Traumatic Brain Injury

A Clinician's Guide to Diagnosis, Management, and Rehabilitation

Jack W. Tsao
Editor

Second Edition

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For Veronica, Emmanuel, Joan, Grace, Peter, Anna, and Mike

Preface

The first edition of *Traumatic Brain Injury: A Clinician's Guide to Diagnosis, Management, and Rehabilitation*, published in 2012, was written to enable medical professionals to quickly learn about the latest issues and treatments in this evolving clinical field. Since that time, there has been increased public awareness of the clinical consequences of even the mildest of head injuries, and the numerous advances in the areas of diagnosis, evaluation, treatment, and pathophysiology have resulted from a concerted effort of countries around the world to increase research funding.

This second edition continues to focus on mild traumatic brain injury—or concussion—and contains updates to all the original chapters as well as adds new chapters addressing clinical sequelae, including pediatric concussion, visual changes, chronic traumatic encephalopathy, and blast-related TBI, the latter two being areas of intense research efforts currently. The chapter authors were asked to focus on key issues of which practicing clinicians should be aware in order to provide the best care to their patients. An updated appendix of ICD codes is included.

I would like to thank my family for their support in the writing and editing process; my colleagues who generously contributed their time to updating or writing new chapters; Richard Lansing, the publishing editor who encouraged me to edit this second edition; and Elizabeth Corra, the development editor who helped guide this edition to its completion. Finally, as many of the authors of this edition continue to serve as US military officers or government employees, I am including the disclaimer here: The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Departments of the Navy or Army, the Department of Defense, or the Department of Veterans Affairs.

Memphis, TN, USA — Jack W. Tsao

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Overview of Traumatic Brain Injury (TBI)

David F. Moore, Michael Jaffee, Geoffrey Ling, and Raul Radovitzky

Historical Perspective

Accounts of neurological trauma are present in the *Iliad* and *Odyssey* of Homer from Greek antiquity where concepts consistent with interpretation loss of consciousness, penetrating brain injury, spinal cord injury, brachial plexus, and nerve injury are present. These injury concepts of the nervous system are well summarized with direct translation from ancient Greek in two review articles by Walshe [1] and Sablas [2]. One important aspect of these oral tradition epics to the ancient Greeks may have been to preserve warrior knowledge about injury vulnerability, allowing more formalized military training. It is clear that even in antiquity, traumatic brain injury (TBI) was described both in the military and civilian context.

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The historical account of concussion is well summarized and described by the paper by McCrory and Berkovic [3]. Initial use of the term "concussion," in the modern sense of an alteration or temporary loss of adaptive brain function or an abnormal brain physiological state, as opposed to distinct brain injury, was used by the medieval Persian physician Rhazes (Muhammad ibn Zakariyā Rāzī**,** 826–925 AD). Subsequent to this and with Chauliac (1300–1368 AD), the concept of a brain concussion or "commotio cerebri" with a relatively benign outcome from "contusio cerebri" or brain injury, such as a skull fracture with a poor outcome, became accepted in Western medicine with some variation. In more recent discussion the consideration of a structural versus a functional cause of concussion has been considered in light of modern medical advances and technologies but still contains significant indeterminacies depending on the length scale of the approach. For example, in acute concussion neuroimaging is typically negative, yet with more extended techniques, such as diffusion tensor imaging and susceptibility weighted imaging, previously unrecognized lesions are becoming increasingly appreciated indicating sustainment of structural abnormalities. The conception of the length scale of injury is fundamental to the subsequent discussion of TBI, since, at a molecular level, membrane disruption may result in alteration in membrane chan-

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nel physiology or mechanoporation with resultant abnormal ionic fluxes and altered cellular and axonal function. Distinct examples of pathological sensitivity to brain trauma are present in abnormalities of calcium channel subunit *CACNA1A* and CACH (Childhood Ataxia and CNS Hypomyelination) [4, 5].

Complexity of Intracranial Anatomy

The brain is a uniquely anisotropic organ with the gyrencephalic cortical gray matter, broadly orthogonal white matter fascicles, and subcortical gray matter nuclei together with multiple solid fluid interfaces between the brain parenchyma and the cerebrospinal fluid (CSF) both internally as represented by the ventricles and externally by the subarachnoid space. The entire brain is tethered by the dura together with the bridging veins and other vascular structures surrounded by the CSF fluid cushion of the subarachnoid space. The skull represents a further protective layer of similar complexity with the diploic bone structure and numerous air sinus cavities together with foramina for exiting and entrance of various neurovascular bundles. The complexity of the intracranial contents is well illustrated in Fig. 1, an axial section of the brain from the Visible Human Project [6].

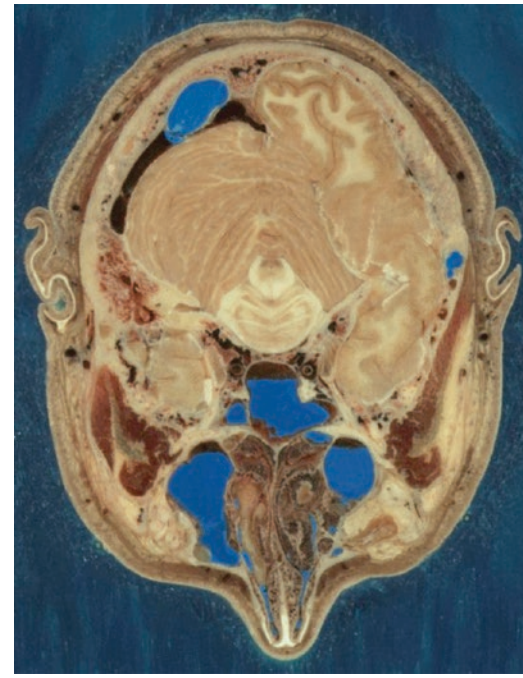

Fig. 1 Illustrating the intracranial contents illustrating the diploic nature of the skull bone and the numerous air sinus spaces together with the venous sinuses and dural sheathing. The gyrencephalic quality of the cortical ribbon is well seen in the occipital–temporal region. The complexity of brain anatomy has significant implications for the transmission of mechanical forces that may injure brain tissue. In particular this is seen in the military context across impact to penetrating to blast brain injury. (Source: Visible Human Project. http://www.nlm.nih.gov/research/visible/visible_human.html. Public Domain)

Definition of Traumatic Head Injury

The current definition of TBI is phenomenological. Often there is confusion in the nosology of TBI especially in relation to mild TBI (mTBI), a term that implicitly refers to the TBI event consistent with acute concussion. TBI is categorized according to the clinical pillars of post-traumatic amnesia (PTA) and/or a disturbance of consciousness – either alteration of consciousness (AOC) or loss of consciousness (LOC). These clinical features, although correlated, allow for independent diagnosis of TBI severity. The overall TBI diagnosis is due to the severity of *Primary Traumatic Brain Damage* – that is, brain injury that results from mechanical forces producing tissue deformation at the moment of injury with direct damage to blood vessels, axons, neurons, and glia. The Glasgow Coma Scale (GCS) is also used as a TBI severity and diagnostic scale with mTBI having a GCS range of 13–15, moderate TBI a GCS range of 9–12, and severe TBI a GCS of 3–8. *Secondary Traumatic Brain Damage* on the other hand, is

Table 1 Ascertainment of TBI according to the accepted severity scales. Definitions of TBI spectrum

GCS	LOC	PTA	TBI
13–15	<1 h	<24 h	Mild or mTBI
9–12	>1 h and < 24 h	>24 h and < 7 days	Moderate
3–8	>24 h	>7 days	Severe

by definition, due to the complications of primary damage, including brain tissue hypoxia, ischemia, hydrocephalus, raised intracranial pressure (ICP), and central nervous system (CNS) infection. The TBI spectrum definitions are summarized in Table 1. TBI is dichotomized into penetrating (pTBI) and closed TBI (cTBI), with the sub-classification of cTBI into mild, moderate, and severe TBI. Although there is variation between epidemiological studies and it is a truism that all epidemiological studies are in some degree biased due to a trade-off between the veracity of ascertainment and the extent of the population sampled, rough categorization suggests ~ 17% of cTBI being severe with ~ 13% being moderate and ~ 70% being mTBI.

The above classification of TBI is inherently clinical and dependent on either direct observation or self-report. The current clinical trend is to attempt to redefine categorization of TBI in a patho-anatomic framework [7]. This is motivated, in part, by the recurrent failure of randomized clinical trials (RCTs) in TBI, including the initial promising results of progesterone in moderate TBI but also by a drive for standardization with the development of common data elements (CDE) to facilitate ongoing and new RCTs [8–11]. CDEs will also be particularly important in cross-sectional and longitudinal epidemiology studies, allowing for "core" datasets to be acquired in studies with undoubted comparative value between study populations. A key epidemiological fact concerning TBI is that ~ 1.7 million civilian TBIs occur annually in the United States with a cost estimated at 60 billion dollars both in direct medical costs and in indirect costs due to lost productivity to society [12, 13].

TBI Spectrum: Neuropathology and Acute, Subacute, and Chronic Effects

In primary TBI the spectrum of injury may range from diffuse or multifocal, resulting in diffuse axonal injury (DAI) and diffuse vascular injury (DVI), to focal, with intracerebral hemorrhage, subdural hemorrhage, epidural hemorrhage, and subarachnoid hemorrhage [14]. Other injuries include direct axonal injury, direct brain laceration, and contusion. Injuries from secondary TBI may also be diffuse, such as diffuse hypoxic-ischemic damage, and diffuse brain swelling, or focal, with focal hypoxic ischemic injury and focal brain swelling. Acute moderate and severe TBI may often require neurosurgical intervention, while mTBI or concussion typically requires limited observation and intervention, with recuperation occurring over several days to weeks. The prolonged sequelae of TBIs are an opportunity for extensive rehabilitation care and therapeutic intervention. Of particular interest is the potential for metabolic abnormalities after concussion that, if not adequately resolved, may predispose the brain to more extensive damage if a further concussion occurs during the period of vulnerability, the second impact syndrome [15, 16] (Fig. 2a–h).

Concussion Biology and Mechanism

The neurobiology of concussion is incompletely understood, and this has resulted in several theories, ranging from interference to the reticular activating system to interference with the cholinergic reticular inhibitory system to a paroxysmal depolarization shift resulting in "kindling" and a potential convulsive episode resulting in concussion (Walker's Convulsive Theory) [15, 17]. From clinical neurology it is a clinical maxim that an alteration in consciousness results from either a bi-hemispheric process or a process in the posterior fossa. In relation to AOC and LOC, it is probable that most concussive processes result from a bilateral process suggesting more of a convulsive process secondary to a paroxysmal depolarization shift, although this cannot be stated with certainty. Similar reasoning is applicable to PTA with a resulting failure to lay down memory engrams bilaterally – the memory consolidation hypothesis.

The mechanical events precipitating concussion have been the subject of debate since the 1940s. In a short abstract by Derek Denny-Brown

and Russell Ritchie from 1940 [18], nembutal-anaesthetized cats were subjected to a concussive blow with the requirement that the head was able to undergo acceleration with associated translation and rotational effects. The blow was able to induce death without any rise in ICP and failed to result in concussion if the head was restrained and did not undergo acceleration. The cause of death appeared to be respiratory depression, but all brainstem reflexes were depressed, with the brainstem respiratory centers being the most sensitive. Denny-Brown commented that "momentary deformity of the skull and stimulation of superficial structures, therefore, appear to play no part" and finishes with "the nervous effect of a blow is, thus, considered to be due to the physical acceleration directly transmitted to each and every centre" [18]. A threshold of 23'/sec was found for the cat with a higher value for the Macaque monkey. Subsequent to this, Holbourn, in 1943, suggested that, due to the incompressible nature of the brain, linear acceleration would be unable to result in brain tissue injury; however, angular acceleration would result in shear strain and subsequent brain injury [19]. This was countered by Gurdjian and Lissner in 1944 [20] who suggested that concussion resulted from the pressure differential and the induced shearing strain on the brainstem with little reference to rotational injury.

More advanced interpretations of TBI using Newton-Euler equations describing combined translational and rotational dynamics indicate that movement may occur in all six degrees of freedom where the coordinate frame does not correspond to center of mass of the rigid body. The equations clearly indicate that the translational and angular accelerations are coupled, resulting in both force and torque components on the brain. The exact components of torque

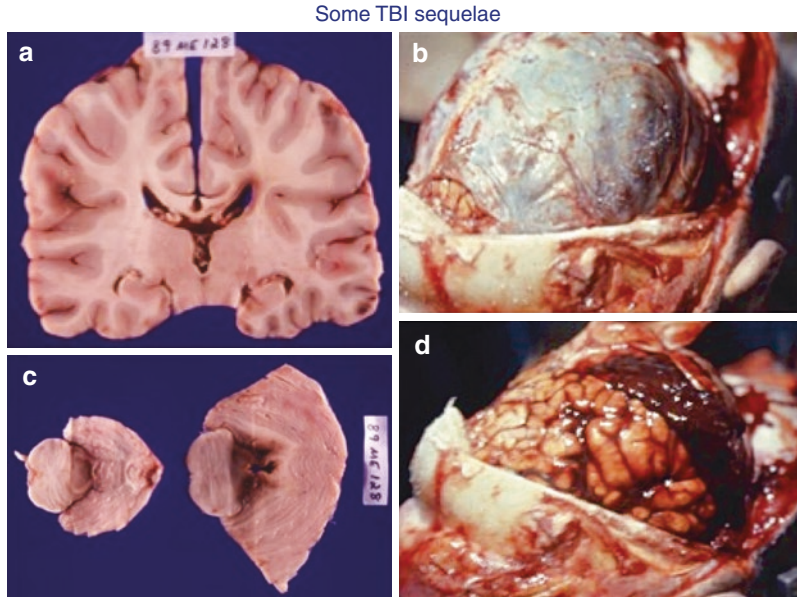

Fig. 2 Illustration of the neuropathology of TBI. (**a**, **c**): illustrate the gross neuropathology of diffuse axonal injury with white matter hemorrhage in the corpus callosum (**a**) and in the pontine white matter (**c**). (**b**, **d**): illustrate a subdural hematoma with (**b**) showing the dura intact and (**d**) the underlying hematoma with the dura reflected. (**e**): demonstrates cerebral contusion with bifrontal and bitemporal contusions. (**f**): left side of image shows a coronal section with edematous and swollen brain compared to normal brain tissue on the right side. (**g**): swollen optic nerve head in sagittal section due to chronically raised ICP. (**h**): delayed apoptosis of neuronal cells following TBI

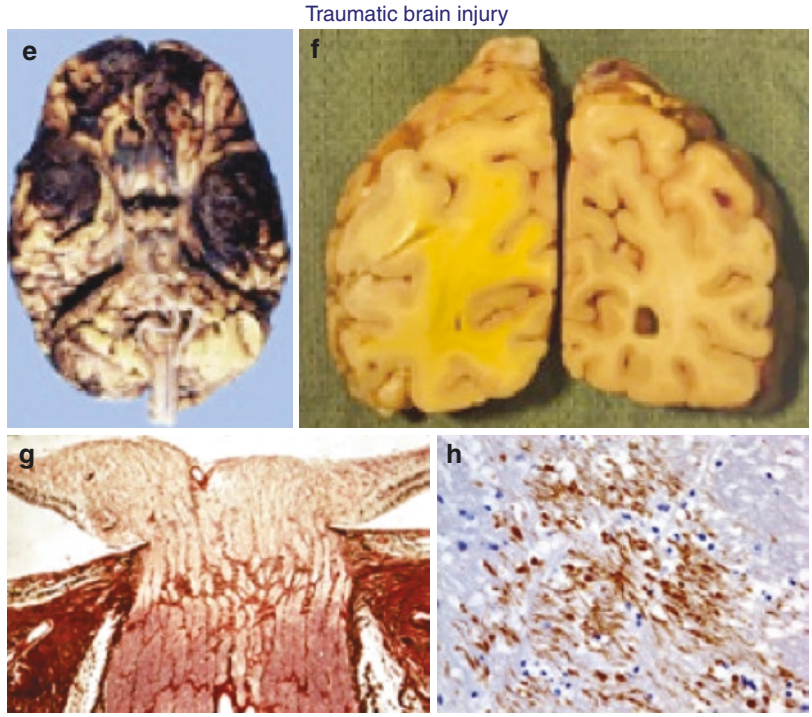

Fig. 2 (continued)

and force will depend on the site and directionality of skull impact together with the duration of the mechanical jolt [21]. The mobility of the skull on the neck also probably contributes considerably to the variation in the forces and, thereby, acceleration components experienced by the brain.

Constitutive Properties

The constitutive property of a material or tissue is the equation and parameter relationship specific for the tissue between the applied stress field (σ) and strain deformation (ε). Typically, this may have a higher-order tensor representation and involve varying elements of elasticity and viscosity. The unique nature of the brain compared to more typical engineering material is that it is a soft material, and further, it is biphasic in that it consists of a water-like component with an embedded matrix resulting in a poro-elastic tissue. Poro-elastic materials have different properties from more conventional materials especially in terms of wave propagation, where poro-elastic mediums support both dilational and transverse waves but also includes a further dilational wave that is of lower propagation velocity and termed by Biot as a dilational wave of the second kind [22, 23]. This consideration and analysis was derived from propagation of elastic waves, with the direction of propagation of the wave being longitudinal as opposed to rotational, or transverse, where the direction of wave motion is normal to the direction of propagation, resulting in a shear wave within the tissue. It is not at all obvious how a pore-elastic medium interacts with blast or shock wave propagation through a tissue. In Fig. 3 a lumped isotropic model of brain tissue is presented with varying mechanical elements that account for tissue visco-elasticity, shear thickening, pore elasticity, and nonlinear tissue relaxation to stress. The brain is highly anisotro-

pic with the potential for material properties to alter in a directional and regional manner so that the constitutive property of white matter is likely to differ from gray matter. The correct characterization of the material and constitutive properties of tissue is an essential prerequisite to the accurate validation of complex finite element models used to enhance understanding of mechanical and blast-related TBI.

Woodpecker Analogy

The woodpecker is a particular instructive "experiment of nature" in relation to concussion. It is a possibility that further understanding of the biological and physical characterization of the woodpecker in relation to head impact may define those biological features that are adaptive and protective against concussion (Fig. 4). In a paper by Oda and colleagues [24], the authors use finite element models (FEM) of the woodpecker skull and examined the properties of the woodpecker that resulted in concussive stress wave dissipation. The analysis found that the unique shape of the head and neck tended to channel the stress wave away from the skull into the neck while the brain is tightly tethered by the dura and the small cerebrospinal fluid space (CSF). Further an adaptive hyoid bone anatomy together with the cancellous nature of the skull bone results in further stress dissipation from the concussion wave due to woodpecker head impact [24].

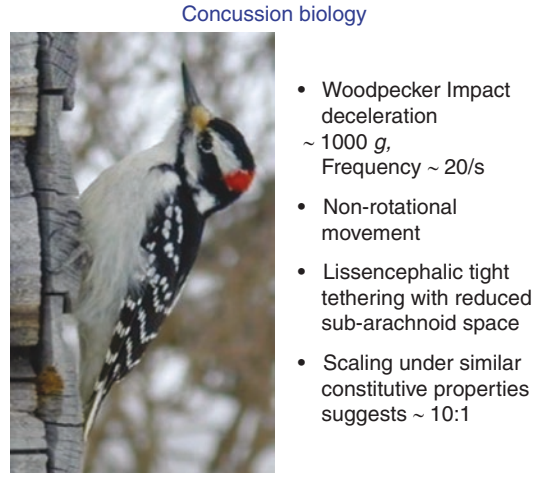

Fig. 4 Concussion biology. The woodpecker species is uniquely adapted to high impact loading on the beak and head with unique biological adaptations to prevent concussion

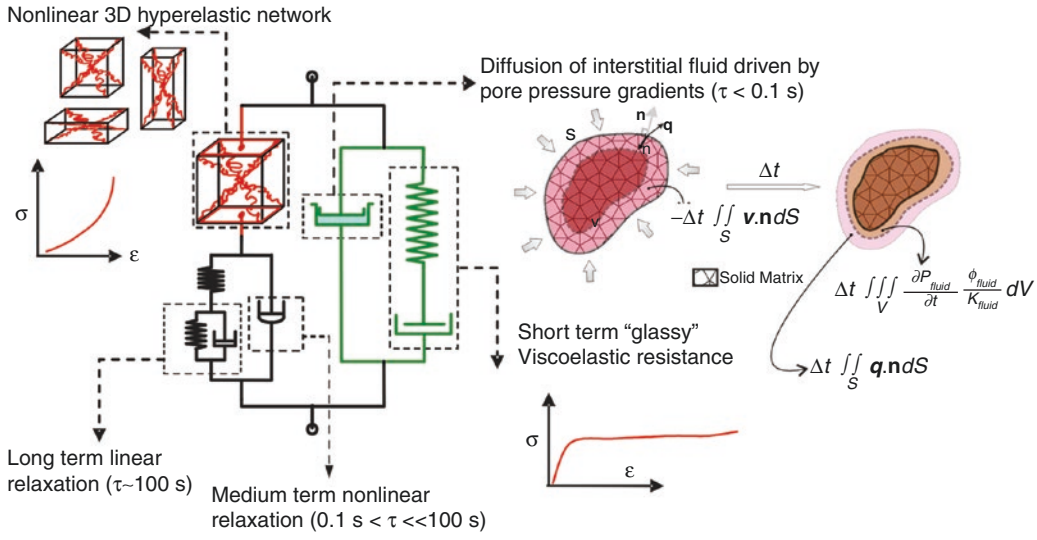

Fig. 3 Constitutive model of brain tissue illustrating visco-elasticity, shear thickening to increasing strain rate, tissue pore elasticity, and nonlinear relaxation effects to mechanical stress. (Courtesy of Dr. Simona Socrate, MIT, and The Institute of Soldier Nanotechnology)

The ability of the woodpecker to sustain repeated concussive impact without biological effect is of significance and bears further study. The potential to inform preventive strategies to minimize concussion should not be underestimated. For example, consideration of head and neck posture during an impending concussion with increased neck rigidity may prevent extensive rotational acceleration and the incipient development of concussion. Recent preliminary data suggest that this biological adaptation may not be so complete. As noted by McKee et al. [25], the accumulation of tau protein appears to be correlated with repeated concussion, resulting in the "end-stage" brain disease now termed chronic traumatic encephalopathy or CTE. Following from this, preliminary data from Farah and colleagues [26] examined a small series of woodpecker brains against control avian species with no such ecological niche and found histological evidence of tau deposition in the woodpecker as opposed to avian controls. Such preliminary data are of substantial interest but needs to be isolated with longitudinal prospective comparisons of a "wild woodpecker" cohort exposed to "natural" concussion compared within species to an atraumatic non-concussed woodpecker cohort in order to establish biological relevance.

Persistent Post-concussive Symptoms

A number of patients after a concussion fail to resolve clinically but develop persistent post-concussive symptoms [27]. This constellation of symptoms usually involves headaches, imbalance or postural disequilibrium and memory difficulties that persist for several months from the concussive event (*International Classification of Diseases, 10th Revision, Criteria for Postconcussion Syndrome (Code 310–2)*. The symptoms are often refractory to treatment but generally abate over months to years [28]. Up to about 15% of patients can be affected in civilian injury and concussion, but these statistics are study and population dependent. Using an Illness Perception Model, Whittaker and colleagues [29] were able to predict persistence of post-concussive symptoms in 80% of diagnosed patients in their population. The work suggests that patients may incorrectly attribute commonly prevalent symptoms to the concussive injury and become more at risk for development of persistent post-concussive symptoms [29]. In a follow-on editorial, Wood comments on the efficacy of cognitive-behavioral therapeutic approaches in persistent post-concussive symptoms using brief early interventions [30]. Such studies may point to efficient mechanisms of preventing this important comorbidity of concussion in the civilian head injury population; however, the possibility of true structural and organic changes must be considered especially due to the known plasticity of the CNS [31].

Strain-Rate Continuum of TBI

Stress is the force per unit area within the tissue, with the resulting strain deformation field depending on the applied stress and the constitutive properties of the tissue. These measurements are often performed in a quasi-static fashion where this may allow reversible mechanical changes in the tissue during application of the stress fields both in compression or tension. For TBI, traumatic events occur in a variety of ways such as during motor vehicle crashes or following penetrating head injury from a bullet wound or blast-associated traumatic head injury. The rate at which stress is applied to the head or brain differs under these differing conditions but is related to the strain rate, with vehicular head injury occurring at a strain rate $< 500\ s^{-1}$, while penetrating injury occurs at a strain rate $\sim 2000\ s^{-1}$. With blast-associated head injury, the rate of strain can be in the range of ~ 2000 to $10{,}000\ s^{-1}$. It is, therefore, possible to consider TBI from these diverse etiologies across a strain-rate continuum with the constitutive tissue properties often responding in a strain-rate-dependent manner [32]. This is particularly important where the requirement

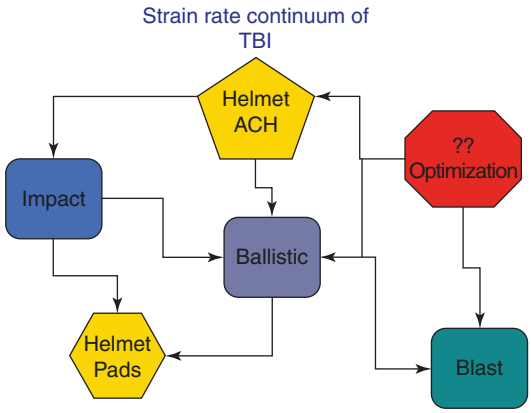

Fig. 5 Strain-rate continuum for traumatic brain injury where the optimization of PPE against impact injury may be enhanced by optimization of helmet pads placed between the helmet shell and the head. The ballistic protection is provided by the material composition of the helmet shell, while mitigation of blast injury may require further head and facial coverage by appropriate protective materials. The simultaneous optimization and characterization of these diverse material properties capable of preventing head injury across the strain-rate domain is formidable

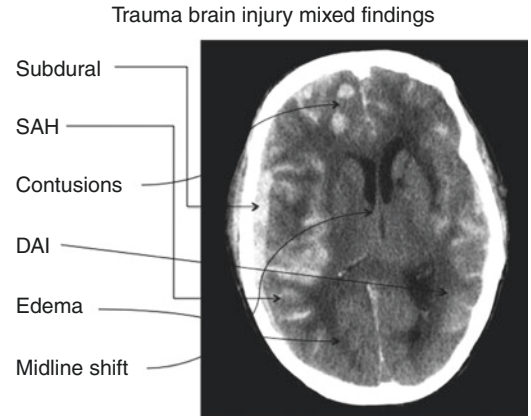

Fig. 6 Computed tomography (CT) axial image illustrating multiple simultaneous pathologies of subdural hematoma, subarachnoid hemorrhage, cerebral contusions, diffuse axonal injury, cerebral edema, and herniation syndromes with midline shift. (CT image courtesy of Dr. James Smirniotopoulos, Radiology, USUHS, and Dr. Gerard Riedy, Radiology, WRAMC)

is to design helmets for prevention of head injury and to obtain full characterization of possible tissue injury parameters. For personal protective equipment (PPE), such as the advanced combat helmet (ACH), it is an exceptionally difficult engineering optimization problem to account for mitigation across all the strain-rate domains. This is illustrated in Fig. 5.

Neuroimaging of TBI

In recent years, the rapid advances of neuroimaging of both structure and function have allowed extensive clinical characterization of TBI both for immediate patient clinical care and for clinical investigation and research purposes. It is now possible to understand various subcategories of TBI, such as DAI with more investigative techniques, including diffusion tensor imaging (DTI) with imaging metrics of fractional anisotropy (FA), mean diffusivity (MD), and radial and axial diffusivity [31, 33–45]. The DTI studies performed, in general, indicated reduction in FA with increases in isotropic DTI metrics such as MD. Injury severity is less in concussion or mTBI, with some resolution appearing to occur across time, although there are currently only a limited number of longitudinal DTI studies in TBI [46]. It can be anticipated that greater use of positron emission tomography and single-photon emission tomography together with functional magnetic resonance imaging will more fully explore the aggregate metabolic, neurochemical, and functional neuronal changes in both resting connectivity and task-related connectivity in TBI. A particularly significant area where noninvasive neuroimaging is likely to contribute to substantial clinical insights is in disorders of consciousness, including in persistent vegetative states and emerging levels of consciousness from the minimal conscious state through to normal conscious cognitive states. The complexity of TBI as highlighted is well illustrated in Fig. 6, where multiple pathological processes are seen that simultaneously play in a single patient.

Military Medicine Perspective on Brain Injury

The effect of blast in relation to TBI has been well described since World War I with shell shock and concussion, particularly in the clini-

cal descriptions of Gordon Holmes (1876–1965) [47]. The contingency operations in Iraq (Operation Iraqi Freedom, OIF) and Afghanistan (Operation Enduring Freedom, OEF) have led to a resurgence of research on the effects of blast and blast-associated polytrauma, probably due to the asymmetrical nature of the conflicts and the extensive use of improvised explosive devices (IEDs). Part of the spectrum of blast-associated polytrauma includes the full range of TBI and, in particular, blast-associated concussion or mTBI. Current estimate for blast-associated TBI is ~ 130,000, with US military service members since 2003 with ~ 4.5% of service members having persistent post-concussional symptoms (http://www.dvbic.org/TBI-Numbers.aspx), Blast may be defined as an "in the atmosphere" explosion characterized by the release of energy in a short period of time and within a small volume resulting in the creation of a nonlinear shock and pressure wave of finite amplitude, spreading from the source of the explosion [48]. The energy conversion from a conventional blast can be chemical, electrical, thermal, and kinetic or pressure energy (Fig. 7). The kinetic energy of the blast is associated with fragments and results in their expulsion in advance of the shock wavefront.

The "ideal case" of a blast pressure wave is the Friedlander waveform with a rapid rise time

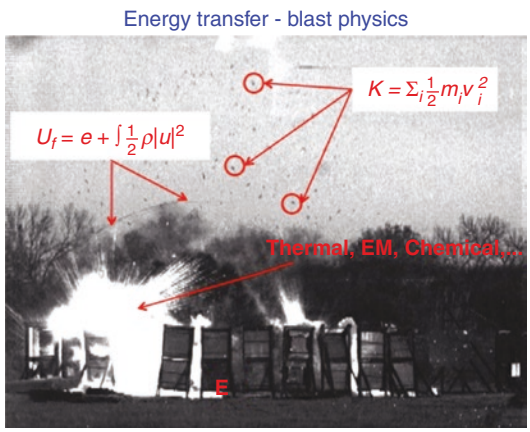

Fig. 7 Energy conversion (E) associated with a blast wave illustrating the shock wavefront together with fragment kinetic energy. Other energy components are the blast-associated electromagnetic (EM) pulse, thermal energy, and chemical conversion

to the peak positive pressure above atmospheric pressure, with the overpressure followed by an exponential pressure fall-off together with a relatively prolonged sub-atmospheric underpressure. Typically, the timescale of the total explosive pressure event is tens of milliseconds. The prolonged underpressure component of the pressure waveform may exceed the critical tensile strength of the fluid component of a tissue, thus allowing the development of cavitation.

Blast injury is defined as *primary* where injury is related to the shock wave overpressure and underpressure propagation through the tissue. *Secondary* blast injury occurs from blast-associated fragments or shrapnel tissue injury. *Tertiary* injury is secondary to falling debris or throwing of the dismounted soldier or vehicle with subsequent tissue injury. *Quaternary* injury develops from a variety of physical processes associated with explosive detonation, such as thermal and/or toxic detonation products, while *quinary* injuries refer to the environmental hazard remaining after an explosive detonation [49–52].

The effects of primary blast on the CNS are still unclear, but in military concussion it is unusual to be exposed solely to primary blast; rather such exposure is associated most commonly with tertiary blast injury [53]. For this reason blast-associated CNS injury is better considered as a constellation of blast component exposures resulting in a blast(+) syndrome of CNS injury. This results in the brain being exposed to mechanical events across the strain-rate continuum as previously discussed. The relationship of particular aspects of the blast wave exposure (that may be very complex due to reflection and augmentation) to clinical CNS injury is also unclear, but ongoing efforts are well developed to computationally model all aspects of blast-associated phenomenon in virtual test facilities with bio-fidelic head models [54]. This approach has been extended with evaluation of personal protective equipment and the interaction with blast waves [55]. In particular, the virtual test environment allowed the development of an animal-to-human scaling law for blast-induced TBI assessment. This work was performed using experimentally validated blast

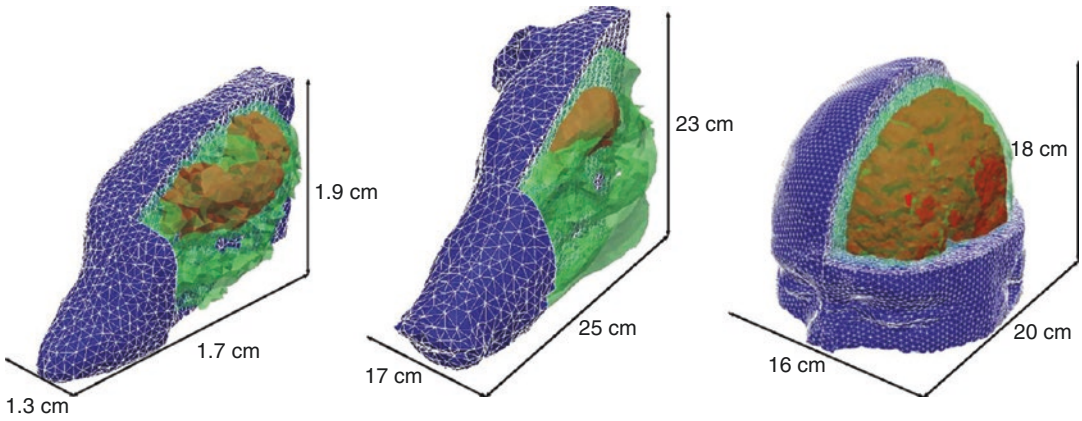

Fig. 8 Image-based finite element models of the head of mouse, pig, and human (not to scale) used in simulations, depicting the relevant tissue structures: skull (green), brain (red), and flesh (blue). (Source: Jeana et al. [56]. Open Access)

code and bio-fidelic models of the mouse, pig, and human skulls and intracranial tissue allowing development of a direct interspecies scaling law for blast exposure (Fig. 8). Human vulnerability to blast exposure was found to exceed that of other species, probably related to the relative mass of soft and bony tissue in other species compared to man [56]. One clinical aspect that has been noted in relation to blast-associated CNS injury is the increase in traumatic cerebral vasospasm, particularly in the setting of penetrating head injury [57].

The peak overpressure is most simply dependent on the distance from the blast source but approximately scales according to the standoff distance divided by the cube root of the explosive weight (Hopkinson Rule). The coupling of the nonlinear blast wave into biological tissue results in increased energy transmission at high strain rates in fractions of microseconds. The biological effect will depend on the constitutive tissue properties together with the largely unknown high strain rate of tissue material properties for brain. Ongoing research is establishing brain material properties across the strain-rate domain from low strain rates seen in impact injury to intermediate and higher strain rates seen in ballistic and blast injury. The above concepts lead to a frame of reference debate in relation to blast-induced military concussion or mTBI where it should be possible to rapidly approximate the potential exposure from any particular event to first-order accuracy.

Explosive detonation results in the formation of a detonation wave of altering chemical composition with the rapid formation of a propagated, nonlinear shockwave representing a large discontinuous increase in pressure, temperature, and density in the gas flow. The propagation of the shockwave develops a 3D complex fluid flow field that is altered by ambient conditions and environmental boundaries. This may result in multiple wave reflections and, potentially, pressure field intensification up to eightfold.

The blast waveform can be regarded as a combination of compressive and tensile components that impose a stress on the tissue in a manner that is dependent on the strain rate together with the constitutive properties of the tissue. This – combined with the potential for CNS injury from ballistic fragment acceleration-deceleration impact injury as well as chemical, thermal, and electromagnetic radiation – results in a highly complex problem where dominating effects become very difficult to parse in terms of their biological effects on the CNS.

Overlap of Wartime TBI and Acute Stress Disorders

The effect of military concussion and the development of persistent post-concussion symptoms together with other comorbidities, such as post-traumatic stress disorder (PTSD) (Fig. 9) and

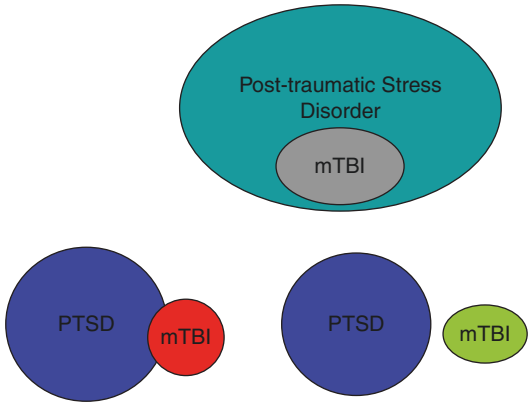

Fig. 9 Overlap of military concussion models and PTSD. The Venn diagrams represent various disease models of military mTBI and PTSD where military mTBI/concussion is regarded as a subset of PTSD to where the two disorders are regarded as independent (separated circles). Clinical perceptions suggest that the two disorder overlap to a greater and lesser degree within any clinical evaluation

depression, is an area of active research [58, 59]. Current studies are cross-sectional in design and may not have accounted accurately for statistical use of structural equation type of models. Further preliminary data from DTI suggest differences in blast(+)-exposed service members compared to non-blast-exposed service members in relation to such metrics as the FA, MD, and radial diffusivity.

Conclusions

TBI has been reported for centuries. Even until recently the serious nature of head injuries was minimized. For a long time, it was believed that woodpeckers could not develop tau pathology as seen in CTE. This has now been shown to be untrue. Blast-associated injuries and symptoms are only manifesting when there are distinct cognitive and functional difficulties, yet these may eventually be proven to be equally detrimental.

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Neuroradiological Imaging of Traumatic Brain Injury

Tuong Huu Le, Alisa Gean, and Shirley I. Stiver

Introduction

Traumatic brain injury (TBI) refers to injury to the intracranial structures following physical trauma to the head. TBI can be classified into *primary* and *secondary* injuries. Primary injuries are the result of direct trauma to the head and occur at the moment of impact. Secondary injuries arise as sequelae, due to activation of excitotoxic, oxidative, inflammatory, and other signaling cascades, following the primary injury. Secondary injuries are potentially preventable and treatable, whereas primary injuries, by definition, have already occurred by the time the patient first presents for medical attention. TBI can be further divided according to *location* (intra-axial or extra-axial) and also by the nature of the *mechanism* of injury (penetrating/open or blunt/closed). The severity of TBI is classified clinically according to the universally accepted Glasgow Coma Scale (GCS). Patients presenting with GCS < = 8 are designated as having a severe TBI, those with GCS between 9 and 12 are categorized as moderate injuries, and mild TBI (mTBI) encompasses patients with a GCS 13–15 [1]. From the moment of impact, TBI is a dynamic process with varying therapeutic windows, and early diagnosis and intervention are imperative for favorable outcomes.

Diagnosis and management of TBI requires a multidisciplinary approach, starting with a history and physical examination, followed by appropriate diagnostic imaging, and subsequent medical and/or surgical intervention as deemed necessary. The goals of imaging include identification of treatable injuries, recognition of sources of potential secondary damage, and analyses of factors that may provide useful prognostic information for long-term outcome. Advances in medical imaging technology have resulted in an explosion of novel imaging modalities that have improved the sensitivity and specificity for early detection of TBI and added a host of valuable prognostic indicators and signs to help guide patient management. Consequently, clinicians are faced with the difficult task of selecting the most appropriate diagnostic test from an array of available imaging techniques [2]. These decisions are of vital importance for optimal management, especially for injuries that require aggressive and timely intervention. This chapter reviews established methodologies and recent advances in imaging techniques together with selection paradigms for their application in the diagnosis of TBI. Characteristic imaging findings for individual TBI lesions will be described in

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detail, including a discussion of the unique imaging features of blast-induced brain injury.

Imaging Selections

Conventional Radiography

Conventional radiography itself (film or digital) is not sensitive for detection of intracranial pathology and should not be performed to evaluate parenchymal damage in TBI [3–5]. Patients who are at risk for acute intracranial injury should be imaged by computed tomography (CT). Skull radiographs may still be useful in a number of trauma settings. Plain skull films may assist in screening for head trauma in young children and infants. CT imaging imparts radiation exposure, and concerns of the long-term cancer risks of this procedure have been raised, especially in the younger population. Protocols to reduce radiation exposure for children undergoing CT imaging have helped to mitigate this risk [6]. Following trauma, children may seem invincible, often with no detectable abnormalities despite having incurred events with significant contact forces to the head. Given the frequency with which children fend off head trauma, CT imaging after each these events could contribute to significant radiation exposure risk. Plain skull films in young childhood head trauma can, with relatively little radiation exposure, screen for a skull fracture. This may be most helpful in young children less than 2 years in whom it may be difficult to elicit symptoms of headache or other complaints. A rule to guide screening for detection of a skull fracture in infants and young children includes the presence of a parietal or occipital swelling or hematoma and age less than 2 months, with sensitivity of 89% and specificity of 87% for detection of a fracture [7]. Skull fracture, with or without signs of neurological injury, is an independent risk factor for a neurosurgically relevant intracranial lesion [8]. Therefore, in the setting of clinically occult TBI, the diagnosis of skull fracture serves to alert the clinician to the possibility of an immediate or delayed neurologically relevant intracranial lesion. Nondepressed, linear fractures can be missed on CT imaging, especially if the plane of the imaging slices lies parallel to the fracture [9]. Review of the scout image can often reveal fractures hidden on axial images. However, the poor resolution and single view afforded by the scout image may still miss and confound the diagnosis of many simple skull fractures. Skull films, typically with anterior-posterior and lateral views, enable better visualization of the extent of skull fractures and of entrance and exit skull defects in penetrating head injury.

Computed Tomography

CT is the primary modality of choice for evaluating head trauma because it is fast and widely accessible, and there are few contraindications to a non-contrast CT scan. Pregnancy, especially in the first trimester, is a relative contraindication for a CT scan. However, in the setting of major trauma, the priority is stabilization and care of the mother [10]. It has been recommended that even a CT of the abdomen to evaluate blunt or penetrating trauma to the abdomen of the mother should not be delayed or deferred because of radiation exposure concerns [10, 11]. Fetal head trauma has been recognized by skull radiography in a few cases of blunt abdominal trauma in pregnant trauma patients [12–15]. Especially in the second and third trimesters, the risk of radiation exposure to the fetus is minor when balanced against the potential benefits of imaging to evaluate the presence and extent of maternal or fetal injury [10, 11]. The risks of ionizing radiation are more significant in infants and children, and protocols which entail lower radiation exposure are recommended in the CT imaging of these patients [16]. In the setting of TBI, one needs to balance the risks of the CT against how the information from the scan might alter the patient's management. Unlike magnetic resonance imaging (MRI), CT can easily accommodate life support and monitoring equipment. In addition, CT is superior to MRI for the detection of skull fractures and radio-opaque foreign bodies. MRI is

contraindicated in the presence of certain ferromagnetic foreign bodies.

In the setting of acute head trauma, a non-contrast CT is recommended for patients with moderate and severe TBI (GCS ≤ 12) and in any patient with evidence of a penetrating injury. For patients with mTBI (GCS > 12), the New Orleans Criteria (Box 1) [17], the Canadian CT Head Rule (Box 2) [18–20], and the National Emergency X-Ray Utilization Study (Nexus-II) (Box 3) [21] can guide whether a CT scan should be performed. While there is some variability among these guidelines, together they suggest that older age, altered level of consciousness, persistent neurologic deficit(s), vomiting, significant skull fracture, and bleeding diathesis or anticoagulation therapy are factors advocating for CT imaging of a mTBI patient [17–20, 22–25]. Similar guidelines have been published by the Pediatric Emergency Care Applied Research Network (PECARN) for the pediatric population [26]. Non-contrast CT scans provide rapid and accurate detection of space-occupying hematomas and associated mass effect. The value of repeat CT imaging to change clinical management is considered to be low in the absence of an observed neurological change or high-risk features, characterized as sub-frontal or temporal contusions, anticoagulation, age over 65 years, or intracranial hematoma of volume greater than 10 ml [2, 27–31].

Box 1 New Orleans Criteria for mTBI: A non-contrast CT of the head is indicated if the patient meets one or more of the following criteria

Headache
Vomiting
Age > 60 years
Drug or alcohol intoxication
Persistent antegrade amnesia (short-term memory deficits)
Visible trauma above the clavicle
Seizure

Data from Haydel et al. [17]

Box 2 Canadian CT Head Rule for mTBI: A non-contrast CT of the head is indicated if the patient meets one or more of the following criteria

GCS < 15 2 hours after injury
Suspected open or depressed skull fracture
Any sign of basal skull fracture
Two or more episodes of vomiting
Age ≥ 65 years
Amnesia before impact of 30 min or more
Dangerous mechanism (i.e., pedestrian struck by motor vehicle, occupant ejected from motor vehicle, or a fall from a height of at least 3 ft or five stairs)

Data from Stiell et al. [18–20]

Box 3 NEXUS-II: CT imaging is not necessary in the absence of all of the following criteria

Age above 65 years
Skull fracture
Scalp hematoma
Neurological deficit
Altered level of consciousness
Abnormal behavior
Coagulopathy

Data from Mower et al. [21]

Intravenous contrast should not be administered before a baseline non-contrast CT has been performed, because the contrast can both mask and mimic underlying hemorrhage. A contrast CT after the non-contrast scan can, however, be very informative in detecting signs of active extravasation and alerting the clinician to a highly unstable lesion that has risk for rapid enlargement. In the trauma setting, adverse reaction to contrast agents, additional radiation exposure, and time constraints typically disfavor a contrast CT as a routine procedure. Contrast CT scans are, however, often obtained as adjuncts to CT angiography (CTA) or CT perfusion imaging studies.

CT angiography (CTA) and CT venography (CTV) utilize iodinated intravenous contrast to delineate the vascular structures at high

(submillimeter) resolution. CTA is best performed with multi-detector CT (MDCT) and rapid bolus contrast injection using a vessel tracking technique. Typical imaging parameters include a slice thickness of 1.25 mm, with a 0.625 mm overlap, and a bolus injection rate between 3 and 4 mL/s. Suspicion for a fracture traversing the path of a major artery or venous sinus is a common basis to perform a CTA or CTV study to evaluate the occurrence of significant vascular injury, such as a dissection, fistula, stenosis, or occlusion [32]. Traumatic vascular injuries can occur even if the fracture is not displaced. In many situations, with the exception of penetrating injury with retained ferromagnetic foreign fragments, MR arteriography (MRA) and MR venography can also be used to delineate these vascular injuries. The choice between CT and MR vascular imaging modalities depends on a number of factors, including time constraints, the likelihood that fracture artifact may confound interpretation of a vascular injury, the stability of the patient to undergo MR scanning, radiation exposure, and the possible need for ongoing surveillance imaging.

Xenon CT incorporates patient inhalation of an approximately 70:30 mixture of oxygen and nonradioactive xenon-131 during a CT scan. The xenon gas is highly lipid soluble and readily crosses the blood-brain barrier. Xenon CT has been used to evaluate cerebral blood flow (CBF) in TBI patients, with isolated reports further exploring how CBF measurements at different carbon dioxide levels and cerebral perfusion levels can be used to study perturbations in cerebral autoregulation and carbon dioxide reactivity [33, 34]. In traumatic contusion injuries, xenon CT has demonstrated that CBF is depressed in a concentric manner about the epicenter of contusions [35]. Quantitative xenon CT measurements of CBF obtained within 12 hours to 3 days following severe TBI have been shown to correlate with outcome, as assessed by the Glasgow Outcome Score (GOS) at 3, 6, and 12 months following injury [36, 37]. Similarly, global and lobar CBF measurements by xenon CT, at varying points across all grades of TBI, demonstrated that both measures correlated with GOS [38]. In a longitudinal study, serial CBF measurements obtained weekly for the first 6 weeks post-injury were analyzed in reference to neurological outcome at 6 months [39]. Outcome following severe TBI was better for those in whom low CBF had normalized by 2–3 weeks following injury, as compared to those with persistently low CBF beyond 3 weeks. The disadvantages of xenon CT imaging include radiation exposure, mild adverse effects on respiration or the sensorium, and a small (estimated to be less than 5%) augmentation of CBF induced by the xenon gas [40, 41].

Perfusion CT measures several indices of brain hemodynamics by tracking transient attenuation changes in the blood vessels and brain parenchyma during the first pass of an intravenously injected contrast bolus [42]. In contrast to PET and xenon CT, which employ diffusible tracers, CT perfusion imaging uses an intravascular tracer. Perfusion CT involves continuous cine scanning with a scan interval of 1 s and a total scanning duration of 40–45 s [43]. Algorithms are often employed to correct for variations in the time for the contrast bolus to reach each tissue voxel of interest [44]. Computer deconvolution generates a tissue residue function, a measure of the contrast remaining in a voxel over time. Color-coded maps of cerebral blood volume (CBV), mean transit time (MTT), and cerebral blood flow (CBF) are generated from a voxel-by-voxel analysis of the tissue residue function [44]. CBF is considered the best measure of how well the brain tissue is perfused, while MTT represents the average time of contrast transit and includes a measure of the time for the contrast to travel from an artery to the tissue. CBV, determined from the mathematical relationship CBF=CBV/MTT, represents the vascular volume containing contrast within a voxel and is a useful measure of the area of an infarct. In severe head injury patients, evidence of normal perfusion or hyperemia on CT perfusion imaging has been shown to correlate with favorable outcome, while findings of oligemia have been associated with unfavorable outcome [45]. One limitation of CT perfusion is the additional radiation exposure that accompanies cine imaging.