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# Imaging Evidence and Recommendations for Traumatic Brain Injury: Advanced Neuro- and Neurovascular Imaging Techniques

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## ABSTRACT

**SUMMARY:** Neuroimaging plays a critical role in the evaluation of patients with traumatic brain injury, with NCCT as the first-line of imaging for patients with traumatic brain injury and MR imaging being recommended in specific settings. Advanced neuroimaging techniques, including MR imaging DTI, blood oxygen level–dependent fMRI, MR spectroscopy, perfusion imaging, PET/SPECT, and magnetoencephalography, are of particular interest in identifying further injury in patients with traumatic brain injury when conventional NCCT and MR imaging findings are normal, as well as for prognostication in patients with persistent symptoms. These advanced neuroimaging techniques are currently under investigation in an attempt to optimize them and substantiate their clinical relevance in individual patients. However, the data currently available confine their use to the research arena for group comparisons, and there remains insufficient evidence at the time of this writing to conclude that these advanced techniques can be used for routine clinical use at the individual patient level. TBI imaging is a rapidly evolving field, and a number of the recommendations presented will be updated in the future to reflect the advances in medical knowledge.

**ABBREVIATIONS:** BOLD = blood oxygen level–dependent; FA = fractional anisotropy; MD = mean diffusivity; MEG = magnetoencephalography; TBI = traumatic brain injury

**T**raumatic brain injury (TBI) is one of the most common neurologic disorders, currently affecting 1.7 million Americans each year.<sup>1,2</sup> The incidence of TBI, especially mild TBI, is underestimated<sup>3</sup> because patients frequently dismiss their symptoms and never present to the emergency department or they believe that the admission of symptoms may compromise their work situation (eg, athletes, military<sup>4</sup>). Although most patients (nearly 80%) with diagnosed TBI are treated and released from the emergency department,<sup>5</sup> the remaining 20% have more severe injuries

resulting in approximately 275,000 hospitalizations and 52,000 deaths each year. Furthermore, TBI contributes to one-third of all injury-related deaths in the United States. The economic cost of TBI was estimated at \$76.3 billion in 2010 (\$11.5 billion in direct medical costs and \$64.8 billion in indirect costs such as lost wages, lost productivity, and nonmedical expenditures).<sup>6</sup> Moreover, affected military veterans generate an annual cost of \$11,700 in medical treatment per patient compared with \$2,400 in TBI-free veterans.<sup>7</sup> Leading causes of TBI in the general population include falls, motor vehicle collisions, assaults, and sports-related injuries.

Advanced neuroimaging techniques, including MR imaging DTI, blood oxygen level–dependent (BOLD) fMRI, MR spectroscopy, perfusion imaging, PET/SPECT, and magnetoencephalography (MEG), are of particular interest in identifying further injury in patients with TBI when conventional NCCT and MR imaging findings are normal, as well as for prognostication in patients with persistent symptoms. Based on the National Institute for Health and Care Excellence (<http://www.nice.org.uk>), adapted from the Oxford Centre for Evidence-Based Medicine (<http://www.cebm.net>) Levels of Evidence (2001), we indicated the quality of publications for diagnostic tests and interventions by assigning stratified and preferential levels of evidence (Table 1) and classes of recommendations (Table 2). Overall, at the time of writing this article, there is insufficient evidence supporting the routine clinical use of advanced neuroimaging for diagnosis and/or prognostication at the individual patient level (class IIb recommendation).

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**Table 1: Levels of evidence for studies of the accuracy of diagnostic tests<sup>a</sup>**

| Levels of Evidence | Type of Evidence                                                                                                                                                              |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ia                 | Systematic review (with homogeneity) <sup>b</sup> of level-1 studies <sup>c</sup>                                                                                             |
| Ib                 | Level-1 studies <sup>c</sup>                                                                                                                                                  |
| II                 | Level-2 studies <sup>d</sup>                                                                                                                                                  |
|                    | Systematic reviews of level-2 studies                                                                                                                                         |
| III                | Level-3 studies <sup>e</sup>                                                                                                                                                  |
|                    | Systematic reviews of level-3 studies                                                                                                                                         |
| IV                 | Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research, or "first principles" |

<sup>a</sup> Adapted from The Oxford Centre for Evidence-Based Medicine Levels of Evidence (2001) and the Centre for Reviews and Dissemination Report Number 4 (2001). Copyright National Institute for Health and Care Excellence February 2004.

<sup>b</sup> Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

<sup>c</sup> Level-1 studies are studies:

- that use a blind comparison of the test with a validated reference standard.
- in a sample of patients that reflects the population to whom the test would apply.

<sup>d</sup> Level-2 studies are studies that have only 1 of the following:

- narrow population (the sample does not reflect the population to whom the test would apply).
- use a poor reference standard (defined as that where the "test" is included in the "reference," or where the "testing" affects the "reference").
- the comparison between the test and reference standard is not blind.
- case-control studies.

<sup>e</sup> Level-3 studies are studies that have at least 2 or 3 of the features listed above.

**Table 2: Classification of recommendations<sup>a</sup>**

|           |                                                                                                                                                     |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| Class I   | Conditions for which there is evidence for and/or general agreement that a procedure or treatment is beneficial, useful, and effective              |
| Class II  | Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment         |
| Class IIa | Weight of evidence/opinion is in favor of usefulness/efficacy                                                                                       |
| Class IIb | Usefulness/efficacy is less well-established                                                                                                        |
| Class III | Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful |

<sup>a</sup> From the American Heart Association Evidence-Based Scoring System.

To date, advanced neuroimaging techniques have been utilized primarily for research, by using a variety of statistical and numeric approaches to assess for differences between study groups. Validated diagnostic tools to interpret advanced neuroimaging techniques within a single patient do not presently exist. The main challenges for developing these tools include the following: 1) lack of large-scale, age-stratified normal data with available advanced neuroimaging techniques by using standardized protocols developed with consensus by clinical and research communities, 2) lack of clear patterns of injury that are predictive of clinical and neuropsychological deficits, and 3) poor definition of standard approaches to account for technical differences between clinical scanners that may introduce artifactual false-positives or -negatives into an assessment.

### **Advanced Diffusion Imaging Techniques, Including Diffusion Tensor Imaging**

Diffusion tensor imaging<sup>8</sup> is a well-established model using data derived from directionally encoded MR diffusion-weighted imaging, estimating the overall direction and degree of restriction of water diffusion. In DTI, each voxel has one or more pairs of parameters: a rate of diffusion and a preferred direction of diffusion,

described in terms of 3D space, for which that parameter is valid. There is a variety of ways that DTI can quantify the diffusion ellipsoid, the most common of which is to compute scalar metrics, comprising fractional anisotropy (FA) for measuring ellipsoid shape and mean diffusivity (MD) for measuring ellipsoid size. TBI-associated changes in DTI scalar metrics have been well-documented, FA in particular.<sup>9–14</sup> In addition to measuring a variety of DTI metrics, data processing and analysis techniques have been developed to utilize these data for visualizing abnormalities in gray matter and white matter tracts.<sup>15,16</sup>

With regard to white matter tracts, the diffusion tensor model is not capable of resolving multiple fiber orientations within a voxel, and improved diffusion models and analysis methods are actively being developed. High-angular-resolution diffusion imaging<sup>17</sup> acquisitions use significantly more diffusion directions compared with many DTI protocols (for instance, 32 or higher). Diffusion kurtosis imaging<sup>18</sup> uses a minimum of 3 b-values (instead of the typical 2 for DTI, eg, 0, 1000, 3000), providing additional metrics related to non-Gaussian (kurtosis) diffusion that can provide a more physiologic basis for white matter modeling<sup>19</sup> and for resolving fiber crossings.<sup>20</sup> Diffusion spectroscopy imaging<sup>21</sup> requires a very comprehensive sampling scheme, making it sensitive to intravoxel heterogeneities in diffusion directions caused by crossing fiber tracts and thus allows more accurate mapping of axonal trajectories than DTI-based approaches. Q-Ball imaging<sup>22</sup> attempts a similar granular mapping resolution by using a much smaller diffusion sampling scheme. Newer acquisition methods, such as multiband,<sup>23</sup> and continued improvement in clinical scanner gradient performance, achieving maximum gradient strengths as high as 80 mT/m, are being developed that allow for faster scan times, making advanced diffusion techniques easier to implement as part of routine clinical protocols.

As mentioned above, DTI cannot resolve crossing fibers, and FA normally decreases in regions of crossing fibers. Methods for resolving crossing fibers include the neurite orientation dispersion and density imaging model<sup>24</sup> (which derives a measurement of intracellular volume fraction, a potential replacement of fractional anisotropy that should be less confounded by crossing fibers), Q-ball imaging<sup>22</sup> (which assumes a Gaussian model), and constrained spheric deconvolution<sup>25</sup> (which creates a model based on the actual diffusion acquisition that is used to perform deconvolution and produces very sharp fiber-orientation distribution functions). Further studies, however, are required to determine whether one of these approaches has a clear advantage compared with the others. Improvements in data quality with higher order eddy current correction,<sup>26</sup> distortion correction, and high-order shimming beyond second order should further improve data fidelity and increase the reliability of subsequent data processing.

Evidence and Recommendations for Advanced Diffusion Imaging Techniques, including Diffusion Tensor Imaging. Most studies of TBI have reported decreases in FA and increases in MD, thought to be secondary to demyelination or disruption of tissue microstructural integrity.<sup>27–36</sup> Some studies have reported both trauma-related decreases and increases in FA, particularly in the subacute phase postinjury. New evidence is converging to suggest

a more complex pattern of trauma-related changes in the white matter. Indeed many studies are reporting that FA values increase in both acute and chronic phases of injury.<sup>12,37-41</sup> Variability in the data regarding the direction of TBI-related change for common DTI metrics may reflect heterogeneity within cohort studies, including variation in TBI severity, variability in spatial injury location, inconsistent imaging parameters, and marked differences between the time of injury and imaging.<sup>42</sup> It is important to note that alterations in DTI metrics including FA are not specific to TBI and have also been documented in a wide variety of CNS disorders, particularly those that affect white matter.<sup>43</sup> When these issues are considered altogether, they suggest a need for more studies to translate this advanced imaging method into a clinically useful and applicable tool for TBI.

Currently, there is evidence from group analyses that DTI can identify TBI-associated changes in the brain across a range of injury severity, from mild to severe TBI. Evidence also suggests that DTI has the sensitivity necessary to detect acute and chronic TBI-associated changes in the brain, some of which correlate with injury outcomes.<sup>44</sup> These data, however, are based primarily upon group analyses, and there is insufficient evidence at the time of writing this article that DTI can be used for routine clinical diagnosis and/or prognostication at the individual patient level.<sup>41,44,45</sup> Even though a few studies have reported *z* score methods for individual patient TBI evaluation, there remains insufficient evidence at the time of writing to suggest that these methods are valid, sensitive, and specific for routine clinical evaluation of TBI at the individual patient level (class IIb recommendation).

### **Functional MR Imaging**

Functional MR imaging relies on blood oxygen level-dependent imaging and the coupling between CBF/metabolism and neuronal activity.<sup>46-50</sup> As metabolic demand increases, there are local increases in CBF, as well as dynamic and related metabolic changes in glucose and oxygen metabolism.<sup>46-50</sup> Transient local increases in CBF and metabolism lead to changes in the ratio of oxygenated-to-deoxygenated hemoglobin, which, in turn, affects the MR imaging signal response.<sup>46-50</sup> BOLD imaging offers millimeter-scale spatial resolution but poor temporal resolution due to the relatively slow hemodynamic response associated with neuronal activity.

BOLD fMRI methods for investigating TBI have utilized task-based methods, particularly working memory paradigms. Task-based methods require participation of the research subject to identify activation of brain regions thought to drive or be associated with task performance. Task-free resting-state BOLD fMRI techniques have also been used, with the advantage of being able to evaluate distributed whole-brain networks without requiring overt behavioral output from subjects. These methods rely upon identification of fluctuations in low-frequency BOLD waveforms throughout the brain, which are thought to reflect underlying neural activity that occurs in the absence of active task performance. Functional connectivity between brain regions is operationally defined as a strong interregional correlation in these low-frequency BOLD waveforms, which is the basis for identifying functionally connected whole-brain networks comprising multi-

ple spatially distributed brain regions. A variety of techniques can be used to study distributed whole-brain networks, such as independent component analysis/seed-based methods. Network properties of the brain can be further characterized by using graph theoretic analysis to identify changes in network function, such as local and global efficiency, as well as small-worldness, among many other network connectivity metrics.

**Evidence and Recommendations for Functional MR Imaging.** fMRI methods demonstrate great potential for evaluating brain subsystems that may underlie TBI-associated behavioral and cognitive impairment, including the detection of whole-brain changes in functional connectivity across a variety of brain networks, as well as more focused task-specific changes in functional activity among targeted brain subregions. Only a few behavioral/cognitive domains have been evaluated with task-based studies, and only a few functional networks, primarily the default mode, have been evaluated with resting-state techniques, which limits the generalizability of these methods to the breadth of TBI-associated sequelae.<sup>41</sup> Important limitations have been raised regarding the use of BOLD fMRI techniques for accurately characterizing changes in patients with TBI because of the possibility that brain injury might uncouple CBF and neural activity.<sup>51</sup> Indeed, there is evidence that TBI is associated with reductions or increases in CBF that have been described during the acute stages of injury.<sup>51,52</sup>

There is insufficient evidence at the time of this writing that fMRI based on BOLD techniques can be used for routine clinical TBI diagnosis and/or prognostication at the individual patient level (class IIb recommendation).

### **MR Spectroscopy**

MR spectroscopy is governed by the same physical principles of magnetism as MR imaging. While MR imaging data are analyzed in the time domain to obtain T1 and T2 relaxation times and then processed to generate an anatomic image, MR spectroscopy data are converted to frequency domain information and processed to form a spectrum of the signal intensities of different brain metabolites according to their Larmor resonance frequencies.

MR spectroscopy can be performed utilizing single-voxel spectroscopy, or 2D or 3D multivoxel chemical shift techniques (MR spectroscopic imaging or chemical shift imaging). Single-voxel spectroscopy has a greater signal-to-noise ratio and is more robust, but only a single spectrum is obtained and the volume of interest placement is crucial. Chemical shift imaging limits sampling error by covering a much larger area, at the expense of a lower signal-to-noise ratio and longer scan times. The 2 most widely used MR spectroscopy techniques are point-resolved spectroscopy sequence and the stimulated echo acquisition mode. Commonly quantified brain metabolites with intermediate (TE = 144 ms) to long (TE = 280 ms) TEs are *N*-acetylaspartate (NAA) for neuronal integrity, creatine (Cr) for cellular energy/attenuation, choline (Cho) for membrane turnover, and lactate for anaerobic metabolism. At shorter TEs (TE = 35 ms), metabolites with shorter T2 relaxation times can be detected, such as glutamate/glutamine (Glx), which are excitatory amino acids released after brain injury,<sup>53</sup> and myo-inositol, thought to be a marker of astroglial proliferation.<sup>54</sup> Each brain metabolite resonates at a



specific frequency and is plotted at a known chemical shift (measured in parts per million) on a graphic spectrum. The area under each spectral peak corresponds to the metabolite concentration and can be reported as a ratio to Cr (such as NAA/Cr and Cho/Cr); Cr has been used as an internal standard since it was thought to remain relatively constant. It is now known that Cr may change in certain conditions<sup>55-57</sup> including TBI<sup>58</sup>; however, Cr-based ratios remain useful when comparing serial measurements or data between institutions. Methods for absolute metabolite quantitation are now used routinely, by using water as an internal reference or phantoms containing known metabolite concentrations.<sup>59-61</sup> When imaging children, normal age-matched controls must be used, since brain metabolites change with maturation and myelination, rapidly in the first year of life, and then continue more slowly through adolescence.<sup>62-66</sup>

**Evidence and Recommendations for MR Spectroscopy.** There is significant heterogeneity in the literature that is, in part, related to the inclusion of patients with variable TBI severity, spatial injury locations, differences between time of injury and imaging, and analysis with various MR spectroscopy techniques. There are currently no large prospective studies examining the sensitivity and specificity of MR spectroscopy in the setting of TBI. A few small studies in patients with moderate-to-severe TBI show promise in the utility of MR spectroscopy as prognostic for outcomes.<sup>67,68</sup>

In mild TBI, the most common finding is a widespread decrease in gray matter and white matter NAA.<sup>69-75</sup> However, disparity exists between studies in the quantification of Cho in TBI; some studies have found increased Cho in various regions in the brain parenchyma,<sup>70,73,76</sup> while others have reported the absence of statistical changes in Cho.<sup>58,74,75,77</sup> A few recent small longitudinal prospective controlled cohort studies have shown an initial decrease in NAA, and increase in Cr and Glx in the white matter, but decreased Glx in the gray matter. In all cases, NAA, Cr, and Glx returned to normal levels by the end of the study, suggesting recovery. However, in a recent pediatric study, initial NAA levels did not change following concussion.<sup>78</sup> A recent controlled cross-sectional prospective study that included patients in the early subacute, late subacute, and chronic stages of mild TBI revealed decreasing trends in thalamic NAA/Cr levels at the early subacute stage and decreases in Cho/Cr occurring in the thalamus and centrum semiovale in the late subacute stage. Positive correlations between early subacute Cr levels in the centrum semiovale and chronic cognitive performance on neuropsychiatric evaluation were noted. Although this provides some insights into brain biochemistry changes at a population level, the authors noted that the applicability of these findings to an individual subject still requires careful examination of data from a larger population.<sup>79</sup>

Studies of MR spectroscopy in chronic mild TBI have found decreases in NAA in the splenium of the corpus callosum,<sup>80</sup> centrum semiovale,<sup>54</sup> and frontal white matter.<sup>75</sup> Chemical shift imaging<sup>70,77,81</sup> and whole-brain NAA studies<sup>69</sup> have also demonstrated decreases in NAA in the white matter. Changes found in Cho, a marker for cellular proliferation or tissue damage, may reflect diffuse axonal injury.<sup>54,70</sup> In the acute phase of head injury, choline-containing metabolites may be released as a result of shear injury and damage to cell membranes and myelin.<sup>67</sup> In chronic brain injury, the mechanism for increased Cho is more

likely diffuse glial proliferation, corroborated by elevated myo-inositol that persists for months after injury.<sup>82</sup> More recent studies have shown changes in the energy marker Cr<sup>58,83</sup>; if Cr is affected by mild TBI, metabolite ratio measurements would not be accurate because it would be difficult to assess if changes were due to the metabolite of interest or in Cr itself.

A number of small prospective cross-sectional and case-control longitudinal cohort studies have associated MR spectroscopy metabolite levels with neuropsychological outcomes in the moderate-to-severe TBI population. Most (but not all) of these studies have demonstrated decreased absolute NAA and NAA/Cr ratios and decreased NAA to correlate with poor outcomes.<sup>54,67,84-86</sup> Decreased NAA/Cr ratios have been detected in the splenium of the corpus callosum and, to a lesser, extent in the lobar white matter.<sup>80</sup>

In pediatric patients with accidental and nonaccidental TBI, MR spectroscopy has shown potential for providing early prognostic information regarding clinical outcomes.<sup>62,87-94</sup> Reduced NAA has been correlated with impaired long-term neuropsychological function in children.<sup>89,90,92,94</sup> Elevated total Cho has also been described and may be related to diffuse axonal injury and/or repair.<sup>84,95</sup> Studies have shown that elevated lactate levels are more common following nonaccidental TBI<sup>62,87</sup> and are strongly correlated with poor outcomes. In children, myo-inositol has been shown to increase as a result of glial proliferation and has also been correlated with poor outcomes after TBI.<sup>82,96</sup>

Currently, there remains insufficient evidence at the time of writing to conclude that MR spectroscopy is sufficiently sensitive and specific for routine clinical use at the individual patient level (class IIb recommendation).

### **Magnetoencephalography**

In MEG, neuromagnetometers surround the head with hundreds of sensors connected to superconducting quantum interference devices that are cooled to 4° Kelvin with liquid helium. The output of each sensor is a waveform that reveals local magnetic fluctuations and how they change with time. These fluctuations are the result of synchronous postsynaptic intracellular electric currents produced by pyramidal neurons of the cerebral cortex that are accompanied by perpendicularly oriented magnetic fields.<sup>97,98</sup> Because the net current of pyramidal neuron depolarization is oriented toward the cortical surface, MEG is most sensitive for detecting signals arising from sulcal walls, which are directed perpendicular to the skull.<sup>98,99</sup> MEG has intrinsically high temporal resolution, limited only by the sampling frequency of the electronics,<sup>100</sup> which is an advantage over other functional neuroimaging methods, such as fMRI. However, MEG has inferior spatial resolution, largely because a single cortical source of signal can be detected by multiple adjacent scalp sensors. As such, data must be processed to translate sensor signal back to the source space.

**Evidence and Recommendations for Magnetoencephalography.** There is insufficient evidence at the time of writing that MEG can be used for routine clinical TBI diagnosis and/or prognostication at the individual patient level (class IIb recommendation). Indeed, only a few studies have used MEG to evaluate the effects of TBI<sup>101-104</sup>; therefore, more work is necessary to define the utility and capabilities of this imaging technique. Very few

medical centers have modern neuromagnetometers, and analysis of MEG data requires advanced expertise in signal processing, which limits its widespread implementation.

### **Perfusion Imaging**

Brain perfusion in patients with TBI has been imaged by using different techniques, including stable xenon-enhanced CT,<sup>105,106</sup> single-photon emission CT (SPECT),<sup>107-113</sup> PET,<sup>114,115</sup> perfusion CT<sup>116-120</sup> and perfusion-weighted MR imaging, including dynamic susceptibility contrast,<sup>121,122</sup> and arterial spin-labeling.<sup>123,124</sup> These brain perfusion imaging techniques each have different drawbacks. SPECT and dynamic susceptibility contrast only generate qualitative comparisons between the right and left hemispheres.<sup>125</sup> Stable xenon-enhanced CT, perfusion CT, and arterial spin-labeling are quantitatively accurate.<sup>126,127</sup>

Stable xenon-enhanced CT requires specialized and expensive equipment. A typical study is relatively long, approximately 10 minutes. Side effects, such as respiratory rate decrease, headaches, nausea and vomiting, as well as convulsions, are observed in 4.4% of patients. Consequently, stable xenon-enhanced CT is difficult to perform, especially in the emergency setting.<sup>128</sup>

Perfusion-weighted MR imaging is also difficult to obtain in the acute setting due to scanner availability and patient contraindications but is an attractive imaging technique for the subacute and chronic phases, especially because it can be combined with other MR imaging sequences sensitive to TBI lesions.

On the other hand, perfusion CT is more readily available in the emergency/acute setting.<sup>120</sup> It can be implemented in all hospital institutions equipped with CT units and injectors, which are usually available 24/7. It necessitates neither specialized technologists nor extra material, but only requires dedicated postprocessing software. It affords real-time postprocessing, with a complete set of parametric maps typically generated within 5 minutes of completing data acquisition.<sup>129,130</sup> Perfusion CT can easily be performed as a complement to conventional noncontrast CT (NCCT) of the head and CT angiography (CTA) of the cerebral vasculature and does not interfere with the contrast-enhanced thoracoabdominal CT survey performed in patients with severe TBI.<sup>116</sup> Patients with severe TBI typically undergo contrast-enhanced chest, abdomen, and pelvis CT routinely to evaluate for aortic injuries. The contrast material administration is performed even in obtunded patients unable to report about possible previous contrast reactions or without knowing about the renal function because the risk associated with these conditions is outweighed significantly by the risk of a missed traumatic aortic injury. The dose of contrast material added for the perfusion CT is minor compared with the dose used for the chest, abdomen, and pelvis.

In patients with severe TBI, perfusion imaging affords insight into regional brain perfusion alterations due to TBI, with the major advantage being detection of regional heterogeneity.<sup>116</sup> Perfusion imaging has a higher sensitivity for the diagnosis of cerebral contusions at baseline when compared with admission NCCT, with a sensitivity reaching 87.5% versus 39.6% for conventional NCCT.<sup>116,120,121</sup> Perfusion imaging can show changes related to the mass effect caused by an epidural or subdural hematoma and the resolution of these changes after hematoma evacuation.<sup>131</sup>

Perfusion imaging can also identify specific patterns, linked to cerebral edema and intracranial hypertension.<sup>117,118</sup> Finally, the number of arterial territories with “low” regional cerebral blood volume (CBV) values on perfusion imaging is an independent predictor of the functional outcome and is seen as early as on admission.<sup>116</sup> The potential repercussions of perfusion imaging on the clinical management of patients with severe TBI remain to be evaluated. However, patients with altered brain perfusion might be considered for more aggressive and early treatment to prevent intracranial hypertension, whereas patients with preserved brain perfusion might benefit from less invasive treatment.

In patients with mild TBI and normal conventional brain imaging findings, perfusion imaging studies have shown scattered perfusion deficits, which are significantly correlated with neuropsychological and neurocognitive impairment, as well as post-traumatic amnesia.<sup>109,110,112,119,122,132,133</sup>

**Evidence and Recommendations for Perfusion Imaging.** All the studies above have involved only limited numbers of patients, and further research is required to validate the findings described above and determine how relevant they are in the management of individual patients with TBI (class IIb recommendation).

### **PET and SPECT**

Most studies utilizing PET and SPECT to investigate TBI have focused on cerebral blood flow and metabolism and demonstrated TBI-associated decreases in cohort studies.<sup>134-138</sup> Recent literature reviews summarizing the possible utility of PET<sup>139</sup> and SPECT<sup>140</sup> in TBI, particularly mild TBI, have drawn this cohort data largely from cross-sectional designs with a smaller number of longitudinal studies also reviewed. Very few randomized controlled trials were discovered when examining the literature. Also, various levels of analytic rigor have been used to identify TBI-associated changes with these imaging methods, including quantitative and visual-based qualitative measures, which are known to have interrater variability. Additionally, very few PET and SPECT studies to date have gone beyond CBF and metabolic mapping to incorporate specific ligands for exploring TBI-related changes at the receptor level, which may open the door to a new generation of sensitive and specific molecular biomarkers of brain injury.<sup>141</sup> Recent PET amyloid imaging, however, suggests that amyloid levels rise in persons with TBI.<sup>142</sup> A small study with a combined amyloid tau ( $\tau$ ) tracer also showed higher levels in those with TBI.<sup>143</sup> The condition, sometimes referred to as “chronic traumatic encephalopathy,” is believed to be progressive tauopathy, seen most commonly in persons with repetitive concussive brain injuries, such as professional athletes and military personnel.<sup>144</sup> Beta ( $\beta$ ) amyloid deposition, while seen in 40%–45% of chronic traumatic encephalopathy, is not as common as  $\tau$  accumulation.<sup>145</sup> As TBI is a recognized risk factor for cognitive decline and dementia,<sup>146</sup> advanced neuroimaging will likely continue to provide key insights into this disease process and possible avenues for routine and personalized clinical use. At present, more work must be conducted to translate these powerful neuroimaging methods into useful, routine clinical tools at the individual subject level, for which there is insufficient evidence at the time of writing this article (class IIb recommendation).

## Summary

- 1) Advanced neuroimaging techniques, including MR imaging DTI, BOLD fMRI, MR spectroscopy, perfusion imaging, PET/SPECT, and MEG, are of particular interest for patients with mild TBI when conventional NCCT and MR imaging findings are negative. These advanced neuroimaging techniques have shown promising results in group comparison analyses.
- 2) At the time of writing, there is insufficient evidence supporting the routine clinical use of advanced neuroimaging for diagnosis and/or prognostication at the individual patient level (class IIb recommendation).

## Imaging of Neurovascular Trauma

Traumatic neurovascular injuries are a rare but known occurrence associated with certain types of blunt trauma to the face and head. They occur in approximately 0.1%–2% of patients with severe trauma, with carotid and vertebral arteries being equally affected.<sup>147,148</sup>

The natural history of these lesions is still being elucidated and optimal treatment plans formulated. A grading scheme, called the Denver grading scale, has been proposed by Biffi et al<sup>149</sup>:

Grade I: intimal irregularity with <25% narrowing

Grade II: dissection with intramural hematoma and >25% luminal narrowing

Grade III: pseudoaneurysm

Grade IV: occlusion

Grade V: transection with extravasation, as well as arteriovenous fistula.

Undetected, traumatic neurovascular injuries can cause ischemic stroke and are associated with high mortality rates. Implementation of the screening protocol can virtually eliminate injury-related strokes in patients without primary thromboembolic neurologic deficits.<sup>150</sup>

Several other injuries and injury patterns can be used to identify patients with a high likelihood of concurrent traumatic neurovascular injuries, and these patterns can be used as indications to screen for traumatic neurovascular injuries. Patients with blunt trauma with a high-velocity mechanism, low Glasgow Coma Scale score, high injury severity score, mandible fracture, complex skull fractures, basilar skull fractures (including carotid canal fractures), scalp degloving, any type of cervical spine injury, traumatic brain injury with thoracic injuries, and/or thoracic vascular imaging are at increased risk for blunt neurovascular injuries (evidence level II).<sup>148,151–154</sup> In patients identified as having these types of concurrent injuries, the overall rate of blunt neurovascular injuries increases up to 27%–30%.<sup>147</sup>

Although digital subtraction angiography is the diagnostic reference standard for detecting blunt neurovascular injuries, a number of retrospective studies and meta-analyses indicate that multidetector CT angiography is an accurate, rapid, noninvasive diagnostic alternative. CTA of the neck extended to include the circle of Willis has a sensitivity and specificity of 90%–100% for diagnosing vascular trauma in blunt vascular injury within the neck (evidence level II).<sup>155–159</sup> Based on the evidence available, CTA of the neck extended to include the circle of Willis should be the first-line investigation for all patients with suspected vascular

trauma and who have no indication for immediate operative intervention (class IIa recommendation).<sup>160</sup> CTA can be used to grade (in the acute setting) and follow-up (in the subacute and chronic settings) blunt neurovascular injuries, providing significant prognostic information and influencing management decisions.<sup>161</sup>

The application of duplex ultrasonography, MR imaging/angiography, and transesophageal echocardiography has been described, but these imaging modalities are usually more difficult to obtain in the acute setting in patients involved in severe trauma (evidence level III) due to availability of techniques and patient contraindications. For the same reason, 4-vessel DSA is only used in the acute setting in patients with inconclusive CTA interpretation or when an endovascular intervention is considered.<sup>150,160</sup>

The description above pertained to blunt neurovascular injuries but also applies to penetrating neck injury. A comprehensive physical examination, combined with CTA of the neck extended to include the circle of Willis, is adequate for triage to effectively identify or exclude vascular and aerodigestive injury after penetrating neck trauma (evidence level III), with endoscopy and angiography serving as second-line evaluation modalities (class IIa recommendation).<sup>162</sup> Traumatic neurovascular injuries are treated medically and, when needed, by endovascular approaches (coil embolization, stent placement), with a low rate of immediate and delayed neurovascular complications (evidence level II).<sup>163,164</sup>

## Summary

- 1) Traumatic neurovascular injuries should be suspected in patients with a high-velocity mechanism, low Glasgow Coma Scale score, high injury severity score, AND mandible fracture, complex skull fractures, basilar skull fractures (including carotid canal fractures), scalp degloving, any type of cervical spine injury, and/or TBI with thoracic injuries, and/or thoracic vascular imaging, as well as in patients with penetrating neck injury (class I recommendation).
- 2) CTA of the neck extended to include the circle of Willis should be the first-line investigation for all patients with suspected vascular trauma and who have no indication for immediate operative intervention (class IIa recommendation).
- 3) A relatively high proportion of traumatic neurovascular injuries are treated by endovascular approaches (coil embolization, stent placement), with a low rate of immediate and delayed neurovascular complications.

## CONCLUSIONS

A number of advanced neuroimaging techniques are currently under investigation in an attempt to optimize them and substantiate their clinical relevance in individual patients; however, the data currently available confine their use to the research arena for group comparisons. TBI imaging is a rapidly evolving field, and a number of the recommendations presented will be updated in the future to reflect the advances in medical knowledge.



## APPENDIX

### American College of Radiology Head Injury Institute

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