative assessment of regional tissue perfusion in terms of absolute flow values. In TDF, the catheter contains a distal thermistor and a second, more proximal, temperature probe; the thermistor is heated to a few degrees above tissue temperature and the temperature probe samples temperature constantly. The temperature difference is thus a reflection of heat transfer and may be translated to a measurement of CBF. Initial data suggest that TDF is able to detect expected dynamic changes in cerebral perfusion and that TDF provides a sensitive real-time assessment of intraparenchymal CBF in agreement with the Xenon-enhanced CT scanning *(123,124)*, and the FDA has approved one such device (QFlow, Hemedex). Although only a limited experience with its use exists, continuous quantitative CBF monitoring in the future will ideally allow detection of clinically significant changes in blood flow that correlate with brain tissue oxygenation and prompt therapeutic interdiction to improve patient outcomes.

Advanced Ultrasonography

Contrast-enhanced ultrasonography (CEU) is a new technique still in development, but one that may have the potential to non-invasively measure CBF in real-time, both regionally and globally. The technique has been described in an animal model to differentiate blood flow between gray and white matter and to monitor changes in CBF with variation in CO_2 levels *(108)*. Briefly, red blood cell size, inert microbubbles are injected intravenously at a continuous rate and imaging of the flow of bubbles into the microvasculature is performed with power modulation ultrasonography after a high frequency ultrasound pulse clears all bubbles in the brain. In a pilot human trial, CEU has demonstrated changes in global CBF after head of bed elevation and after decompressive craniectomy, and is able to visualize regional CBF as well as CBF in and around mass lesions such as intracerebral hemorrhages (Heppner/Ellegala et al., publication pending) (Figure 1). Further, the estimated CPP was found to be different from actual cerebral perfusion as measured by CEU coinciding with previously published reports. This technique is currently in development and undergoing clinical trials.

Conclusion

Given the cellular density and the physiological complexity of the human brain, the expectation that the assessment of

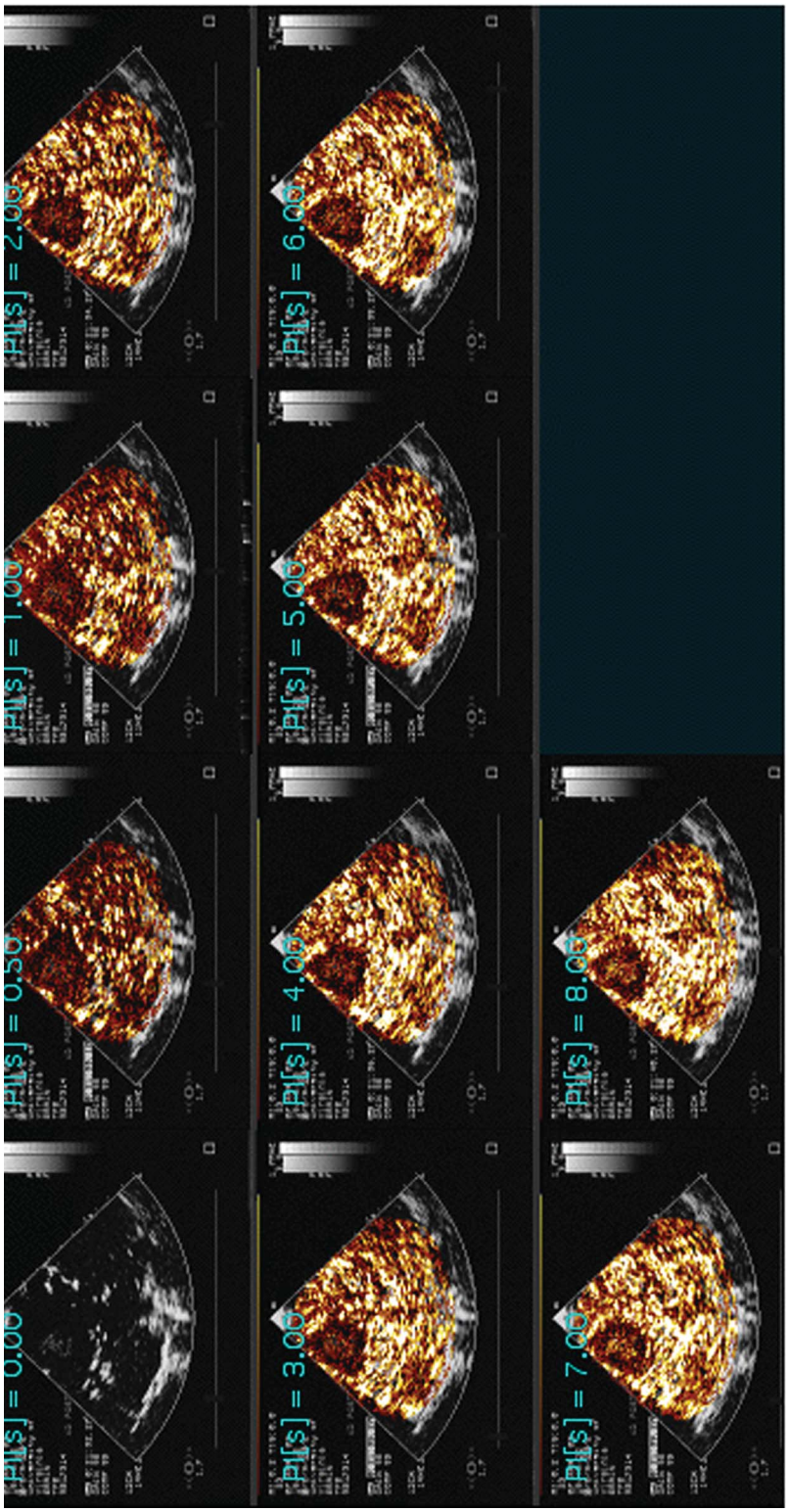

Fig. 1. Demonstration of global blood in a patient 1 day after a traumatic brain injury with an area of focal hypoperfusion corresponding to an area of hemorrhagic contusion.

cerebral oxygenation or metabolic status could be reduced to a single variable or even to a single monitoring device is perhaps unrealistic *(105)*. It is perhaps for this reason that recommendations for a multiparametric approach to the neuromonitoring of cerebral pathophysiology are frequently encountered *(10,60,77,91,99,111,119,120)*.

The increasing recognition that ischemic compromise of cerebral oxygenation and metabolism may be the common endpoint for a variety of craniocerebral insults has suggested new approaches to alleviating the staggering burden of emergent neurological disease, both locally in the United States and globally. In addition to primary prevention and the implementation of standardized, evidence-based treatment protocols such as those advocated by the Brain Trauma Foundation and the American Association of Neurological Surgeons, the development of technologies offering continuous, quantitative, sensitive, dynamic, and direct assessment of cerebral oxygenation, metabolism, and blood flow represents our best hope of improving neurocritical treatment and clinical outcome in patients with craniocerebral injury *(15)*.

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