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Review

A Review of the Effectiveness of Neuroimaging Modalities for the Detection of Traumatic Brain Injury

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Abstract

The incidence of traumatic brain injury (TBI) in the United States was 3.5 million cases in 2009, according to the Centers for Disease Control and Prevention. It is a contributing factor in 30.5% of injury-related deaths among civilians. Additionally, since 2000, more than 260,000 service members were diagnosed with TBI, with the vast majority classified as mild or concussive (76%). The objective assessment of TBI via imaging is a critical research gap, both in the military and civilian communities. In 2011, the Department of Defense (DoD) prepared a congressional report summarizing the effectiveness of seven neuroimaging modalities (computed tomography [CT], magnetic resonance imaging [MRI], transcranial Doppler [TCD], positron emission tomography, single photon emission computed tomography, electrophysiologic techniques [magnetoencephalography and electroencephalography], and functional near-infrared spectroscopy) to assess the spectrum of TBI from concussion to coma. For this report, neuroimaging experts identified the most relevant peer-reviewed publications and assessed the quality of the literature for each of these imaging technique in the clinical and research settings. Although CT, MRI, and TCD were determined to be the most useful modalities in the clinical setting, no single imaging modality proved sufficient for all patients due to the heterogeneity of TBI. All imaging modalities reviewed demonstrated the potential to emerge as part of future clinical care. This paper describes and updates the results of the DoD report and also expands on the use of angiography in patients with TBI.

Key words: electrophysiology; imaging; spectroscopy; tomography; ultrasound

Introduction

The incidence of traumatic brain injury (TBI) in the United States was 3.5 million cases in 2009, according to the Centers for Disease Control and Prevention.[1] Recent data indicate that 1.37 million Americans are treated and released from an emergency department (ED), 275,000 are hospitalized and discharged alive, and 52,000 die as a consequence of traumatic brain injury (TBI).[2] It is further estimated that TBI is a contributing factor in a third (30.5%) of all injury-related deaths in the U.S. It is more difficult to estimate how many individuals are seen in outpatient departments and office-based clinical settings, but recent estimates using data from the National Hospital Ambulatory Medical Care Survey and the National Ambulatory Medical Care Survey indicate that an additional 84,000 patients with TBI are seen annually in hospital outpatient departments and 1,080,000 are seen by office-

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based physicians and in community health clinics. Thus, the total number of TBIs for which individuals seek medical attention in the U.S. annually approaches 3.5 million.[1] This data excludes military and veterans hospitals.

Compared with their civilian peers, service members have an increased risk for sustaining brain injury, even during peace time. Noncombat-related TBIs are reported to occur in military service members at a rate 1.6 and 2.5 times greater for men and women, respectively, than observed in their civilian counterparts.[3] Service members are generally young and predominantly male, both of which are risk factors for sustaining brain injury.[2] Further, the environmental demands of training and service impart additional risk of injury.

TBI represents one of the signature injuries of Operations Iraqi Freedom and Enduring Freedom.[4,5] A survey of U.S. Army infantry soldiers returning from Operations Iraqi Freedom and Enduring Freedom ($n=2525$) in 2006 found that 377 (15%) reported experiencing events associated with mild TBI (mTBI), including loss of consciousness (LOC); being dazed, confused, or ''seeing stars''; or not remembering the injury.[6] A review of clinical records of U.S. Marine Corps and Army service members who sustained a brain injury ($n=2074$) between 2004 and 2008 established that 1852 (89%) of those brain injuries were mTBI. Improvised explosive devices accounted for the injury mechanism in 1650 (80%) of service members with TBI.[5] Further, the rate of combat-related hospitalization for TBI in Operations Iraqi Freedom and Enduring Freedom deployed service members between 2003 and 2008 was reported as 10.4 per 10,000 troop strength. Rates were higher for U.S. Marine Corps and Army service members, at 13.5 and 10.9 per 10,000, respectively, compared with U.S. Navy and Air Force service members, at 5.7 and 1.6 per 10,000, respectively.[4]

TBI can result in diverse mental and physical sequelae that often are as unique to individual casualties as personality.[7,8] These include cognitive deficits, such as memory disorders,[9,10] attention loss,[11,12] and impaired executive functioning.[13] Mental health issues, such as post-traumatic stress disorder (PTSD) and depression, also are strongly associated with TBI, especially in combat.[6,14–16] Physical disturbances also are observed with TBI. Headache.[9,17–19] sleep disturbances,[20–22] and gait disorders[23] often are associated with TBI. TBI also can increase long-term health risks for debilities such as Alzheimer's disease[24–27] and parkinsonism.[28–30]

The diverse and variable outcome of patients following TBI and the multiple definitions of TBI make interpreting results across research studies complex. In 2008, the Department of Defense (DoD) and the U.S. Department of Veterans Affairs (VA) developed a definition of TBI,[31] stating that ''TBI is a traumatically induced structural injury and/or physical disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least one of the following clinical signs, immediately following the event: (a) any period of loss or decreased level of consciousness; (b) any loss of memory for events immediately before or after the injury; (c) any alteration in mental state at the time of the injury (e.g., confusion, disorientation, slowed thinking, etc.); (d) neurological deficits (weakness, loss of balance, change in vision, praxis, paresis/plegia, sensory loss, aphasia, etc.) that may or may not be transient; or (e) intracranial lesion.'' Further, TBI is classified according to injury severity as mild, moderate, or severe. Table 1 provides one widely-used set of criteria.[32] Despite these efforts, this classification schema remains limited. The detection of mTBI, based on an identification system that uses LOC as a principal diagnostic criterion to discern among patients with outcomes of interest, misclassifies patients whose LOC may not reflect actual brain injury.[33] Mild TBI, as defined by this classification, includes normal structural imaging by traditional computed tomography (CT), yet more recent advanced imaging studies have demonstrated the presence of intracranial abnormalities.[34–36] Further, a symptom-based classification fails to recognize the heterogeneous mechanisms of injury, that include contusion, hemorrhage, and neuronal, glial, axonal, and vascular injury.

Table 1. Classification of TBI

Mild	*Moderate*	*Severe*
Normal structural imaging	Normal or abnormal structural imaging	Normal or abnormal structural imaging
LOC = 0-30 min	LOC > 30 min and < 24 h	LOC > 24 h
AOC = a moment up to 24 h	AOC > 24 h; severity based on other criteria	AOC > 24 h; severity based on other criteria
PTA = 0-1 d	PTA > 1 d and < 7 d	PTA > 7 d
GCS score = 13-15	GCS score = 9-12	GCS score = 3-8

TBI, traumatic brain injury; LOC, loss of consciousness; AOC, alteration of consciousness/metal state; PTA, post-traumatic amnesia; GCS, Glasgow Coma Scale.

While history, mechanism, and physical examination remain mainstays of diagnosis in TBI, medical imaging also is a key modality for assessment of TBI in both the clinical and research settings. Currently, there is no definitive objective diagnostic tool for TBI that effectively describes the multiple domain insults a TBI casualty can suffer to include polytrauma and effects of emergent field management and transport. In response to an August 2012 White House executive order,[37] the DoD, VA, Department of Education, and Department of Health and Human Services developed a National Research Action Plan to establish surrogate and clinically actionable imaging biomarkers for early diagnosis and treatment effectiveness of TBI and to improve data sharing among agencies, thus reducing redundancy and accelerating progress. The technologies currently being assessed in the research setting include new protocols for magnetic resonance imaging (MRI), validation of imaging modalities (e.g., diffusion tensor imaging [DTI], functional MRI [fMRI]), assessment of effectiveness for identifying structural and functional abnormalities, and development of imaging biomarkers (structural and functional signatures) of TBI for different severities and etiologies. The most active research efforts within the DoD include MRI (with DTI, magnetic resonance spectroscopy [MRS], and fMRI), positron emission spectroscopy (PET), ultrasound (three-dimensional [3D], transcranial Doppler [TCD]), and functional near-infrared spectroscopy (fNIRS). Other forward-looking efforts within the DoD are aimed at developing lightweight systems that can provide structural and functional imaging in deployed and austere conditions, including TCD ultrasound, low-field MRI, and vibroacoustic ultrasound.

Additionally, in 2011, governmental experts were charged with developing a report to Congress titled ''Comparative Effectiveness of Neuroimaging Modalities on the Detection of Traumatic Brain Injury.'' This report[38] evaluated the comparative effectiveness of seven neuroimaging modalities as imaging biomarkers for the detection of TBIs. The report included CT, MRI, TCD, PET, single photon emission computed tomography (SPECT), electrophysiologic techniques (magnetoencephalography [MEG], electroencephalography [EEG]), and fNIRS. Based on a review of more than 450 abstracts, teams of domain expert reviewers considered the

quality of the evidence supporting each modality for use both in the clinic and in research settings. Of the seven modalities, the authors agreed that all techniques had moderate to high research utility for the spectrum of TBI. However, clinical utility was more limited. Based on the published data included in the review, MRI was only of moderate clinical utility, and only CT and TCD were of high clinical utility. Further, CT and TCD were only of high clinical utility for moderate and severe TBI. The report cites a series of roadblocks that limit the ability to draw conclusions, such as 1) numerous definitions of mild, moderate, and severe TBI; 2) nonstandardized clinical protocols that vary from institution to institution; and 3) nonstandardized research methodologies (e.g., lack of instrumental interoperability between manufacturers). This article expands on the clinical and research utility of these neuroimaging techniques.

With respect to the use of imaging in the field, neuroimaging techniques for the diagnosis and assessment of TBI in the acute setting support optimal medical and surgical interventions. Neuroimaging also can provide minimally invasive surgical surveillance and detection of late-onset complications. The primary techniques for detecting and diagnosing TBI in the field include examination, plain film or fluoroscopy, CT, and while not typical of theater equipage, MRI.[39] In the military deployed environment, medical care is divided into five echelons or roles/levels that are standard across NATO forces. Role 1 is immediate buddy care and care by a medic (Army, Air Force) or corpsman (Marines, Navy). Currently, the only imaging modality used at this level is the portable ultrasound, which is not yet capable of structural transcranial imaging. Role 2 includes the Battalion Aid Station, which may have ultrasound or radiographic capabilities depending on mission; the Forward Surgical Team with x-ray, ultrasound, and occasionally fluoroscopy; and their Marine, Naval, and Air Force forms. Role 3 includes the Combat Support Hospital, hospital ship, and related service-specific assets that can have CT.[40,41] The presence of two MRI systems in Afghanistan is a unique and doctrinally challenging situation given their footprint, weight, and technical requirements.[39] While these neuroimaging techniques more closely resemble patient care within the U.S., the use of both MRI and CT in the field is limited in favor of medical evacuation for moderate or severe injuries. Role 4 is a fully capable regional medical center, and Role 5 is a stateside hospital.

Computed Tomography Scanning

Cranial CT scanning is the most common imaging modality used during the acute phase of head injury to detect subcutaneous or subgaleal hemorrhage, skull fractures, epidural and subdural hemorrhage, and parenchymal injury. It also can assist in identifying missile path and retained fragments of missile, bone, and other foreign objects. CT uses narrow x-ray beams traversing the cranium at carefully controlled angles. The differential attenuation of the x-rays by structures of varying electron density provides the data used for digital image reconstruction. This technique permits construction of two-dimensional images, ''slices,'' that include only structures in the area of interest. The information gained can in turn be manipulated to reconstruct images in any plane or to create 3D volumetric representations. Since its introduction in the 1970s, CT technology has revolutionized the management of TBI and has doubtless saved many lives. Although it is a mature technology, recent advances such as multi-detector CT have enabled the use of CT technology for rapid, noninvasive imaging of brain vasculature. In a study of 2152 ED patients with mTBI and a Glasgow Coma Scale (GCS) score of 14 to 15, Livingston and colleagues calculated a 99.7% negative predictive value for the preliminary reading of the head CT with regard to the subsequent need for neurosurgical intervention.[42] Despite its clear utility, concerns remain about the overuse of CT scanning in patients with TBI, particularly in children and in those with mild injury.[43]

CT scanning in moderate and severe TBI

The primary role of CT scanning has been the acute identification of focal injuries that may require emergent neurosurgical interventions, such as extra-axial or parenchymal hemorrhage, midline shift, and incipient herniation. It also is helpful in identifying conditions that may require intensive care monitoring, such as small- and medium-sized hematomas that may subsequently expand, diffuse cerebral edema, or traumatic subarachnoid or intraventricular hemorrhages that may result in post-traumatic hydrocephalus. As such, CT scanning is most beneficial in patients with moderate and severe TBI (GCS score < 13 on presentation to the ED),[44] as it can readily identify those patients who require an emergent neurosurgical intervention, which is often life-saving. The ''Guidelines for the management of acute traumatic brain injury,'' evidence-based guidelines formulated by the Brain Trauma Foundation and widely adopted throughout the world,[45,46] largely base recommendations for surgical interventions on CT findings. Approximately 10% of patients with severe TBI require a craniectomy based on the findings from an initial CT scan. According to the Brain Trauma Foundation guidelines, these findings include extra-axial hematomas (epidural or subdural hemorrhages) larger than 30 mL in size or associated with greater than 5 mm of midline shift and parenchymal hematomas in a noneloquent cortex greater than 20 mL in size. Patients in whom the original CT scan shows small- or moderate-sized parenchymal hematomas, traumatic subarachnoid hemorrhage, or extra-axial hemorrhages (subdural or epidural hematomas) are admitted to the hospital and usually rescanned within 24 h or sooner if there is a deterioration of neurologic status, as clinically significant expansion of intracranial hematomas is common.[47]

Contrast-enhanced CT has a limited role in the evaluation of TBI. Routine administration of contrast in the acute setting after TBI wastes time and may obscure small hemorrhages. Contrast-enhanced CT angiography, particularly using modern multidetector CT scanners, is increasingly becoming the technology of choice for evaluating suspected traumatic vascular injury, such as vessel dissections, pseudoaneurysms, or occlusions. Patients at high risk for vascular injuries—such as those with penetrating TBI (gunshot wounds or stabbing), basal skull fractures, or trauma to the neck—may benefit from CT angiography to detect vascular injury in time to institute therapy and thus prevent infarction. Traditional catheter angiography or magnetic resonance (MR) angiography are alternate technologies useful in this setting. The availability of high speed helical CT scanners and image reconstruction software allows measurement of parametric images of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) alongside CT angiography and imaging data.[48] As expected, traumatic contusions are associated with low CBF and CBV and prolonged MTT. Even in patients with mild TBI and normal non-contrast CT, perfusion CT imaging can identify regional decreases in CBV,[49] which correlate with abnormalities detected in diffusion tensor magnetic resonance imaging.[50] These techniques may have value in evaluating select TBI patients and for clinical research, but are not considered routine clinical practice.

Despite its proven utility for identifying patients requiring surgery, CT scanning is only marginally useful for predicting outcomes after moderate and severe TBI.[51,52] Up to 20% of patients with moderate-to-severe TBI have a normal or near-normal CT scan on the day of admission, a reflection of the fact that CT is not a sensitive technique for the detection of diffuse microstructural white matter damage, termed diffuse axonal injury (DAI). In pathologic studies, DAI is identified in most cases of lethal brain injury and it is likely that DAI is a major mechanism of severe disability in TBI survivors. In contrast, many patients with medium- or even large-sized intracranial hemorrhages on an initial CT scan make excellent functional recovery with adequate neurosurgical and neurological care.[53]

CT scanning in mTBI

One of the most important challenges for the treating physician in the ED is deciding whether neuroimaging is needed in patients presenting with mTBI. A noncontrast CT scan is usually the test of choice, but fewer than 10% of patients with mTBI have abnormalities detected on an acute CT scan[54] and most of those abnormalities are of little neurosurgical consequence. The need for neurosurgical intervention is extremely uncommon in patients presenting to the ED with mTBI, and CT scanning is not without drawbacks. These drawbacks include cost, the potential risks of transporting patients outside the ED if the imaging suite is not colocated, and exposure to ionizing radiation. Ionizing radiation is a particularly important concern when treating children, as CT scanning may expose them to an increased risk of cancer for many years.[43] The goal of evidence-based management is to perform the minimum number of head CTs while ensuring that patients with potentially dangerous intracranial hemorrhages are identified.

Numerous studies have addressed clinical criteria that physicians can use to determine whether a patient with mTBI should undergo head CT. The two most commonly used clinical criteria are the New Orleans Criteria and the Canadian CT Head Rule.[55,56] Follow-up studies have evaluated the effectiveness of these and other criteria in terms of sensitivity and specificity for identifying clinically significant intracranial injury in adults. Based on the data available from these studies, the American College of Emergency Physicians (ACEP) and the Centers for Disease Control and Prevention (CDC) issued a clinical policy statement in 2008[57] on indications for obtaining head CT scans in adults with head trauma, summarized in Table 2 (see also Jagoda and colleagues[58]).

It is likely that observation in the ED for 6–8 h or brief admission to the hospital can be used as an alternative to CT scanning in patients without altered mental status or signs of skull fracture.[59] Additional factors that may play a role in the decision to observe a patient instead of CT scanning include the presence of risk factors as identified in Table 2, worsening symptoms, and age younger than 12 months. Infants are more difficult to examine and they have an increased incidence of asymptomatic intracranial hemorrhages. Home observation is another option for those with a normal mental status, normal neurologic exam, and the availability of a companion.

Approximately 20% to 30% of patients who sustain mild brain injury with intracranial abnormalities identified by acute CT have significant problems returning to work.[54] Evidence of parenchymal injury is associated with incomplete recovery. Similarly, low rates of incomplete recovery are noted, even when the CT is normal. The predictive value of a model of mTBI does not improve with the inclusion of CT findings in a scheme based on age, extracranial injuries, and alcohol use.[54,60] This lack of predictive value is likely due, in part, to the inadequate sensitivity of CT scanning for DAI and perhaps other pathological conditions, such as diffuse vascular injury.

Table 2. Indications for Head CT Scan in Adults (≥16 Years of Age) with Head Trauma

Level A recommendation (generally accepted principles for patient management that reflect a high degree of clinical certainty)
Head CT is indicated for patients with a loss of consciousness or posttraumatic amnesia only if one or more of the following is present: 1. Headache 2. Vomiting 3. Age > 60 years 4. Drug or alcohol intoxication 5. Deficits in short-term memory 6. Physical evidence of trauma above the clavicle 7. Post-traumatic seizure 8. GCS score < 15 9. Focal neurologic deficit 10. Coagulopathy
Level B recommendation (recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty)
Head CT should be considered for patients without a loss of consciousness or posttraumatic amnesia if one or more of the following is present: 1. Focal neurologic deficit 2. Vomiting 3. Severe headache 4. Age ≥ 65 years 5. Physical signs of a basilar skull fracture 6. GCS score < 15 7. Coagulopathy 8. Dangerous mechanism of injury (e.g., ejection from a motor vehicle, a pedestrian struck by a vehicle, or a fall from a height of more than 3 feet or 5 stairs)

CT, computed tomography; GCS, Glasgow Coma Scale.

A common clinical mistake is that patients with mTBI and normal CT scans are discharged from EDs with inadequate instructions as to what to expect in their recovery. Although most patients with mTBI and normal CT scans recover within 1 to 4 weeks, a significant subset (as many as 10% to 20%) do not, and these patients should be counseled to seek medical attention if symptoms persist for longer than 7 days. Although there are no therapies specific to the treatment of TBI, there are specific therapies for many of the potentially affected domains, such as balance, cognition, and emotional lability. Therefore, appropriate counseling may be able to hasten recovery and prevent reinjury during the recovery period and to mitigate the often serious psychosocial consequences of mTBI.

Discussion

There is high-quality evidence that CT scanning is clinically valuable in the evaluation of patients presenting to EDs with moderate and severe TBI. In these patients, CT scanning is highly sensitive in identifying intracranial hemorrhages that require neurosurgical interventions, and can often be life-saving. High-quality

evidence is also present in the literature that CT scanning is not useful for the prediction of functional recovery, even in moderate and severe TBI. In mTBI, moderate quality evidence suggests that CT scanning is of limited usefulness in the clinical evaluation of patients presenting to the ED. In clinical practice, cranial CT scanning is likely overused in the evaluation of mTBI. Given the inherent limitations of CT scanning, it is possble that further studies designed to identify patients with mTBI who are at risk of persistent post-concussive symptoms and long-term disabilities will be in the area of blood biomarkers, which already show some promise for detecting patients with mTBI who can be safely discharged without a CT scan.[61]

Magnetic Resonance Imaging

MRI uses a combination of static and dynamic magnetic fields in conjunction with radiofrequency pulses to generate a signal from water protons within the human body. For example, T1- or T2-weighted images measure differences in the longitudinal recovery or transverse decay of excited protons, which permits characterization of subtle differences between normal tissues and disease processes. T1-weighted images often are useful for anatomic detail due to the natural contrast provided by fat- or lipid-containing structures, while T2-weighted images often are useful for identifying pathology due to the increased fluid or water in many disease processes. Brain MRI also routinely includes T2-weighted images modified by diffusion sensitizing gradients (diffusion weighted imaging [DWI]) and inversion radiofrequency pulses to null cerebrospinal fluid signal (fluid attenuated inversion recovery [FLAIR]). Less routine and more specialized MR techniques include *in vivo* functional imaging (fMRI), sequences that are highly sensitive for microhemorrhages (e.g., susceptibility weighted imaging [SWI]) and techniques that may depict the microstructure of the brain and produce a map of the fiber bundles [DTI]).

Overall, even standard MRI techniques at 1.5 T (Tesla) are more sensitive than noncontrast CT scanning for a wide range of brain pathologies—especially those that affect the white matter, such as multiple sclerosis and DAI, also known as ''traumatic axonal injury'' or ''shearing injury.'' Because MRI is more sensitive, it is a logical second test, particularly when a CT scan fails to explain a patient's symptoms and clinical signs. However, current clinical guidelines for acute evaluation of TBI continue to emphasize the role of CT scanning.[58,62] There is a role for MRI in the subacute or chronic setting for patients with mTBI/post-concussive syndrome to evaluate persistent neurologic symptoms not explained by CT findings. Valuable clinical sequences include DWI for acute ischemia and white matter injury, T2-weighted images (especially T2 FLAIR) for edema, and T2*-weighted images (gradient echo [GRE]) for hemorrhage. Routine T1-weighted images are helpful for identifying the subacute or methemoglobin phase of blood products.

Currently, routine brain MRI often reinforces findings already demonstrated in an initial screening head CT. This reinforcement could be a negative MRI study in a patient with mTBI or better delineation of a known hematoma in a patient with moderate-to-severe TBI. Occasionally, edema-sensitive sequences, such as DWI and FLAIR, or blood-sensitive sequences, such as GRE and SWI, will discover small cortical contusions that are obscured by the adjacent bone on a CT scan, or small white matter lesions in characteristic locations for DAI: gray-white junction (grade I), corpus callosum (grade II), and brainstem (grade III). This increased sensitivity for small cortical or white matter lesions is an important advantage of brain MRI: only 10% of DAI is positive on CT because more than 80% of lesions are nonhemorrhagic and are therefore better detected with a combination of DWI, FLAIR, and GRE.[63] The impact on clinical management and decision-making is less clear, given a lack of medical or surgical therapy for DAI. Such subtle MRI findings may be useful for guiding counseling, as the presence of MRI abnormalities appears to be associated with incomplete recovery and persistent post-concussive symptoms.[64]

Susceptibility weighted imaging

For the patient with persistent TBI-related symptoms not explained by routine neuroimaging, the most promising imaging markers attempt to detect traumatic axonal injury, which is microscopic and poses significant technical challenges. Advanced MRI techniques like SWI, DTI, and fMRI attempt to detect traumatic axonal injury through associated disruption of adjacent small vessels, normal fiber architecture, and normal functional networks, respectively. Of these techniques, SWI can be used readily in clinical practice and can be thought of as an advanced version of GRE, while DTI and fMRI are presently confined to the research arena for reasons that will be discussed below.

SWI is a high-resolution, 3D T2*-weighted sequence that combines information on dephasing or signal loss from a magnitude image similar to GRE, with additional information on phase shifting from a phase image. This technique results in increased sensitivity for paramagnetic blood products, such as deoxyhemoglobin, intracellular methemoglobin, and hemosiderin.[65] Despite this sensitivity, SWI alone is not helpful in determining the age of lesions, as both acute and chronic blood products demonstrate signal loss on T2* imaging. Pediatric TBI studies have found six times as many DAI lesions with SWI as with GRE,[66] and additional lesions were found 30% of the time using SWI, compared with CT scanning and conventional MRI (T1/T2-weighted sequences).[35] Comparable studies have not yet been performed in adults.

Tong and colleagues[67] found that a greater size and number of lesions in SWI correlated with both lower early GCS score and poorer 6- to 12-month clinical outcomes. Park and colleagues[68] used SWI to detect more cerebral microbleeds in mTBI patients than controls, and these microbleeds tended to be located in the frontotemporal white matter rather than the deep gray nuclei (as seen in hypertensive microangiopathy). A quarter of the patients were SWI negative; all of them had normal GCS and Glasgow Outcome Scale scores of 15 and 5, respectively. An advantage of SWI is its clinical versatility. Its potential non-TBI applications include elevated deoxyhemoglobin in vascular malformations or ischemia, hemorrhage or vascularity in tumor analysis, and iron deposition in neurodegenerative diseases.[69,70] The flip side of this clinical versatility is a lack of specificity for TBI, and radiologists transitioning from GRE to SWI for the detection of microhemorrhages need to account for the increased conspicuity of venous deoxyhemoglobin and other susceptibility effects. A disadvantage of SWI is the indirect approach to detection of axonal injury through microvascular shear injury, analogous to using calcium scoring as a proxy for angiography in coronary disease.

Diffusion tensor imaging

DTI can be thought of as an advanced version of DWI, which uses the asymmetrical diffusion of water molecules as a model for the integrity of normal fiber bundles and white matter microstructure. Conventional DWI applies a diffusion-sensitizing gradient to a fast T2-weighted sequence (echoplanar imaging) to measure the

Brownian motion of water molecules by reducing or dephasing the signal in an exponential relationship to the apparent diffusion coefficient (ADC) or equivalently, the mean diffusivity (MD). DTI applies the same diffusion-sensitizing gradient but repeats the process multiple times, typically between six and 60, in different directions, and generates a diffusion tensor instead of a diffusion coefficient for each voxel.[71] The second-order tensor or matrix can be visualized as a diffusion ellipsoid, of which the long axis represents axial diffusivity (AD) and the short axes represent radial diffusivity (RD). Diffusion in normal white matter ought to be directional or anisotropic due to the fiber-tract architecture; therefore, changes in AD or RD are possible markers of axonal injury.

Other DTI metrics include MD, which is the average of the diffusion measurements along the three axes, and relative or fractional anisotropy (RA or FA), which is a summary measure of the asymmetry of the diffusion measurements (eigenvalues) along the three axes. RA or FA is the most promising metric for white matter integrity because it reflects the shape of the diffusion ellipsoid, in contrast to MD, which reflects the overall size or volume. FA is normalized so that it ranges from 0 for isotropic or spherical diffusion (e.g., cerebrospinal fluid), to 1 for completely anisotropic or essentially linear diffusion. Mouse models for TBI, using controlled cortical impact injury, confirm reduced RA due to reduced AD in white matter, such as the corpus callosum and external capsule, despite normal conventional brain MRI, and correlate the DTI findings to histological findings of axonal injury.[72] Interestingly, developing edema in the subacute time frame, which runs from 1 week to 3 months, can increase both AD and RD, which may pseudonormalize AD, although FA remains markedly abnormal as a sensitive indicator of axonal injury because water diffusion becomes less directional.[73]

DTI has shown similar sensitivity for white matter injury in human studies, albeit limited to comparisons between groups rather than analysis of individuals. Reduced FA in acute mTBI has been demonstrated by using region of interest analyses in white matter regions, such as the centrum semiovale, corpus callosum, and internal capsule.[74–78] These studies also have revealed that the reduced FA can improve or persist over time and shows correlation with long-term cognitive function on follow-up neuropsychological testing; however, heterogeneity in data acquisition and analysis techniques, as well as patient outcome measures, are significant barriers to the clinical use of DTI metrics.[79] Conversely, multiple studies describe increased FA in the acute setting due to decreased RD, which is attributed to cytotoxic edema with axonal swelling.[80–83]

The significance of decreased versus increased FA in acute TBI is unknown. Longitudinal studies have shown decreased FA in the acute phase and then decreased FA and increased MD in the chronic phase, which is suggestive of axonal injury followed by demyelination or gliosis.[84,85] MacDonald and colleagues described FA reductions in 38 of 63 U.S. military personnel with blast-related mTBI, as well as increased MD on the initial scan in the subacute time frame, then normalized MD on the follow-up scan at 6 to 12 months, which was suggestive of resolved edema and inflammation.[36] This finding does not contradict previously described reports of increased MD from demyelination or gliosis in the chronic time frame, as those studies included patients with moderate and severe TBI. Comparison of mild versus moderate or severe TBI has confirmed differences in the DTI abnormalities, with mTBI showing relatively normal RD, without evidence of chronic irreversible myelin damage[86] and affecting fewer regions of the corpus callosum.[87] DTI also has been used to document in a small number of patients what was believed to be isolated primary blast injury, a difficult injury to identify, in which the patient is exposed to the blast shock wave without secondary (foreign objects striking the casualty) or tertiary (the casualty being moved or thrown by the blast) effects, by showing lesions in the left middle cerebellar peduncle.[88]

Significant challenges remain for the clinical use of DTI as a biomarker for TBI. Unlike SWI, the FA or MD maps generated by DTI require statistical, not visual, interpretation, and different techniques include manual region of interest analysis, automated region of interest analysis, tract-based voxel-wise analysis, and quantitative tractography.[89] In addition to heterogeneity in data analysis techniques, there is heterogeneity in data acquisition techniques, from the choice of equipment and magnetic field strength to the sequence parameters, such as b-value and number of diffusion sensitizing directions. While research studies can identify group differences in DTI metrics between mTBI patients and controls, these statistical findings have no clinical significance for the prognostic or therapeutic stratification of individual patients. A significant problem is the lack of normative FA values, which is complicated by baseline variation among individuals,[90,91] and temporal variation that depends on patient age, as well as the amount of time elapsed since the traumatic brain injury.[92] Any future translation of DTI measures from research arena to clinical practice will depend on standardization and proof of inter-observer reliability among varying data acquisition/analysis techniques with longitudinal, not cross-sectional, studies to establish their clinical predictive value.

Functional MRI

Functional MRI employs the blood-oxygen–level dependent (BOLD) technique to map neural activity rather than axonal integrity, detecting abnormalities of the functional network rather than the structural network. Neuronal activity is dependent on glucose and therefore stimulates a hemodynamic response that brings in more oxyhemoglobin as well. The associated decrease in paramagnetic deoxyhemoglobin can be measured on dynamic T2*-weighted images to generate a BOLD signal as the patient focuses on a task or rests at baseline, also known as task-based fMRI or resting state fMRI, respectively. These are somewhat analogous to stress electrocardiography and resting electrocardiography for the evaluation of cardiac electrophysiology. Because there is syndrome overlap between mTBI and psychiatric conditions such as PTSD and depression, both of which include many symptoms related to cognitive or executive function, task-based fMRI studies of the prefrontal cortex in symptomatic patients may be able to disentangle the two.

Scheibel and colleagues described increased frontal activation during working memory or cognitive control tasks in civilians with moderate-to-severe TBI relative to controls. This increased frontal activation shows correlation between higher activation and better task performance, which in turn suggests that frontal overactivation represents compensatory recruitment of neural resources in the setting of network damage.[93–95] They also have described increased activation within the anterior cingulate gyrus and medial frontal cortex of military personnel with mild chronic blast-related TBI relative to controls, which became more extensive after adjusting for PTSD and depression.[96] Studies of concussed athletes also have shown increased degree and dispersion of activation on working memory tasks,[97,98] which often becomes more prominent under higher processing loads.[99,100] Chen and colleagues have reported decreased activation of the dorsolateral prefrontal cortex in

concussed athletes during memory tasks, although they confirm the same dispersion or activation of outside regions as described in other studies.[101–103]

Variable patterns of prefrontal activation in mTBI are attributed to variable tasks or experimental designs that place different types or levels of demand on cognitive resources. This disparity highlights a need for standardization, similar to previously described challenges with DTI. Post-concussive syndrome appears associated with alterations of the ''resting state'' or ''default network,'' which is a possible alternative to task-based fMRI.[104] As many fMRI projects involve small numbers of patients and specific functional or stimulation paradigms and often are reported using ''pooled'' data rather than individual patient variations, additional research is needed before fMRI measures can translate into clinical practice for the prognostic or therapeutic stratification of individual TBI or PTSD patients.

Other techniques

Besides SWI, DTI, and fMRI, other advanced techniques for TBI include volumetry, MRS, magnetization transfer imaging (MTI), and magnetic resonance elastography (MRE). Vascular techniques include MR perfusion and permeability imaging, as well as conventional MR angiography.

Volumetry typically requires a high resolution 3D T1-weighted sequence (e.g., magnetization-prepared rapid acquisition gradient echo [MPRAGE] or spoiled gradient [SPGR]) and can be performed with manual regions of interest or automated techniques, such as voxel-based morphometry. Volume measurement reveals chronic atrophy in moderate-to-severe TBI patients, which correlates with deficits in attention or memory.[105–107] One study found that the duration of post-traumatic amnesia can predict long-term atrophy,[108] while another observed that post-traumatic atrophy can be regionally selective and can affect many of the same regions as Alzheimer's disease.[109] An analysis of mild-to-moderate TBI patients did not reveal significantly different volumes from controls[110] but it did reveal different or greater changes in volume over time, which also has been shown in longitudinal analysis of moderate-to-severe TBI.[111]

Another technique for detecting white matter injury is MRS, which measures neurochemical status based on the relationship between chemical shift and molecular environment. Important metabolite peaks include choline (Cho), creatine (Cr), and *N*-acetylaspartate (NAA); membrane marker Cho increases and neuronal marker NAA decreases in acute severe TBI, and improvement versus persistence of the decreased NAA/Cho ratio in the chronic setting correlates with functional status.[112–114] Simultaneous measurements of cerebral blood flow confirm that hypoperfusion or ischemia is not responsible for the reductions in NAA, which is synthesized within the mitochondria.[114] One study of mTBI revealed a change of less than 20% in thalamic metabolite concentrations relative to controls,[115] while another study of concussed athletes revealed decreased NAA/Cr at 3 days that recovered by 30 days, even though symptoms had resolved at 3 days. Interestingly, the NAA/Cr in those who continued training and suffered another concussion recovered later at 45 days, even though symptoms had resolved at 30 days.[116]

Yet another technique for detecting white matter injury is MTI, which measures the transfer of magnetization from bound to free water protons by comparing signal before and after an off-frequency radiofrequency pulse that saturates the bound water protons. This technique generates the magnetization transfer ratio (MTR), which is higher in the presence of myelin and other macromolecules. Decreased MTR in a swine model of DAI matches with histologic evidence of axonal injury,[117] and decreased MTR in normal-appearing white matter of TBI patients is associated with poorer neurologic outcome,[118] although there is normal variation of MTR depending on age and gender.[119]

A final technique for detecting white matter injury is MRE, which synchronizes mechanical excitations with phase contrast imaging to measure tissue elasticity. While there is limited data on tissue elasticity in human TBI patients, *ex vivo* analysis of rats subjected to controlled cortical impact injury has revealed 23% to 32% lower stiffness in the injured hemisphere, compared with the healthy one.[120]

Advanced techniques for evaluation of vascular pathology include both perfusion and permeability imaging. In the clinical setting, perfusion-weighted imaging is often performed by measuring T2* signal change during the first pass of an intravenous bolus of gadolinium contrast (dynamic susceptibility contrast) and generating maps of relative cerebral blood flow/cerebral blood volume (rCBF/CBV) for evaluation of ischemic or neoplastic disease. Group analysis of rCBV maps in military patients with mTBI showed perfusion deficits in the cerebellum and anterior cingulate, which correlated with neurocognitive results and neurobehavioral symptoms.[121] Perfusion maps also can be generated without intravenous gadolinium by using radiofrequency pulses to create endogeneous contrast and label arterial water molecules before they enter the cranial vault (arterial spin labeling). This technique is used more commonly in the research setting, where it can be used for absolute or repeated CBF/CBV measurements in exchange for longer imaging times. Arterial spin labeling studies have uncovered decreased thalamic perfusion in mild, moderate, and severe TBI patients in group analysis versus controls, with additional findings in posterior cingulate and frontal cortices for moderate-to-severe TBI.[122,123] Dynamic contrast enhanced T1-weighted images can be used to assess vascular permeability and blood brain barrier integrity. Dynamic contrast enhanced studies in rabbit models have found a correlation between increased vascular permeability as quantified by the volume transfer coefficient (Ktrans) and the severity of the experimental TBI, as well as functional outcome at 30 days.[124,125] For the evaluation of large vessel pathology, such as dissection or vasospasm, conventional MR angiography of the head or neck can be performed using routine noncontrast (time of flight or phase contrast) or contrast-enhanced techniques, depending on injury mechanism/severity or transcranial Doppler measurements.

Discussion

The literature contains many excellent recent reviews of imaging in TBI,[126] as does the American College of Radiology (ACR) Appropriateness Criteria (clinical guidelines), to serve as references for clinical decision-making. A host of ongoing, funded TBI research projects also are using ''advanced'' MRI. These protocols—most of which are publicly available—are actively exploring the most promising MR techniques for *in vivo* human imaging. For example, the protocols under study by the Uniformed Services University of the Health Sciences, the National Institutes of Health, and the Center for Neuroscience and Regenerative Medicine, are testing a variety of imaging methods, including fMRI, DTI, and SWI. CT scanning and ''standard'' MRI (including DWI/ADC, FLAIR, and susceptibility imaging) are accepted and reasonably validated. DTI and fMRI remain largely research tools due to heterogeneity of protocols and unclear significance of mean

differences uncovered during group analyses for the individual patient, but they have the potential to be clinically useful.

It should be noted that the neuroimaging decision in the acute setting is one of necessity, not modality, which is the reason for clinical decision rules, such as the New Orleans Criteria and Canadian CT Head Rule.[127] Clinical policy from the ACEP and the CDC upholds serial GCS assessment and head CT scanning as the best tools in the acute setting and makes no recommendation for MRI.[58] While blinded comparisons have revealed increased lesion sensitivity using MRI as compared with CT in acute TBI, particularly for small contusions and shearing injuries,[64,128,129] these findings rarely affect management. A 3-year study of early imaging on trauma admissions at Massachusetts General Hospital showed CT and MRI findings were identical in 67% of cases; CT findings led to TBI-related interventions in 63% of cases, and MRI findings affected management in 0% of cases.[130]

There is a paucity of clinical–pathological correlations for many of the MRI observations. Pathological validation will require the acquisition of multiple human brain specimens, for which the DoD TBI brain bank was recently established.

Research in neuroimaging is primarily focused on mTBI or concussion because it is the most common type of head injury, the most difficult to diagnose, and the least associated with radiologic biomarkers. There is conflicting data on the significance of intracranial lesions on conventional brain MRI scans for mTBI. Some analyses based on MRIs done in the chronic period have shown no correlation with neurocognitive symptoms or outcomes,[131,132] while a recently published multi-center study has demonstrated a strong correlation and prognostic value of MRI findings in the acute and subacute period in predicting Extended Glasgow Outcome Scale score at 3-month follow-up.[64] Our current assessment is that brain MRI offers moderate clinical utility in both CT-negative and CT-positive TBI. However, there is significant research utility for MRI in the evaluation of TBI. Ongoing research using MRI should include the following: 1) reliable and reproducible DTI measurements of FA and AD/RD for non-hemorrhagic microstructural change and for detection of microscopic axonal injury in CT-negative TBI and 2) standardization of task-based or resting state fMRI paradigms in the evaluation of persistent post-concussive symptoms.

Each of these research arms should include clinical correlation with neuropsychological symptoms and outcomes in longitudinal studies of patients with (or at risk for) mTBI to ensure that measurements from advanced neuroimaging techniques add value to and affect the course of patient care. In addition, validation of MRI observations by correlation with pathology is essential both to confirm and understand the cellular processes of astrocytic and neuronal injury in TBI.[126,133]

Transcranial Doppler Ultrasonography

Outcome from TBI is determined by two substantially different factors: 1) the primary insult occurring at the moment of impact and 2) the secondary insult, which consists of the consecutive pathologic processes initiated at the moment of injury with delayed clinical presentation. A recent single center prospective observational study in patients with moderate-to-severe TBI showed that 70% of patients experienced neurological complications, and outcomes were worse for those patients.[134] For moderate-to-severe TBI patients, delayed cerebral ischemia (DCI) from the presence of post-traumatic vasospasm (VSP) and intracranial hypertension (ICH) are major contributing factors for secondary injury.

Multiple imaging modalities have been employed to assess VSP, with TCD ultrasonography and digital subtraction angiography being the most studied. TCD is a portable device that uses a handheld 2 MHz transducer placed on the surface of the scalp to measure the cerebral blood flow velocity (CBFV, in cm/sec) and pulsatility index (PI) within the major intracranial arteries involved in the circle of Willis.[135,136] Due to its noninvasiveness and ease of application, TCD examinations have gained an important role in the early phase, as well during the assessment of patients with cerebral ischemia due to VSP in the setting of aneurysmal or traumatic subarachnoid hemorrhage, (aSAH) or tSAH, respectively. TCD also can be used to detect abnormally high intracranial pressure (ICP) and as an adjunct to clinical examination in the confirmation of brain death.[137]

TCD and vasospasm diagnosis after subarachnoid hemorrhage

The extent and timing of post-traumatic cerebral hemodynamic disturbances due to VSP have significant implications for the monitoring, treatment, and outcome of patients with TBI. TCD is increasingly being used for the diagnosis, surveillance, and monitoring of VSP after SAH of any etiology.[135,138–141] TCD studies of diagnostic accuracy for detection of VSP and prediction of DCI vary widely in their conclusions with regard to the sensitivity and specificity of TCD.[142,143] Aaslid, and later others, described the use of TCD for VSP detection; all these authors correlated TCD data with digital subtraction angiography (DSA).[144,145] The sensitivity and specificity of TCD in the prediction of VSP vary according to the vessel, diagnostic criteria, and timing of correlative DSA,[135] and are complicated by the absence of validated TCD criteria for diagnosis of vasospasm for different age groups.

In addition, CBFV by TCD can be influenced by an absence of temporal bone windows and by the skill level of neurosonographers. One review of 26 studies comparing TCD and DSA showed a 99% specificity for the absence of VSP by TCD in the middle cerebral artery (MCA) when DSA is also negative, and, thus, TCD had a high positive predictive value to identify patients with VSP.[143] TCD appears to be highly predictive of an angiographically demonstrated VSP in the MCA; however, its diagnostic accuracy is lower with regard to VSP in the anterior cerebral artery[146] and basilar artery.[147] In this regard, the positive predictive value of a combination of assessments (clinical, CT, and TCD) to detect VSP after SAH may be superior in accuracy, compared with single, independent tests.[148] In general, increased mean CBFV on TCD will diagnose VSP and monitor its development (deterioration or regression) involving large intracranial arteries after SAH. In addition to the value of CBFV, Rajajee and colleagues retrospectively studied 81 patients with aSAH who underwent TCD between Days 2 and 14 and reported that low PI (mean, 0.71 ± 0.19) was found to be an independent predictor of DCI.[149] In the intensive care unit (ICU), patients after aSAH often will be treated with triple-H therapy (hypertension, hypervolemia, hemodilution) that results in increased CBF to the brain.[138] Therefore, it is important to complement full TCD examination with measurement of the Lindegaard Index, defined as the ratio of the mean CBFV of the MCA to that of the extracranial portion of the ipsilateral internal carotid artery. This ratio increases with the severity of VSP. Normal values for this index range from 1.1 to 2.3 and, in the absence of VSP, will be less than 3.[150] If the CBFV is found to be elevated but the ratio is less than 3, then the elevation is thought to be due to hyperemia. A ratio greater than 6 is consistent with severe VSP.[150,151]

In patients with TBI, DSA demonstration of cerebral VSP has been well documented with incidence ranging from 2% to 63%.[152–154] Kordestani and coauthors demonstrated that delayed cerebral VSP is strongly associated with tSAH, and is usually distributed across all levels of TBI severity, as defined by the GCS score.[155] Post-traumatic VSP can be seen in patients with tSAH, intraventricular hemorrhage, subdural hematoma, and contusions.[156] The results of the study by Lee and colleagues suggest that the VSP is an important post-traumatic secondary insult and could be diagnosed by TCD.[157]

VSP may occur sooner following TBI than following aneurysmal rupture, but the 10 to 12 day duration is similar for both conditions.[158–160] VSP has been shown to occur following tSAH in 2% to 41% of TBI patients by DSA[153] and in as high as 60% of patients by TCD, [161,162] even in the absence of tSAH.[163,164] It is recommended that serial TCD examinations be started in the first 72 h post-injury, to detect VSP.[165]

In the past decade, TBI has been associated with the severest casualties from Operations Iraqi Freedom and Enduring Freedom. Armonda and colleagues indicated that VSP occurred in a substantial number of patients with wartime-induced severe TBI.[166] Recently, signs of mild, moderate, and severe VSP were observed in wartime TBI patients by TCD in 37%, 22%, and 12% of patients, respectively.[167] VSP detected by TCD may precede neurologic deficits and prompt earlier intervention.[168] Hemodynamic changes seen in intracerebral vasculature after tSAH can be diagnosed and monitored using TCD; therefore, the primary application of TCD in tSAH is in the daily surveillance of VSP.[151,167]

Angiographic VSP has been classically reported to occur between Days 4 and 14 after aSAH,[169] but variations to this timeline do occur, and VSP has been reported as early as within 48 h in up to 13% of patients and as late as Day 16[170] or 17.[171–174] VSP could be evident up to Day 20 by TCD.[142, 175] In addition, it was shown that DCI could happen up to Day 14 after aSAH,[142] and if information obtained from TCD findings was used more often in aSAH patient management, outcomes might be improved.[176]

TCD is useful in monitoring the temporal course of VSP after tSAH. Even though repeat DSA is unavoidable in most tSAH patients, TCD can guide the timing of this procedure and the tailoring of aggressive treatment regimens. The key is not to predict compromised perfusion by TCD, but to identify patients going into VSP and to quickly confirm VSP when subtle signs are present and before apparent neurologic deterioration. It is useful to perform a TCD test on admission or as soon as possible after surgery and to perform daily TCD studies when a patient is in the ICU. Daily TCD can be the least expensive option to identify patients at risk for deterioration. The presence and temporal profile of CBFVs in all available vessels must be detected and serially monitored. TCD studies should be performed after endovascular treatment to identify patients with recurrent VSP. The high sensitivity of TCD in identifying abnormally high CBFVs resulting from the onset of VSP demonstrates that TCD is an excellent first-line examination to identify those patients who may need urgent, aggressive treatment. A dedicated and experienced team of neurointensivists, neurologists, neurosurgeons, and neuroradiologists is required to provide the best available care and outcome for those patients suffering TBI and to reduce adverse outcomes associated with tSAH.

Future studies are clearly needed to determine the extent to which post-traumatic VSP causes DCI and whether its development is directly affected by tSAH. However, although no adequate study has been conducted, TCD is thought to be valuable in the day-to-day evaluation of tSAH patients and to assess the effect and durability of neuroradiologic or endovascular interventions.

VSP following TBI is a significant source of morbidity and mortality. Too often, the first sign is a neurologic deficit that may be too late to reverse. TCD assists in clinical decision making regarding further diagnostic evaluation and therapeutic interventions. As TCD-defined VSP preceded the neurological deficit in 64% of cases,[168] earlier intervention might reduce the incidence of VSP-related stroke in military or civilian hospitals with similar practice patterns.

TCD and intracranial pressure

Raised ICP is a life-threatening condition that can result in brainstem compression and compromised brain circulation. Increased ICP is associated with increased morbidity and is an independent predictor of mortality and of a composite endpoint of functional and neuropsychological outcome at the 6 month follow-up in moderate or severe TBI patients.[177] However, even in patients initially diagnosed with mild or moderate TBI, slow growth of a hematoma with consequent development of ICH will adversely affect outcome, therefore monitoring of ICP is a reasonable approach to discovering a progressive increase in ICP in TBI patients.[178]

The primary purpose of TCD ultrasonography is to determine the velocity of flowing blood by quantitative interpretation of TCD waveforms. Although the qualitative contour of the TCD waveform during ICP elevation falls into a recognizable pattern, the interpretation depends on the experience and expertise of the TCD examiner and interpreter. Objective, reproducible, and verifiable measures of TCD waveform changes are necessary for TCD findings to be used with certainty for evaluation of high ICP. One method of quantifying these changes is utilization of the PI. The PI is a reflection of downstream resistance and is affected by ICP and/or diffuse atherosclerosis. The PI reflects the amount of resistance in the more distal cerebral blood vessels.[151,179] PI is a calculated index of the TCD waveform that takes into account the peak systolic CBFV and the end-diastolic CBFV, and compares the changes in these variables against the change in the standard measure of the entire waveform, such as mean CBFV.

When ICP is above 20 mm Hg, the PI has been evaluated as an alternative to direct ICP measurement.[180] There is also a significant correlation between the cerebral perfusion pressure (CPP) and PI.[181] In a prospective study, it was shown that TCD ultrasonography is valid in predicting the patient's outcome at 6 months and correlates significantly with ICP and CPP values when it is performed within the first 24 h after severe TBI.[182] A pediatric study showed that the high sensitivity of admission TCD to predict ICH and abnormal CPP after severe TBI demonstrates that TCD is an excellent first-line examination in determining those children who need urgent aggressive treatment and continuous invasive ICP monitoring.[183] Another recent prospective observational cohort study enrolled 98 patients with mild and moderate TBI and an initial GCS score of 9 to 15 whose initial CT scan showed either absent or mild lesions. TCD measurements of bilateral MCAs were obtained on admission to the ED and results demonstrated that in patients with no severe brain lesions on CT scan, a TCD on admission, complemented with brain CT scan, could accurately screen patients at risk for secondary neurological complications.[184] A recent pilot study suggests that in patients with severe TBI, TCD could be used in prehospital care to detect patients whose CPP may be impaired. [185] In the ICU setting, serial TCD monitoring allowed

identification of an imminently fatal complication in time to allow a life-saving intervention.[186]

TCD is the noninvasive ultrasound modality capable of identifying patients who are progressing to ICH, and it also can monitor the effectiveness of any pharmacological intervention and detect normalization of the ICP. However, three conditions must be fulfilled: mean arterial pressure, carbon dioxide tension, and cardiac output must be within normal limits and not significantly different, compared with the previous day. Several publications indicate the clinical value of TCD for measuring the MCA CBFV and PI as possible predictors of outcome in severe TBI management.[186–188] Some authors even suggest that early use of PI measurement permits the identification of patients with low CPP and a high risk of DCI. In emergency situations, PI can be used alone or when ICP monitoring is contraindicated or not readily available.[189] TCD can be used to evaluate ICP, either independent of or in conjunction with other invasive and noninvasive imaging studies. The literature does not yet suggest use of PI as an accurate method to quantitatively assess ICP in mm Hg. However, in numerous publications, it was shown that PI correlates well with ICP as measured by invasive methods.[190,191]

At present, the role of TCD for ICH evaluation could be defined as follows: 1) TCD waveform changes indicate abnormally high ICP, especially above 20 to 30 mm Hg; 2) TCD changes may alert neuro-ICU personnel and may indicate a malfunctioning of the ICP probe; 3) an abnormally and globally decreased pattern of the CBFVs in parallel with increased PIs indicates an onset of diffuse intracranial hypertension; and 4) sudden onset of asymmetrical CBFVs and PI changes may indicate a potential midline shift. More studies are needed before TCD can be substituted for direct measurement of ICP. However, even today, quantitative and qualitative change in TCD values and waveform morphologies may persuade physicians to undertake other diagnostic steps or to change medical treatment, thereby improving care of these patients and their outcomes.

Brain death

The irreversible and complete loss of all brain functions has been accepted in many countries as a criterion for death. The irreversibility can be determined after an adequate observation period or by ancillary testing, such as EEG, DSA, or nuclear imaging. Barbiturate therapy or hypothermia may preclude proper diagnosis of brain death either clinically or by EEG. Specific intracranial flow changes indicating total cerebral circulatory arrest (CCA) can be visualized by TCD and can provide direct information about the physiological status of CBF that signifies the CCA. Appropriate TCD criteria have been defined and guidelines for the use of TCD for confirmation of total CCA are published.[192]

A systematic review of articles in English on the diagnosis of brain death by TCD, published between 1980 and 2004, showed a sensitivity of 95% and a specificity of 99% to detect brain death.[193] Meta-analysis of all 10 studies analyzed showed a sensitivity of 89% and a specificity of 99%.[193] TCD can rule out CCA if positive diastolic flow is detected at any ICP value. TCD also can confirm clinical diagnosis of brain death by demonstrating complete CCA. TCD offers serial noninvasive assessments and can minimize the number of nuclear flow studies needed to confirm the arrest of cerebral circulation and represents a useful adjunct test for the evaluation of CCA associated with brain death.

Discussion

Given the large societal burden from morbidity and mortality associated with TBI, this disease entity has been the focus of extensive research over the past several decades. Because primary injury in TBI is preventable, whereas secondary injury is merely treatable, most of the research effort has been targeted at identifying those factors that contribute to secondary injury and minimization of their deleterious effects. VSP and ICH are major post-traumatic deleterious effects that continue to adversely affect a significant proportion of the TBI population and remain a challenge for all clinicians. At the present time, no proven treatment regimen aimed specifically at decreasing the potential detrimental effects of post-traumatic VSP exists. Therefore, vigilant diagnostic surveillance, including serial daily TCD studies and the prevention of secondary brain damage due to VSP and ICH, are crucial.

The quest for ''fine-tuning'' of this TCD application continues. Trending of the CBFVs and day-to-day comparison of the changes are critical and provide good predictive value. The limitations of TCD indicate that this modality should not be used in isolation in the neuro-ICU. The gold standard remains the neurologic evaluation, when limited additional surrogates should be used, such as monitoring of brain tissue partial pressure of oxygen, continuous EEG (cEEG), CBF, CT-perfusion, and NIRS. Frequently, DCI occurs earlier than natural history would suggest; daily TCD can be the least expensive option for identifying patients at risk for deterioration. The high sensitivity of TCD to identify abnormally high CBFVs resulting from the onset of VSP demonstrates that TCD is an excellent first-line examination for determining those patients who may need urgent, aggressive treatment.

TCD can noninvasively identify patients who are progressing to VSP. Research directed toward the establishment and validation of TCD criteria for VSP for different age groups will improve TCD's accuracy to predict clinical deterioration and infarction from DCI.

In addition, TCD provides additional real-time information about CPP. Invasive ICP monitoring is an established tool for managing patients with TBI. However, it provides information about ICP only. In TBI patients being treated without invasive monitoring, TCD provides important information about ICP and cerebral hemodynamics. In patients undergoing invasive ICP monitoring, serial TCD examinations provide complementary information.

TCD is an important tool for monitoring the natural course of TBI, evaluating the effect of medical treatment or intervention, forecasting, and identifying high-risk patients after TBI. Despite a lack of good prospective data on TCD evaluation and outcome in TBI patients, TCD as a noninvasive, inexpensive, and simple procedure that should be engaged in the daily management of TBI patients.

Positron Emission Tomography

PET is a nuclear medicine imaging technique that provides measurements of physiological and biochemical processes *in vivo.* The PET scanner provides tomographic images of the distribution of radiopharmaceuticals that are labeled with radioactive, positron-emitting atoms. The most commonly used positron-emitting atoms and their physical half-lives are oxygen-15 (^{15}O; 2 min), carbon-11 (^{11}C; 20 min) and fluorine-18 (^{18}F; 110 min). A wide variety of PET radiopharmaceuticals labeled with one of these atoms is available

for brain studies, including those to image cerebral blood flow and blood volume; glucose, oxygen, and protein metabolism; several neuroreceptor-neurotransmitter systems; cellular proliferation; amyloid deposition; and neuroinflammation.

PET images are typically analyzed in conjunction with anatomic images, CT scanning, or MRI. Robust methods are available to co-register PET and anatomic images, so that regional physiologic abnormalities can be related to anatomic structures and focal lesions. PET studies of chronic TBI often include a neuropsychological evaluation of patients. PET studies in acute TBI have been performed in a few specialized centers that can perform PET in very ill patients who require extensive monitoring. Some acute TBI studies have been combined with microdialysis to provide measurements related to energy metabolism, such as levels of tissue lactate, pyruvate, and glucose, where an elevated lactate/pyruvate ratio typically reflects anaerobic metabolism of glucose. It should be noted when considering the findings reviewed here that studies of acute TBI are typically performed at only one time point after injury, resulting in a snapshot during what may be an evolving, dynamic pathophysiological process.

SPECT, another nuclear medicine technique that is described elsewhere in this review, also provides tomographic images of radioactivity in the body but is different in several ways from PET. Most SPECT studies use radiopharmaceuticals designed to image brain perfusion. There is a much wider variety of PET radiopharmaceuticals clinically used to study brain function are ^{18}F based and are usually available through a radiopharmaceutical distributor. However, some F18 radiopharmaceuticals will require a nuclear chemical compound capability. Non-^{18}F–based radiotracers used in brain imaging usually require an on-site cyclotron to produce the positron-emitting labels. The instrumentation to image radioactivity differs between PET and SPECT, because of the different types of radioactivity used. In general, PET has better sensitivity and image resolution, as well as better ability to quantitate local radioactivity concentration.[194,195]

^{18}F-labeled fluorodeoxyglucose studies

^{18}F-labeled fluorodeoxyglucose (FDG) is the most widely used PET radiopharmaceutical for brain imaging. FDG is a labeled analogue of glucose that is taken up and retained by brain tissue in proportion to local glucose metabolism. Glucose is the main source of energy for the brain, and glucose metabolism is closely coupled to local neuronal activity, especially synaptic activity. FDG permits the measurement of the cerebral metabolic rate of glucose (CMRglc). Therefore, FDG has been extensively used to image local brain function in neuropsychiatric diseases, including chronic TBI. FDG also has been used to study disturbances of energy metabolism in acute TBI.

FDG studies of acute, severe TBI have reported CMRglc values in contusional, pericontusional, and distant brain regions, as well as global brain values. Within a contusion, metabolism typically is greatly decreased, reflecting local tissue damage. Pericontusional hypometabolism is often present, as well as a widespread decrease in cerebral cortical metabolism involving brain that is normal on anatomic imaging.[196–198] Consistent with the widespread decrease in cortical CMRglc, tracer kinetic analysis showed a decrease in the rate of phosphorylation of FDG by hexokinase, a key initial step in glucose metabolism.[198,199] Very early after severe TBI, however, there may be increased glucose metabolism adjacent to a contusion or hematoma; global cortical hypermetabolism also has been described in some patients.[200] A diffuse loss of contrast between gray and white matter in FDG images has been attributed to a relative preservation of white matter CMRglc in relation to depressed gray matter CMRglc.[198] One study found no correlation between global cortical CMRglc and level of consciousness on the GCS at the time of PET,[196] although correlations with regional CMRglc in thalamus, cerebellum, and brain stem have been reported.[201] Over many months, glucose metabolism increases throughout the brain, although not necessarily to normal levels; this increase correlates poorly with the degree of clinical improvement.[197]

^{15}O Studies

Another PET approach to study acute TBI uses radiopharmaceuticals labeled with ^{15}O. Measurements are made of CBF with ^{15}O-labeled water ($H_2{}^{15}O$), cerebral blood volume with inhaled $C^{15}O$, and cerebral oxygen metabolism ($CMRO_2$) and oxygen extraction fraction (OEF; the percentage of oxygen that is extracted by brain tissue from incoming arterial blood) with inhaled $^{15}O_2$. Because of the short, 2 min half-life of ^{15}O, all these measurements can be made during one scan session. These methods are technically more demanding than the FDG technique.

^{15}O PET studies have been performed in moderate-to-severe acute TBI within a few days of injury. They assess the level of tissue oxygen metabolism and blood flow globally and regionally and whether CBF is adequate to supply the tissue's oxygen metabolic needs (as reflected by the OEF). In and near contusions, there is decreased CBF and $CMRO_2$.[200–203] Often, more widespread metabolic dysfunction is present, with decreased $CMRO_2$ and CBF in distant areas of brain that are structurally intact (similar to observed decreases in CMRglc).[204] Distant areas also have shown an abnormality in cerebrovascular autoregulation (i.e., the maintenance of CBF at a constant level as cerebral perfusion pressure varies). Contrary to what might have been expected, cerebral ischemia, defined by an abnormally high OEF, has not been a prominent finding in acute TBI, and when present, it involves a relatively small volume of brain.[204,205] This finding indicates that the observed reductions in $CMRO_2$ are not because of a decrease in CBF to a level insufficient to support oxygen metabolism. Decreased oxygen metabolism with relatively maintained glucose metabolism in white matter has been reported, suggesting nonoxidative glucose metabolism.[206] Findings of an elevated lactate/pyruvate ratio with normal or moderately elevated OEF in the area of microdialysis probes also suggest the occurrence of anaerobic glucose metabolism and metabolic disruption that is not related to cerebral ischemia or inadequate oxygen delivery.[205,207] A recent study using ^{15}O tracers and FDG focusing on pericontusional tissue found no evidence of ischemia. There was, however, in this study increased CMRglc in relation to $CMRO_2$, suggesting disrupted energy metabolic pathways or possibly increased nonoxidative glucose consumption by inflammatory cells.[203]

^{15}O methods have been used to study the physiologic effects of various treatments for severe TBI, including hyperventilation, increasing cerebral perfusion pressure, hyperoxia, intravenous (IV) osmotic agents, and glycemic control. Hyperventilation, which decreases arterial partial pressure of carbon dioxide and causes vasoconstriction, is widely used to reduce intracranial pressure. A concern is whether the associated decrease in CBF causes cerebral ischemia. Hyperventilation does reduce regional and global CBF, but even in regions with very low CBF, there is no decrease in $CMRO_2$ because of an accompanying increase in OEF.[208] Increasing cerebral perfusion pressure results in little or no increase in CBF in contusions and pericontusional tissue in spite of their low

baseline CBF; increases in CBF in distant areas suggest abnormal cerebrovascular autoregulation.[209] Therefore, this intervention is unlikely to be of benefit.

The effect of increasing the level of oxygen in blood (hyperoxia) also has been studied. It did not increase cerebral hemispheric oxygen metabolism,[210] although it did increase $CMRO_2$ somewhat in areas of low baseline metabolism.[211] Administration of osmotic agents, mannitol or hypertonic saline, is widely used to reduce the increased ICP that develops due to mass lesions or cerebral edema after severe TBI. Two PET studies measured the effects of these agents in patients with ICH. One study showed that they increased CBF in brain regions with baseline hypoperfusion, with an associated decrease in OEF and no change in $CMRO_2$; there was no change in global CBF.[212] The increased local CBF was attributed to a decrease in blood viscosity. Bolus intravenous administration of mannitol to reduce ICH does not acutely lower CBV.[213] These studies provide evidence for an alternative mechanism—acute reduction of brain water—to explain the effect of mannitol. Another study examined the effect of tight (80–110 mg/dL) versus loose (120–150 mg/dL) glycemic control, using both FDG PET and microdialysis.[214] Tight glycemic control, in contrast to mild hyperglycemia, resulted in increased global and gray matter CMRglc in 10 of 13 patients, and more frequent metabolic disruption manifested by reductions in brain glucose and elevated lactate/pyruvate ratios. The authors concluded that delivery of more glucose to brain by means of mild hyperglycemia may be beneficial.

Studies have explored the relationship between measurements of CBF and $CMRO_2$ in the acute phase of severe TBI and tissue damage assessed by MRI at follow-up. One study identified thresholds for the development of irreversible tissue damage using PET data from tissue that remained undamaged. Although tissue with CBF or $CMRO_2$ values below these thresholds was likely to evolve into lesions, many lesions had PET measurements above these thresholds; therefore, it was not possible to predict the full extent of irreversibly damaged tissue.[202] Another study showed that across patients, the ultimate degree of lobar brain atrophy correlated with lowered $CMRO_2$ in temporal ($r = -0.40$), frontal (–0.29), and parietal (–0.35) lobes and also with lowered CBF (r values of –0.42, –0.50, and –0.27, respectively); p values ranged from 0.000 to 0.033.[215]

Because local CBF changes parallel local neuronal activity, PET images of CBF obtained with $H_2{}^{15}O$ during neurobehavioral tasks can be used to map brain function. Brain mapping with $H_2{}^{15}O$ has largely been supplanted by BOLD functional MRI, which has greater spatial and temporal resolution, but PET is still of value in wounded warriors with retained shrapnel who cannot undergo MRI. A few PET studies of CBF have been reported in chronic TBI patients, mainly while performing memory tasks.[216,217] In general, patterns of activation were similar to those of control subjects but with an altered degree of activation.

Chronic TBI

Several FDG studies have investigated chronic TBI.[218] Both global and extensive regional hypometabolism have been observed in these studies. Mechanisms of diffuse hypometabolism in brain tissue distant to an area of a focal lesion, if there was one, include actual loss of neurons and decreased neuronal activity due to loss of afferent projections from other brain regions, possibly due to axonal damage in white matter. Region-specific correlations between PET and cognitive impairment have been reported, although such correlations are not consistently found.

Fontaine and colleagues[218] reported that memory and executive function significantly correlated with CMRglc in mesial prefrontal, lateral prefrontal, and cingulate cortex, while behavioral disorders correlated with mesial prefrontal and cingulate CMRglc. One group used statistical methods to compare images from patients and controls on a pixel-by-pixel basis.[219–221] In a small group of patients with neuropsychological deficits and diffuse axonal damage, hypometabolism was prominent in cingulate cortex, lingual gyrus, and cuneus; individual patient analysis showed differences in the extent of cingulate hypometabolism.[220] Another study in patients with cognitive impairment showed hypometabolism in cingulate gyrus, thalamus, temporal lobes, and frontal regions. The only correlation found between extensive neuropsychological testing and CMRglc was a correlation of full-scale IQ with CMRglc in the right cingulate gyrus and bilateral medial frontal gyrus.[221] Despite the paucity of correlations, areas with decreased CMRglc, including prefrontal, cingulate, and temporal cortex, are in general implicated in executive and memory function.

In a large group of patients with a range of impaired consciousness, bilateral hypometabolism was found in medial prefrontal and frontobasal regions, the cingulate gyrus, and the thalamus. The extent and degree of hypometabolism was greater in vegetative versus minimally conscious versus cognitively impaired patients.[219] A similar study in chronic patients after severe TBI found decreased CMRglc in thalamus, precuneus, and large frontal and temporal regions, with greater decreases in vegetative or minimally conscious patients versus patients with persistent posttraumatic amnesia versus patients who had recovered from posttraumatic amnesia.[222] In boxers who experienced repeated episodes of head trauma, hypometabolism was found in the frontal lobe, posterior parietal lobe, posterior cingulate gyrus, and cerebellum bilaterally; neuropsychological data were not available.[223] Of particular interest is a recent study of Iraq war veterans with chronic mTBI after repetitive military blast exposure.[224] In this study, decreased CMRglc was observed in the cerebellum, vermis, pons, and medial temporal lobe; the subjects also exhibited behavioral symptoms and impaired information processing.

Several PET studies have examined chronic TBI using radiopharmaceuticals to probe different aspects of TBI pathophysiology. [^{11}C]flumazenil binds to the central benzodiazepine receptor site of the $GABA_A$ receptor that is present throughout cerebral cortex. It is a marker for cortical neuronal integrity or density. Decreased tracer binding, consistent with neuronal loss, has been seen in medial frontal gyri, anterior cingulate cortex, and thalamus, areas that often have decreased CMRglc in chronic TBI.[225] One study showed decreased [^{11}C]flumazenil binding only if there was low $CMRO_2$, suggesting that decreased cortical metabolism is in some cases associated with neuronal loss.[226] A study using [^{11}C]MP4A, a tracer for cortical acetylcholinesterase activity, showed decreased cholinergic function in parietal and cingulate cortex; this finding may be relevant to the use of acetylcholinesterase inhibitors to treat the cognitive symptoms of chronic TBI.[227]

Two recent reports of studies use the radiopharmaceutical [^{11}C]PK11195, a marker for neuroinflammation that reflects microglial activation and increased macrophages.[228,229] These studies demonstrated ongoing neuroinflammation that was widespread in the brain, yet more prominent in deeper brain structures. This neuroinflammation was present as late as 17 years post-TBI. These studies suggest a role for neuroinflammation in the pathophysiology of chronic TBI and a possible target for treatment.

Two other molecular targets for PET are tau protein and amyloid. Tau is found in neurofibrillary tangles in Alzheimer's and

other neurodegenerative dementias, as well as in chronic traumatic encephalopathy (CTE), a neurodegenerative disease in athletes with a history of repetitive brain trauma (e.g., symptomatic concussions). Manifestations include impaired memory and executive function, depression, poor impulse control, and eventually parkinsonian symptoms and dementia. A recent PET study used [^{18}F] FDDNP, which binds to both tau tangles and amyloid plaques, in five retired football players with mood and cognitive symptoms.[230] This PET study showed increased radiotracer binding in amygdala and subcortical regions. The authors attribute the findings to fibrillary tau deposition, assuming a paucity of amyloid relative to tau in CTE. Radiotracers, such as [^{18}F]T807, that bind specifically to tau have been developed, and preliminary PET images in one study show increased binding in patients with clinical Alzheimer's disease.[231] [^{18}F]T807 has high specificity for the paired helical fragment form of tau. Through this specificity, it has the potential to characterize lesions related to TBI or Alzheimer's disease neurodegeneration. Its use in chronic TBI patients will be of great research interest. Gandy and colleagues provide a recent review of CTE focusing on the association between pathophysiology and clinical findings.[232] Mitsis and colleagues compared and contrasted two cases that include imaging with [^{18}F]T807 and with amyloid imaging.[233]

[^{11}C] PiB and similar radiopharmaceuticals labeled with 18F that bind to β-amyloid plaques have been extensively used to study patients with Alzheimer's disease and other neurodegenerative dementias.[234] There have been two recent studies that used [^{11}C] PiB in TBI. Hong and colleagues reported 15 patients who suffered moderate-to-severe TBI up to a year before the PET scan.[235] Compared with controls, there was increased tracer binding in cortical gray matter and striatum but not in thalamus or white matter. The specificity of the binding was supported by a companion study that showed neocortical [^{3}H] PiB binding in regions with β-amyloid deposition in postmortem brain tissue from TBI patients.[235] Another study reported [^{11}C] PiB binding in three of 12 patients with neuropsychological impairment studied 5 to 129 months after injury.[236] Further studies will be required to determine the prevalence and time sequence of β-amyloid deposition in TBI, and its relation to degree of initial injury and subsequent impairment.

Discussion

PET has been used for over three decades as a research tool to study the pathophysiology of an array of brain diseases. It has led to a deeper understanding of the physiological and biochemical abnormalities underlying these conditions. PET brain studies are used clinically in the evaluation of patients with dementia and brain tumors and in the preoperative work-up of patients with intractable focal epilepsy. PET remains a powerful tool for clinical research in TBI. PET measurements of CBF, oxygen metabolism, and glucose metabolism have been used to study the pathophysiology and effect of treatment in acute TBI, and the relationship between clinical deficits and brain abnormalities in chronic TBI. Several radiotracers are available to study other aspects of TBI pathophysiology, including neuroreceptor abnormalities, neuroinflammation, and amyloid deposition. The clinical utility of PET in the management of individual patients with TBI, however, has not yet been demonstrated. Virtually all subjects used in PET studies of TBI so far have been civilians with head injury. There is much interest, however, in imaging wounded warriors, and the strength of PET as a clinical research tool should lead to a better understanding of service-related TBI.

Single Photon Emission Computed Tomography

Central nervous system SPECT may be used with a variety of radiopharmaceuticals with differing mechanisms of action (see Table 3 for details), yet when one discusses SPECT imaging for TBI, one usually refers to the two most common and U.S. Food and Drug Administration–approved cerebral perfusion/blood flow imaging radiopharmaceuticals: [^{99m}Tc] Hexamethylpropylenamine oxime (HMPAO) and [^{99m}Tc] Ethylcisteinate dimer (ECD). These radiotracers travel to regions of the brain proportional to perfusion and then become fixed within the neurons. Therefore, measurement of regional cerebral blood flow (rCBF) is both a direct and an indirect measure of metabolism. The current clinical use of SPECT with perfusion agents includes evaluation for TBI, strokes, transient ischemic attacks, dementia, movement disorders, and seizures. Current research efforts are directed at the SPECT evaluation of several central nervous system receptors, such as benzodiazepine, dopamine, Aβ amyloid, and tau.[237] Specifically, [^{123}I] Iomazenil ([^{123}I] IMZ),[238] [^{123}I] 2-Beta-carbomethoxy-3beta-(4iodophenyl)tropane ([^{123}I] beta-CIT) and [^{123}I] Iodobenzamide ([^{123}I] IBZM),[239] image the benzodiazepine, striatal dopamine transporter (DAT) and D2 receptors, respectively. Koizumi and colleagues evaluated the potential of neuronal recovery using [^{123}I] IMZ SPECT to observe that decreased binding occurred at the benzodiazepine receptors in the acute phase but improved in the chronic phase in moderate and severe head injuries.[240] As nuclear medicine continues to progress through the era of molecular imaging, numerous novel radiopharmaceuticals currently in development or being used for research purposes may be available clinically in the near future.[241] Researchers also are showing a renewed interest in the autoregulatory vascular and rCBF effects that occur as a result of head trauma.[242]

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Table 3. SPECT Imaging Radiopharmaceutical Utilization

Agent	*Blood–brain barrier*	*Perfusion*	*Brain tumor imaging*	*Cisternography*
[^{201}Tl (as Thallium Chloride)	X		X	
[^{99m}Tc] DTPA (Diethylenetriaminepentaacetic acid)	X			X
[^{123}I] IMP (Iodoamphetamine)		X		
[^{99m}Tc] ECD (Ethylcysteinate dimer)		X		
[^{99m}Tc] HMPAO (Hexylmethylpropyleneamineoxime)		X		
[^{111}In] DTPA (Diethylenetriaminepentaacetic acid)				X
[^{99m}Tc] Sestamibi			X	

available clinically in the near future.[241] Researchers also are showing a renewed interest in the autoregulatory vascular and rCBF effects that occur as a result of head trauma.[242]

Nuclear medicine brain SPECT potential for TBI neuroimaging

TBI may encompass a multitude of pathological findings, and clinical presentation, such as post-concussive syndrome, may represent an overlap of other concurrent disease processes or pre-existing processes. A ''gold standard test'' with which to compare imaging modalities does not currently exist. SPECT evaluation in TBI relies on visual, semi-quantitative,[243] or quantitative analysis against a normal region of brain activity, control, or normal database.

One potential reason for the diminished use TBI SPECT research imaging may be emergence of PET imaging, the numerous promising PET radiotracers, and the increased availability of F18 radiopharmaceuticals. The physical properties and collimation for positron emitters are key features that make the resolution of PET superior to SPECT. Subsequently, PET has superior signal to noise ratio because of the technology capitalizing on PET tracers' innate radioactive decay properties.[244,245] However, some of the benefits brain SPECT has over brain PET include flexibility in use (no need for nearby cyclotron or radiotracer distributer), radiotracer with longer half-lives (greater flexibility for functional images and for delayed imaging). Generator-acquired brain PET agents such as Gallium-68, which do not require a nearby cyclotron, are being used in brain malignancy research but have no currently published reports with regard to TBI imaging.

SPECT may now be used interchangeably between SPECT and fused camera systems' SPECT/CT. Just as SPECT offers improved resolution over planar imaging, SPECT/CT imaging allows for better resolution over SPECT. Many of the research studies involving SPECT and TBI did not include SPECT/CT technology.[240,246] Since the advent of SPECT/CT, there is evidence of improved resolution and quantitative imaging and promise of future refinement greatly increase the utility of SPECT/CT.[244] Limitations of SPECT, compared with other imaging techniques, include decreased resolution; increased time needed to prepare, acquire and interpret the study; use of ionizing radiation; and the decreased specificity of perfusion deficits.[247] Finally, many of the previous studies which have pitted MRI against SPECT have not contained comparisons with DTI or fiber tract imaging technology.

Moderate and severe TBI.

Clinically, SPECT is used to corroborate anatomic imaging findings or to evaluate for clinical deficits, such as abnormal neuropsychological testing, when no lesion can be identified on anatomic imaging, especially in moderate TBI.[248] Usually because of the severity of the clinical presentation, CT scanning is the first imaging modality. SPECT perfusion is a complementary tool for the clinical evaluation of TBI in the acute, sub-acute, and chronic settings because it reveals additional abnormalities, in particular when the anatomically-identified lesion does not explain clinical deficits. Anatomic imaging and SPECT imaging may each identify lesions that the other modality misses.[132,249,250] This complementarity also is evident in mTBI.

Mild TBI.

In concussion (mTBI), one of the greatest benefits of SPECT is its negative predictive value; a negative examination usually portends a good prognosis for a TBI patient, namely, recovery from post-concussive symptoms.[251,252] Davalos and Bennett conducted a well-crafted methodology to follow up to the 1996 American Academy of Neurology (AAN) assessment of brain SPECT using the same criteria as the Therapeutics and Technology Assessment Subcommittee of the AAN.[251] The authors found that only nine of an original Medline search result of 95 met the criteria. However, the authors found similar results that the AAN had discovered: SPECT may be more sensitive than CT or MRI, discordance of some rCBF deficits and anatomic defects, and the high negative predictive value of SPECT in mTBI. Since 2002, TBI research involving traditional perfusion SPECT and other functional SPECT radiopharmaceutical strategies have proven useful in evaluating and/or correlating neuropsychological and other focal neurological deficits with rCBF abnormalities.[239,250,253,254]

The scientific quality of the evidence for TBI SPECT imaging should be stronger. However, while there are numerous studies, a large prospective, randomized, double-blind, placebo control study does not exist for mild,[132,238,246,249,250,255] moderate[256] or severe[240,256,257] TBI. Several of the cited journal articles blame a lack of standardization of SPECT research protocols as the major source of disparity. Although professional societies such as the ACR and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) have published imaging guidelines, a specific standardized approach for all researchers to implement nuclear medicine SPECT for TBI imaging does not exist.[235,258,259] Other limitations noted include significant variability in the time frame in which imaging takes place after TBI, selection of objective testing to be universally used in research to confirm clinical data with imaging, an accounting of medication/psychiatric diagnoses and other compounding factors, and lack of a standardized way to quantify TBI image findings.[251,260]

Discussion

The literature does not support using SPECT imaging as the only means of diagnosing TBI but supports that it may be a useful adjunct to clinical diagnosis and should be studied further.[241,261] The AAN's last evaluation of the body of literature occurred in 1996.[260] However, the body of research and expert review since that time suggest a re-evaluation may change SPECT's overall accepted utility in TBI. SPECT is a promising capability for evaluating mTBI and a useful adjunct for patients with persistent symptoms and otherwise normal evaluation.[259,262,263] It has an advantage over anatomic imaging in assessing brain parenchymal activity and physiologic changes. The overall quality of evidence for the SPECT published research is moderate for detecting mild, moderate, and severe TBI when subjects present a neurological deficit upon examination. While SPECT perfusion imaging is able to identify abnormalities in mild, moderate, and severe TBI when subjects present a neurological deficits currently CT and MRI have a more prominent role in the evaluation of acute, subacute, and chronic TBI. The most recent ACR/SNMMI analysis rates the appropriateness of perfusion SPECT for the evaluation highest for the ''subacute or chronic closed head injury with cognitive and/or neurologic deficit(s).''[262,264,265] In the ACR's most recently update, ''Appropriateness Criteria: Head Trauma,'' it has given two studies a rating of 2 (i.e., moderately well designed study that addresses most common biases).[264] One of the ACR-cited studies, Jacobs and colleagues, reported a 97% recovery at 3 months for mTBI patients who had a normal perfusion SPECT.[265] SPECT is able to identify perfusion/blood deficits in mild, moderate, and severe TBI that anatomic imaging inaccurately identifies or misses

altogether. Generally, SPECT imaging systems are not as ubiquitous as CT scanning or MRI imaging systems. Ease and speed of use when compared with MRI and CT imaging is a disadvantage for SPECT evaluation of TBI, even when it is available.

SPECT represents an affordable modality and is available in most medical centers.[241,266–268] Many SPECT imaging systems may be fused SPECT/CT imaging systems, allowing the CT and SPECT to be performed almost simultaneously, thereby improving the localization of abnormal findings. Additionally, newer instrumentation and computer algorithms have and promise to show improved resolution.[244] SPECT is exquisitely suited for the evaluation of patients who may have ferrous foreign body, shrapnel, or hardware that would preclude MRI examination. The disadvantages of SPECT, in addition to those mentioned, include the challenges that imaging presents in the deployment of the system to austere/remote environments; the significant training requirement of the staff operating the system; the availability of the radiotracers; accessibility to SPECT imaging systems; radiation exposure; nuclear regulatory laws in the area in which the SPECT is located; and the availability of support service staff. When added to other imaging systems, such as CT scanning and MRI, SPECT provides a potentially powerful tool to assist in the diagnosis and management of mTBI in the future.[267] As more information is obtained about SPECT findings in this population and new promising radiopharmaceuticals are developed, SPECT will prove an important adjunct or primary diagnostic tool capable of quantifying and following mTBI patients, as well as providing useful prognostic information to better direct the care and management of these individuals.[241]

Electrophysiologic Techniques

Clinical electrophysiologic techniques are used commonly in the evaluation and study of cerebral function following TBI.[269] These assessment tools employ technologies that permit noninvasive recording of the electrical or magnetic activity of the brain. Conventional EEG is the prototypic clinical electrophysiological assessment and was the first neurodiagnostic tool to allow characterization of disturbances in cerebral physiology produced by TBI.[270,271] This clinical electrophysiologic technique employs digital recording of cerebral function acquired from 21 electrodes arranged on the scalp according to the International 10–20 System that generates waveform tracings suitable for visual inspection by a qualified electroencephalographer.[272,273] It served as the basis for the development of more technologically sophisticated and higher-density (e.g., 32-, 64-, 128-, and 256-channel) EEG recording and data analytic techniques, as well as a method by which to detect the weak magnetic fields produced by electrical activity in the brain (i.e., MEG).

Analyses of data derived from these recording techniques reveal information on the state of local and distributed cerebral neural networks at rest, in response to sensory or cognitive stimuli, and/or during active information processing.[269] The information they provide enables characterization of patterns of abnormal brain function that are characteristic of TBI[274,275] and that may inform on prognosis and outcome following TBI.[276,278–280] They may be used to identify the electrophysiologic correlates of TBI-related disturbances in consciousness, cognition, sleep, sensorimotor function, post-concussive symptoms, and neurotransmitter disturbances related to neurotrauma-induced problems of these types.[269,281] Properly applied, EEG- and/or MEG-based assessment methods have the potential to offer methods by which to distinguish between TBI and other states of brain health or disease (i.e., provide TBI biomarkers), identify the neurobiological bases of acute and chronic post-concussive symptoms, guide treatment planning, and inform treatment response expectations.

The principal advantage of all EEG- and MEG-based assessments of brain function over other forms of functional neuroimaging is their ability to measure brain activity at millisecond-level temporal resolutions under cognitively and behaviorally passive or active conditions.[272,279,282] Co-registration of data acquired through high-density EEG and/or MEG recordings with structural neuroimaging, such as MRI, provides information about brain activity with spatial resolutions comparable to those of fMRI—especially when guided by fMRI-determined regions of interest for a particular brain state or function.[283–288] Additionally, most EEG-based recording systems are relatively inexpensive and portable, compared with currently available structural and functional neuroimaging technologies, making them easily deployable in both clinical and naturalistic (i.e., sports, in-theater) settings. The combination of high temporal resolution, reasonable spatial resolution, flexibility of use, portability, and relatively low cost make clinical electrophysiological techniques appealing methods with which to evaluate persons with TBI and disturbances in psychological health.

The various forms of clinical electrophysiologic techniques are not of uniform value in identification of TBI, characterization of the neurophysiology of its consequences, or prediction of its outcomes. Comprehensive reviews of these issues are beyond the scope of the present work but are available in the literature.[279,281,282,289] In the present work, these techniques are addressed only in terms of their relevance to the detection and diagnosis of mild, moderate, or severe TBI and the quality of the evidence in the literature supporting their clinical use for these purposes.

Conventional electroencephalography

Conventional EEG is used commonly in the early neurocritical care assessment and monitoring of persons with moderate-to-severe TBI[290] but generally is not used in early post-injury assessment of persons with mTBI.[218,281,291] When conventional EEG is applied to the evaluation of persons with TBI of any severity, abnormal findings typically include generalized or focal slowing and attenuated posterior alpha, the severity and duration of which vary with injury severity. The frequency of such findings is quite low among persons with durations of LOC of less than 2 min, compared with persons with LOC of more than 2 min (17% versus 56%, respectively).[292] Indeed, some studies report no early post-injury EEG abnormalities in this population at all.[293] When present among persons with mTBI, however, the presence of EEG abnormalities in the first 24 h post-injury is associated with less robust long-term recovery from injury.[294] Conventional EEG abnormalities resolve in the vast majority of persons with mTBI during the first several months post-injury.[269,282,295]

Among persons with moderate or severe TBI, the correspondence between early post-injury clinical symptoms, recovery of consciousness, and conventional EEG findings is relatively robust.[296,297] Among persons with mTBI, the correspondence between conventional EEG abnormalities and clinical symptoms, as well as the correspondence between conventional EEG and findings on other neuroimaging studies, is inconsistent at best.[269 282,291]

The differential diagnosis for abnormal EEG patterns among persons with post-concussive symptoms in the early and late periods after TBI of any severity is broad, and a large number of factors other than neurotrauma influence the apparent development

and persistence of conventional EEG abnormalities in the post-injury period.[269,272] These factors include but are not limited to advanced age, comorbid pre- and post-injury conditions (especially intoxications with illicit substances or medications, anxiety, pain, and co-occurring neurological problems, such as cerebral hypoxia or ischemia), the time post-injury at which the EEG is performed, and the technical quality of the recording. In the setting of moderate or severe TBI, the electroencephalographic evidence of encephalopathy may be exaggerated by these factors. In the context of mTBI, these factors may account entirely for post-injury conventional EEG abnormalities, which (when present at all) tend to be subtle, in the spectrum of normal findings, and often not obvious in the absence of a personalized pre-injury or late post-injury comparison study.[269]

Most studies evaluating the conventional EEG correlates of TBI (especially mTBI) are inconsistent in the definitions of TBI used, the homogeneity of study samples, and the time post-injury at which they are studied; they use a broad range of recording and data assessment methods, do not incorporate appropriate injury and psychiatric comparison groups, and do not control for the confounding effects of psychiatric or neurologic conditions, substance use, or medications on EEG findings. These methodological problems severely limit confidence in the sensitivity and/or specificity of conventional EEG findings to TBI.

In light of these considerations, the quality of the evidence is low with respect to the use of conventional EEG to detect or diagnose TBI in the early or late periods following a possible injury, or to distinguish between TBI and other causes of disturbed cerebral function. Although conventional EEG may be useful as a supportive tool in the assessment of persons with TBI, the available evidence leaves uncertainty about whether applying this assessment method to the diagnosis of TBI represents a wise use of resources.

Quantitative electroencephalography

Digital recording combined with computer-assisted EEG analysis enables quantitative interpretation of EEG data (qEEG). Several measures can be derived from this electrophysiologic technique for this purpose, including frequency composition of the EEG over a given period (spectral analysis); absolute or relative amplitude (μV/cycle/second) and power (μV^2/cycle/second) within a frequency range or at specified channels; relationships in the timing of activity between two channels (i.e., phase); coherence (i.e., a squared correlation coefficient that estimates the consistency of relative amplitude and phase between any pair of signals in each frequency band); and symmetry of activity between homologous pairs of electrodes. These data can be managed in a purely mathematical manner or they may be presented graphically. One graphical method represents them against the electrode system at the scalp surface (historically referred to as brain electrical activity mapping),[298] or they may be represented on the cortical surface using techniques such as low resolution electromagnetic tomography.[299]

In contrast to conventional EEG, abnormal qEEG findings are reported commonly in studies of persons with TBI.[269,282,291] These abnormal qEEG findings typically include reduced mean alpha frequency,[300–304] increased theta activity,[305–308] and increased theta-alpha ratios.[300,309,314] These observations drove the development of combinations of qEEG findings that are used to generate statistical discriminant functions with which to diagnose TBI and in particular, mTBI.[274,275,310–313] Substantial controversy remains regarding the products of these efforts.[269,282,291,314,317]

The most widely known of the qEEG discriminant functions was developed by Thatcher and colleagues based on frontal and frontal-temporal coherence increases and phase decreases, decreased anteroposterior power differences, and reduced posterior cortical alpha power, among TBI subjects, compared with the healthy comparison subjects.[275] In a later work by Thatcher and colleagues,[274] it is suggested that stable and reliable qEEG residua of, and/or compensations to, neural injury develop early and remain detectable into the late post-injury period.

The qEEG mTBI discriminant function[276] distinguished between persons with mTBI and healthy comparison subjects with an overall accuracy of 94.8% and also was supported in that report by a discriminant accuracy of 93% through independent cross-validation at a different location and on a different computer. However, test–retest application of this discriminant function yielded classification accuracies of 80%, 89.2%, 92.3%, and 77.8% at 17.2, 26.5, 43.3, and 223.6 days, respectively. Trudeau and colleagues[319] used this discriminant function to study an independent sample of veterans with PTSD with and without reported histories of blast-related TBI. In that study, Thatcher and colleagues' mTBI qEEG discriminant function correctly identified 88% of those in the group with PTSD and blast-related TBI and 75% of those in the group with PTSD without blast-related TBI for a yield of 12% false negatives and 25% false positives.[275] Importantly, this mTBI qEEG discriminant function failed to distinguish between veterans with and without interview-determined histories of premorbid TBI (including mTBI). This failure raises questions about both the sensitivity and specificity of this approach to TBI diagnosis.

Even if the sensitivity and specificity of Thatcher and colleagues' mTBI qEEG discriminant function[275] were deemed acceptable for clinical practice, the dichotomous classification schemes used in this and subsequent studies have little bearing on everyday clinical practice. Clinicians rarely are asked to distinguish between persons with TBI and healthy comparison subjects (who, as such, would not be seeking clinical evaluation or brought to a clinician's attention). Instead, clinicians are tasked to use the best available clinical data to detect TBI and to distinguish between patient presentations to which TBI, whether recent or remote, is the primary contributor, and those better accounted for, in part or in whole, by other neuropsychiatric conditions such as PTSD, depression, substance use disorders, or headache disorders. With this as the clinical task, qEEG discriminant functions that distinguish only between individuals with TBI and those that are entirely healthy are of little clinical value.

Further undermining the application of qEEG discriminant functions to clinical practice is a lack of specificity of the qEEG findings to TBI. Many conditions that produce acute, subacute, and/or chronic disturbances in cerebral function also produce qEEG findings that are indistinguishable from those produced by TBI.[269,282,291,302,317] For example, Coutin-Churchman and colleagues[302] failed to discriminate between neuropsychiatric diagnoses using an independently developed qEEG discriminant function in a sample of 340 subjects, including four subjects with histories of TBI. Although the small size of the TBI subsample in this study precludes drawing conclusions about the specificity of this qEEG discriminant function to TBI (or, more accurately, the lack of such), the study highlights the absence of robust multi-diagnostic qEEG-based discriminant functions that leaves this clinical electrophysiologic technique unable to clarify the differential diagnosis for symptoms like those experienced by persons with histories of TBI.

By contrast, a subsequent qEEG-based measure developed by Thatcher and colleagues,[318] the TBI severity index, may inform retrospective characterization of TBI severity among those in whom the diagnosis of TBI is not in question. This TBI severity index had an overall classification accuracy of 96% at the extremes of TBI severity (with a sensitivity of 95% and a specificity of 97%), retrospectively predicted GCS score, duration of post-traumatic coma, and post-TBI performance on a broad range of neuropsychological tests. This approach to retrospective TBI severity determinations awaits peer-reviewed publication of replication, by an independent research group using a new sample of well-characterized subjects with TBI, in which appropriate controls for the effects of comorbid neuropsychiatric conditions, medications, and other potential confounds are incorporated. Accordingly, it remains a potentially interesting application of qEEG to TBI diagnosis but it is one that is not yet developed sufficiently for routine clinical use.

Collectively, the available evidence suggests that qEEG offers promise as a method with which to detect TBI and to characterize TBI severity. However, the quality of the available evidence is low. The problems with studies performed to date include variable case definitions of TBI, the extent to which comorbid conditions were assessed and statistically addressed, failure to address the specificity of reported qEEG abnormalities to TBI versus other neuropsychiatric conditions, discrepant findings in reports applying qEEG mTBI discriminant functions to populations with comorbid neuropsychiatric disorders such as PTSD, and lack of peer-reviewed, independent replications of previously published findings. Further research is likely to have an important impact on confidence about the specificity and sensitivity of qEEG-based diagnostics. At present, however, the application of qEEG to the diagnosis of TBI is not regarded as a wise use of resources.

Evoked potentials and event-related potentials

Evoked potentials (EPs) are recorded at scalp electrodes in response to the presentation of a stimulus (e.g., visual, auditory, somatosensory) and automatic preconscious information processing along the nervous system pathways that conduct sensation to sensory cortex.[320] EPs encompass those responses occurring 1–150 msec after presentation of the stimulus used to evoke them. Event-related potentials (ERPs) are the cortically generated, scalp electrode-detected responses that occur 70–500 msec after a cognitive, sensory, or motor event to which they are related.[321] The small amplitudes of EPs and ERPs (0.1-10 microvolts) render these types of electrical activity difficult to discriminate from the background EEG waveforms in which they occur. Computer-assisted signal averaging of many stimulus-evoked response sets, therefore, is usually required to improve detection of EPs and ERPs.

The value of these types of clinical electrophysiologic techniques is their capacity to index basic information processing systems in the brain, the anatomy and clinical correlates of which are reasonably well defined, especially with respect to sensory, motor, cognitive, and affective phenomena. At the same time, their sensitivity to all manner of neurological conditions that affect the structural and functional integrity of these systems renders abnormal EPs and ERPs nonspecific.

Consistent with these suggestions, EPs and ERPs are sensitive indicators of the integrity of the neural systems subserving information processing in the brain. EPs and ERPs have been used to assess brain function across the spectrum of injury severity and of times post-injury, and contribute usefully to characterizing the extent and severity of post-traumatic information-processing abnormalities and to predicting outcomes after TBI.[281,322–324] It is possible that diagnostic-specific patterns of EP and ERP abnormalities will yield methods by which to diagnose TBI and to distinguish it from the many other conditions that produce such abnormalities. However, such methods have not been developed, validated, or replicated, and are not available for clinical use at the present time.

With respect to the use of EPs and ERPs to detect and diagnose TBI, the quality of the evidence is low. Although these clinical electrophysiologic techniques may provide evidence that contributes to the assessment of persons with mild, moderate, or severe TBI in the early and late post-injury periods, applying EPs and ERPs to the diagnosis of TBI does not represent a wise use of resources.

Magnetoencephalography

Electrical currents within cortical neural ensembles generate weak magnetic fields. These magnetic fields—especially those emanating from cortical columns oriented tangentially to the scalp surface (i.e., sulcal dipoles)—are amenable to recording via a superconducting quantum interference device, or SQUID. A SQUID consists of metal coils cooled to superconducting temperatures that are arranged in high-density arrays of approximately 250–300 magnetic field detectors, whose layout is analogous to that used in International 10-20 system-based high-density EEG recordings.[325] The data yielded by MEG is complementary to that acquired using EEG-based techniques and expands the range of clinical electrophysiologic techniques with which to evaluate persons with TBI.

MEG remains an underused technology in TBI research[258,326–331] and is not used routinely in clinical practice. The available data does not support the use of MEG in the diagnosis of TBI, as the quality of the evidence published to date is low with regard to this specific clinical application. However, MEG findings reported in the literature at the time of this writing appear to offer the possibility of distinguishing between individuals with and without TBI and, with further development, may better inform estimates of the sensitivity and specificity of MEG findings to TBI.

Even if MEG develops as a TBI diagnostic technology, however, the expense, technological requirements, and technical expertise that performing, analyzing, and interpreting MEG recordings entails is likely to limit its application to the diagnosis of TBI. Accordingly, considerable uncertainty remains about whether pursing MEG-based TBI diagnostic methods represents a wise use of resources.

Discussion

Clinical electrophysiology offers a variety of powerful and informative methods for studying cerebral function and dysfunction following TBI. EEG, qEEG and topographic qEEG, EPs and ERPs, and MEG measure different aspects of brain activity noninvasively and with temporal resolution vastly superior to that achieved with presently available functional neuroimaging methods. However, this review suggests that the available evidence is insufficient to support the use of conventional EEG, qEEG, EPs, ERPs, and MEG for the detection or diagnosis of mild, moderate, or severe TBI. The evidence is also insufficient to draw any conclusions about the comparative effectiveness of these technologies with others used for this purpose.

Functional Near-Infrared Spectroscopy

Functional NIRS is an established technique to noninvasively measure local hemodynamic changes in brain areas near the head

surface. Tissue absorption of transmitted light remains a limitation of this technique; although the penetration depth is good in near infrared wavelengths, fNIRS is still effectively limited to the cortex. Despite this limitation, multi-channel fNIRS systems can produce maps of brain activation during cognitive, perceptual, and motor tasks,[331–334] and may have utility for imaging brain activation in neurological disease or after TBI. The technique takes advantage of the fact that biological tissues are relatively transparent to light in the near-infrared (700–1000 nm) range.[335] Light sources, usually lasers, are applied to the scalp, and surrounding detectors (optodes) a few centimeters away detect the light as it scatters and diffuses through the underlying tissues. The system detects changes in the absorption spectrum of the tissue corresponding to local changes in oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) concentrations related to regional brain activity. The blood flow response to brain activation shows overshoot in blood flow, which is familiar to fMRI users who use the BOLD contrast in the same way.[334,336] Functional NIRS has the additional advantage of directly measuring HbO, HbR, and total hemoglobin concentration.

Where appropriate paradigms have been established and cross-validated, fNIRS, with its simple and inexpensive apparatus, may represent an acceptable alternative to the current functional imaging ''gold standard,'' fMRI. It should be emphasized that unlike fMRI, which can provide registered functional and anatomical images, fNIRS images require registration with individual data or a standard anatomical system for interpretation and analysis. This modality requires co-registration with anatomical images and the need to develop simple, reproducible techniques for image construction. Several techniques have been developed to co-register functional images from fNIRS with structural images into a common space. However, this registration depends on the ability to reliably localize the optodes on the scalp. One technique is to use probabilistically-determined locations based on a preexisting neurological atlas[337–340] for positioning the light sources and the detectors needed to acquire an fNIRS image. However, optode position is difficult to estimate without instrumentation, and errors can lead to unreliable fNIRS measurement.[341]

Another solution is to acquire a structural head image, including the locations of the optodes.[342] However, this method does not allow positioning of optodes over specific brain areas or consistent optode positioning for repeated experiments. Additionally, the anatomical and functional images have to be acquired within a short time frame and the structural imaging device may have limited availability. Co-registering the physical points that are the optode coordinates with two- or three-dimensional anatomical images can be done with 3D digitization and stereotaxic systems. The challenge lies in finding the appropriate registration algorithm. The alignment between the structural image, most often MRI, and the point surface measurement is achieved using easily identifiable landmark points, surface fitting alignment on the scalp, or a combination of the two.[343] Such methods commonly are used for transcranial magnetic stimulation (TMS) and give good localization.[344] Frameless stereotaxy has the advantage of being able to co-register optode coordinates and the subject's MRI, thereby allowing group analysis by registering group data in the same space and avoiding the need for anatomical scanning with the optodes in place.

fNIRS in TBI

Often, persons with mTBI have difficulty with attention, concentration, memory, and judgment. Recent advances in imaging technology have allowed measurement of changes in blood flow in response to external stimuli. With fNIRS, it is now possible to collect data on the level of blood in the prefrontal cortex and correlate it with external stimuli. This may be advantageous for patients without access to fMRI or who are unable to keep still during fMRI procedures.

Because of the nature and consequence of the injury, cognitive tasks, such as working memory or attention deficit, are widely used in clinical diagnosis. Functional MRI is the technique of choice with its formidable spatial resolution, but accessibility for the patient may limit its use. Application of a functional imaging modality may be key in TBI diagnosis. In fact, mTBI-induced differences in working memory and functional activities were observed by fMRI, even when differences in behavioral performance between mTBI patients and controls were absent. This finding suggests that functional imaging may increase the sensitivity of mTBI diagnosis, compared with neuropsychological evaluation alone.

The characteristic TBI symptom, altered executive function, is associated with lesions of the prefrontal cortex. Functional NIRS may therefore be employed to investigate cognitive paradigms, which produce hemodynamic response functions located in this area. In 2012, Hibino and colleagues[345] investigated the cerebral reaction to nine cognitive rehabilitation tasks in a TBI group and a control group. Different regions were activated during the tasks in TBI patients, compared with controls. Recently, study on verbal working memory in TBI showed significant differences in hemodynamic measures between the control group and the TBI group, even without differences in behavioral performance.[346] Like the working memory paradigm, Amyot and colleagues[347] adapted to the fNIRS environment a cognitive activation paradigm,[348] which produces robust anterior frontal activation on fMRI. This study was able to replicate the basic findings of the fMRI study in group and individual measures using a simple fNIRS technique combined with frameless stereotaxy and a novel angular method to localize scalp activations and co-register them with MRI.

The results[347] of this study are shown as parametric maps of cortical activation wrapped on the surface of the Montreal Neurological Institute (MNI) standard brain atlas. These activation maps are averages across 20 normal subjects, determined while the subjects made discriminations between simple and complex daily tasks. The results agree with fMRI data[348] showing that activation in the medial prefrontal cortex scales with the normed complexity of the daily activity task set used.

In functional brain imaging and spectroscopy, transition from group studies to individual assessments of cognitive function remains challenging. However, only accurate classification of the degree of impairments in individual TBI patients can lead to individual diagnosis and treatment.

The study of cortical activation by fNIRS is a step in the direction of deriving quantitative measures of cerebral function and cerebrovascular reactivity within healthy individuals. The prefrontal cortex is particularly vulnerable in TBI,[349] physiological markers of brain function are most important for diagnosis in mild injury and for prognosis across the severity spectrum. Physiological surrogates for behavioral outcomes are also needed for therapeutic trials.

The ability to assess frontal lobe function in a rapid, objective, and standardized way, without the need for expertise in cognitive test administration, might be particularly helpful in mTBI, where objective measures are needed.[350] Although one of the drawbacks of fNIRS is the lack of anatomical information to accurately locate

the coordinates of the activation site, this difficulty has been overcome using a combined stereotactic/fNIRS system. Through the use of this system, along with the spherical coordinate registration, the functional images can be registered with a brain atlas, such as MNI, for group analysis.

The methodology presented in Amyot and colleagues,[347] like the working memory study with fNIRS,[343] can be used to show cortical activation sites and intensities. Using the parametric effect of the task as biomarker provides a potential discriminator of cognitive function in TBI patients.

Discussion

Despite the limitations of fNIRS,[351] fNIRS technology has some advantages over fMRI due to its portability, lower cost, and higher temporal resolution, which allows quick screening of subjects. Further, fNIRS is more tolerant of patient movement. Thus, the challenge for tests of fNIRS in the clinical setting is to provide a quick, quantitative measure of regional blood flow change produced by a standard paradigm, which recruits relevant areas within individuals, for comparison with a normative database.

Quantitative comparison of the locations and intensities of cortical activations detected with fMRI and fNIRS techniques agree and suggest value in comparison of individual topographical variation using fNIRS measurements as a discriminator for TBI. Based on initial results, fNIRS is capable of detecting a quantitative relationship between cognitive load and intensity of a blood flow change. More research is needed to validate the potential for fNIRS to distinguish cognitive functional impairment in TBI patients. This field is relatively new in comparison with fMRI and more research must be done before use of this technique can be recommended to assess the degree of TBI.

Summary

The ACR Appropriateness Criteria (clinical guidelines), the New Orleans Criteria, and Canadian CT Head Rule[127] serve as valuable references for clinical decision-making. Clinical policy from the ACEP and CDC upholds serial GCS assessment and head CT as the best tools in the acute setting and makes no recommendation for MRI.[58]

There is high-quality evidence that CT scanning is clinically valuable in the evaluation of patients presenting to the ED with moderate and severe TBI. In these patients, CT scanning is highly sensitive for identifying intracranial hemorrhages that may require neurosurgical interventions. High-quality evidence also exists that CT scanning is not useful for the prediction of functional recovery, even in moderate and severe TBI. In mTBI, moderate quality evidence suggests that CT scanning is of limited usefulness in the clinical evaluation of patients presenting to the ED. In clinical practice, cranial CT scanning is likely overused in the evaluation of mTBI.

MRI offers moderate clinical utility in both CT-negative and CT-positive TBI. However, MRI shows significant utility for research into the evaluation of TBI. Research arms should include clinical correlation with neuropsychological symptoms and outcomes in longitudinal studies of patients with (or at risk for) mTBI. In addition, validation of MRI observations correlated with pathology are essential both to confirm and understand the cellular processes of astrocytic and neuronal injury in TBI.[126,131]

TCD is an important tool for monitoring the natural course of TBI, for evaluating the effect of medical treatment or intervention, for forecasting, and for identifying high-risk patients after TBI. Despite a lack of good prospective data on TCD evaluation and outcome in TBI patients, TCD as a noninvasive, inexpensive, and simple procedure that should be engaged in the daily management of TBI patients.

Post-TBI tSAH and VSP continue to adversely affect a significant proportion of the TBI population and remain a challenge for all clinicians. At the present time, no proven treatment regimen aimed specifically at decreasing the potential detrimental effects of posttraumatic VSP exists. Therefore, vigilant diagnostic surveillance, including serial TCD studies and the prevention of secondary brain damage resulting from VSP and ICH, are critical.

TCD can noninvasively identify patients who are progressing to VSP. It is highly sensitive to abnormally high CBFs resulting from the onset of VSP. As VSP sometimes occurs earlier than natural history would suggest, daily TCD can be the least expensive option for identifying patients at risk for deterioration. In TBI patients being treated without invasive monitoring, TCD provides important information about ICP and cerebral hemodynamics. In patients undergoing invasive ICP monitoring, serial TCD examinations provide complementary information.

PET remains a powerful tool for clinical research in TBI. PET measurements of CBF, oxygen metabolism, and glucose metabolism have been used to study the pathophysiology and effect of treatment in acute TBI and the relationship between clinical deficits and brain abnormalities in chronic TBI. Several radiotracers are available to study other aspects of TBI pathophysiology, including neuroreceptor abnormalities and neuroinflammation. The clinical utility of PET in the management of individual patients with TBI, however, has not yet been demonstrated.

SPECT is another promising capability to evaluate mTBI. It has an advantage over anatomic imaging in assessing brain parenchymal activity and physiologic changes. The overall quality of evidence for the SPECT published research is moderate for detecting mild, moderate, and severe TBI when subjects present a neurological deficit upon examination. The quality of evidence for mTBI patients is strong for determining a positive prognosis in patients with normal SPECT perfusion imaging. SPECT can identify perfusion/blood deficits in mild, moderate, and severe TBI that anatomic imaging inaccurately identifies or misses altogether.

As more information is obtained about SPECT findings in this population and new promising radiopharmaceuticals are developed, SPECT will prove an important adjunct or primary diagnostic tool capable of quantifying and following mTBI patients, as well as providing useful prognostic information to better direct the care and management of these individuals.

Despite the limitations of fNIRS,[351] fNIRS technology in some circumstances has advantages over fMRI due to its portability, lower cost, and higher temporal resolution, which allows quick screening of the subjects. Further, fNIRS is more tolerant of patient movement. Initial results suggest fNIRS is capable of detecting a quantitative relationship between cognitive load and intensity of a blood flow change. More research is needed to validate the potential for fNIRS to distinguish cognitive functional impairment in TBI patients. This field is relatively new in comparison with fMRI, and more research must be done before use of this technique can be recommended to assess the degree of TBI.

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