Pathophysiology of Traumatic Brain Injury
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ABSTRACT
Traumatic brain injury is a major source of death and disability worldwide. Significant success has been achieved in improving short-term outcomes in severe traumatic brain injury victims; however, there are still great limitations in our ability to return severe traumatic brain injury victims to high levels of functioning. Primary brain injury, due to initial injury forces, causes tissue distortion and destruction in the early postinjury period. Clinical outcomes depend in large part on mediating the bimolecular and cellular changes that occur after the initial injury. These secondary injuries from traumatic brain injury lead to alterations in cell function and propagation of injury through processes such as depolarization, excitotoxicity, disruption of calcium homeostasis, free-radical generation, blood-brain barrier disruption, ischemic injury, edema formation, and intracranial hypertension. The best hope for improving outcome in traumatic brain injury patients is a better understanding of these processes and the development of therapies that can limit secondary brain injury.

METHODS
Two searches were conducted with an Ovid search engine of Medline databases. The first search limited of English language reviews within the last 5 years on physiology or pathophysiology of TBI in human subjects yielded 27 articles. A second Ovid search of Medline under the parameters of TBI, English language, core clinical journals, clinical trials over the last 10 years, and age over 19 yielded 32 articles. We reviewed and used the guidelines of the Brain Trauma Foundation to provide a management basis.
for focusing our discussion and deciding which articles to include in this review. Also included in this review are prior reviews of TBI by experts in the field.

**BIOMECHANICS OF BRAIN INJURY**

The initial injury can be not only the result of direct trauma but also the result of acceleration, deceleration, or rotational forces either concurrent with or independent of direct trauma. This cascade of events leads to inertial forces on the brain tissue and cells. Biomechanical theories have historically described 2 inertial phenomena: linear acceleration and rotational head movement. It is thought that linear acceleration forces lead to superficial brain lesions, whereas rotational movements may explain deeper cerebral lesions and the concussion mechanism. The tissue strains induced by both linear and rotational forces create spatiotemporal gradients. Because the brain is a viscoelastic organ with little internal structural support, it poorly tolerates such forces. The gray matter closest to the surface of the brain is most susceptible to linear forces, which may cause cortical contusions and hemorrhage. The deeper cerebral white matter axons can be physiologically and mechanically injured by rotational forces. This disruption of deeper white matter is called diffuse axonal injury. Deep gray matter nuclei and axonal tracts in the midbrain and brainstem may also be damaged by rotational forces.

The linear and rotational acceleration theories are considered by many to be incomplete and may not adequately explain injury to deeper cortical structures in the absence of injury to more superficial cerebral structures. Although largely theoretical in its application to TBI, the stereotactile theory may explain these injuries. The stereotactile theory considers the spherical shape of the cranial vault in the setting of skull-brain relative movements and skull vibrations and their ability to generate secondary pressure waves. As brain tissue generally has the same density on concentric planes, these waves may propagate as a spherical wave front. The spherical nature of this wave front and the pressure gradient propagates and focuses its energy on deeper cerebral structures.

Apart from the forces incurred from the initial trauma, the prolonged compressive forces of brain edema and hematomas can further impair brain function by distorting brain tissues, elevating intracranial pressure (ICP), and reducing cerebral blood flow (CBF). Penetrating brain injury obviously harms brain tissues that are directly in the path of the projectile, but the resultant blast effect also produces significant structural damage to adjacent tissues. With penetrating injury, the trajectory and location of the wound are the most significant factors in outcome.

**BIOMOLECULAR RESPONSE TO BRAIN INJURY**

Compared to the primary injury, secondary injuries to the brain are more indolent and progressive and may ultimately be the deciding factors in the patient’s recovery. The early primary injury period is characterized by the destruction of brain tissue but not widespread degeneration of neurons, glial cells, or axons; these later effects are in essence the results of secondary injury. For patients who survive the initial injury, morbidity and mortality will be determined by secondary injury processes. Despite numerous efforts to pharmacologically intervene in secondary injury, none have demonstrated clinical efficacy. Clearly, there is ample opportunity to improve the care of these patients, and much of the promise lies at the cellular and subcellular level.

Substantial work in animal models, cell preparations, and human data have elucidated a number of biomolecular responses to TBI (see Figure 1). Excitatory amino acid release, oxygen radical reactions, and nitric oxide production are closely intertwined in the brain cell response to injury. One theory is that excitatory amino acids are released and the associated calcium influx into neurons and other brain cells is the sentinel event following TBI. Excess intracellular calcium then promotes oxygen radical reactions. High calcium and the presence of free-radical molecules create an unstable environment in the cell that may lead to increased production and release of nitric oxide and excitatory amino acids (eg, glutamate). Nitric oxide may participate in oxygen radical reactions and lipid peroxidation in neighboring cells, with a subsequent release of excitatory amino acids. Thus, each component of the triad—glutamate, free radicals, and nitric oxide—has the potential to enhance the activity of the others. If endogenous protective mechanisms such as free-radical scavengers do not halt this cycle, widespread cellular damage or necrosis will result.

The initial cellular response to injury is widespread and massive depolarization of neurons, glial cells, and cerebral vascular endothelial cells. Excess glutamate is thought to be the cause of the depolarization of traumatized cells in TBI, but there is

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debate about whether high glutamate concentrations following TBI are a product or cause of the initial massive depolarization. Given its pathological excitatory nature, glutamate is a significant contributor to brain cell death and dysfunction in TBI. Alterations in both presynaptic and postsynaptic glutamate receptors are central to this excitotoxicity.13 Failure of presynaptic ion pumps and calcium-mediated exocytosis lead to glutamate release. Likewise, traumatized postsynaptic glutamate transmitters have altered function and composition and contribute to TBI excitotoxicity. Glutamate receptors can be broadly categorized as \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors or \( N \)-methyl-D-aspartic acid (NMDA) receptors. NMDA and AMPA receptors, when activated, normally allow the influx of calcium. Both receptor types have increased calcium influx and neuronal hyperexcitability in the setting of TBI. In experiments on strained neurons, AMPA receptor changes included hyperexcitability, increased ionic currents, and increased intracellular calcium.14 In animal models, compounds that block NMDA receptors have been associated with improved neurological outcome.

Disruption of calcium homeostasis by glutamate-mediated ion channels, depolarization, or other cellular processes is a key aspect in the progression of secondary injury in TBI. Calcium affects a wide array of cellular functions. Excess calcium leads to disruption of protein phosphorylation, microtubule construction, protease formation, and a number of other enzyme functions.15 Sequestration of calcium can also affect the mitochondria. High mitochondrial calcium may result in swelling, depolarization, and a loss of function.16 This may lead to the initiation of cell death directly via apoptosis or indirectly through loss of oxidative phosphorylation and failure of triphosphate production adenosine (ATP).17 As ATP provides the energy for the vast majority of cellular functions, including the maintenance of ionic gradients, the inability to generate ATP is tantamount to cell death. Excessive calcium sequestered in the mitochondria also leads to the generation of reactive oxygen species, including the superoxide anion and nitric oxide.18

NMDA receptor activation is associated with the production of nitric oxide, which can combine with mitochondrially derived superoxide anions to produce the highly reactive nitrating species peroxynitrite. Although nitric oxide is a relatively weak free radical, peroxynitrite is a remarkably powerful one and has been shown to trigger DNA fragmentation, lipid peroxidation, and disruption of amino acids.19 Oxygen radicals remove a hydrogen atom from unsaturated fatty acids, and this leads to membrane lipid peroxidation. Widespread lipid peroxidation can compromise cellular membranes, resulting in cell lysis and death. Animal studies have demonstrated lipid peroxidation within hours of TBI, and blocking NMDA receptor–mediated nitric oxide

Fig 1. Biochemical responses to primary injury. **Abbreviations:** AMPA, \( \alpha \)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA, \( \gamma \)-aminobutyric acid; NMDA, \( N \)-methyl-D-aspartic acid; NO, nitric oxide; ROS, reactive oxygen species. Reprinted with permission from *Ann Emerg Med.*36 Copyright 2001, American College of Emergency Physicians.
production and peroxynitrite formation has inhibited ischemic infarction in animal models of stroke.  

Oxygen radicals may also be produced by a number of other processes, and their prevalence can be devastating to cells. Depolarization and calcium influx result in an increase in free fatty acids and arachidonic acid. Arachidonic acid is metabolized in the cyclooxygenase pathway, producing lipid hydroperoxides and oxygen radicals. Cerebral hypoperfusion and resultant cellular ischemia may also favor free-radical formation. Catecholamines released in the postinjury period may oxidize or degrade to produce hydrogen peroxide, which can also participate in oxygen radical reactions. Because of widespread hemorrhage, ample iron is available via the heme complex to catalyze free-radical formation by these processes.

In nonpenetrating TBI, the early postinjury period is characterized by widespread dysfunction of brain tissue, but the structure of neurons, glial cells, and axons is generally preserved. For example, diffuse axonal injury is the result not of large-scale disruption or transaction of axonal tracts but of changes on a subcellular level that alter axon function and nerve signaling. Some of these changes are the result of shearing forces that alter neurofilaments and axonal permeability. Axons may undergo axonal disconnection remote from the initial injury. Increased permeability of the axons leads to calcium influx. Increased intracellular calcium is associated with protease activation, microtubule destruction, cytoskeletal breakdown, and axonal disconnection. Axonal injury is a powerful predictor of morbidity and mortality. The loss of axonal function and structure appears to be a major factor in long-term outcome from TBI. Patients with diffuse axonal injury detected by magnetic resonance imaging are more likely to develop persistent coma and are less likely to return to their previous level of function.  

Sites in the injured brain with diffuse axonal injury have been observed to develop regenerative growth cones, but there is no evidence of recovery of neurological outcome. Neurogenesis is still limited to the laboratory, but there may be opportunities for pharmacologically mediated recovery of some function. White matter injury, as is true for the majority of secondary injuries, is a progressive and delayed process.

The alteration of cellular protein synthesis is a key part of the pathological response and repair following TBI. Cellular injury results in the up-regulation of the genes that code for some proteins and the down-regulation of others. Mediators of injury such as cytokines play a role in modulating cellular protein production. Posttranslational modification of proteins may produce changes in protein levels that can be detected in serum or cerebrospinal fluid (CSF). This holds some promise in the development of biomarkers to assess the severity of TBI and also to help understand some of the cellular processes that may occur in the injury and postinjury period. Understanding protein regulation and response following TBI may also lead to future interventions to reduce secondary injury.

A family of enzymes called calpains are another important class of mediators of cellular injury following TBI. Calpains are calcium-mediated proteases that under normal cellular conditions have a variety of cellular regulatory functions, including cytoskeletal maintenance. They have been shown to have a significant role in TBI as key enzymes targeting axonal proteins leading to cytoskeletal breakdown and disruption of axonal transport. In animal models, targeted inhibition of these enzymes has shown great promise in limiting secondary injury to axons.

Regulation of cell cycles and cell death (apoptosis) is a key feature in both the pathogenesis of TBI and protective mechanisms. Although cell death may be the result of a fatal insult to the cell structure or function, it may also be the product of programmed cell death or apoptosis. Caspase is a key enzyme in this pathway and is often a marker of cell death induction. Although it would be easy to assume that cell death would be undesirable, it may also serve a protective role. Likewise, proliferation of cells may be detrimental. The regulation of cell cycles has been an area of intense research, and there are close relationships between TBI and cell cycle regulation. It has been shown that although neurons often die in the setting of TBI, glial cells and astrocytes may proliferate. Inhibitors of apoptotic pathways have in some experiments been demonstrated to improve recovery.

There are numerous other mediators that may play a role in the bimolecular response to TBI. Endogenous opioids, adenosine, catecholamines (dopamine and norepinephrine), and a number of cytokines are among the additional factors in TBI. In most cases, it is unclear if they play a primary role in the neuropathology of TBI or are a reaction to other biological processes. Although interventions have been encouraging in animal models, clinical TBI trials using drugs to reduce the effects of mediators of injury have ubiquitously been unsuccessful. Processes such as apoptosis may have a protective effect in TBI, and in many cases, we cannot be sure that the bimolecular response in question is pathological and not beneficial. Furthermore, brain
tissue is not homogeneous, and what might be pathological to a glial cell may be beneficial to the neuron. There are very significant differences in function and injury response on both macroscopic and cellular levels.

**PHYSIOLOGICAL PARAMETERS IN BRAIN INJURY**

Given its relative size, the metabolic requirements of the brain are staggering. The brain requires large amounts of oxygen and glucose to remain functional. There are a number of mechanisms by which the human body protects the brain and maintains a constant supply of blood and nutrients. The cranial vault provides protection from the external environment, and the blood-brain barrier (BBB) maintains the integrity of the cerebral milieu, which is distinct from that of the rest of the body. This barrier is created by specialized vascular endothelial cells and a network of tight junctions that prevent the passive diffusion of electrolytes, and large proteins. The BBB and autoregulation of CBF are dependent on a number of local, chemical, and endothelial factors and neurotransmitters released from local neurons. The BBB can fail because of a number of insults in the setting of TBI, including ischemic changes to vascular endothelial cells leading to a loss of the integrity of the cerebral environment and failure of autoregulation.

Cerebral autoregulation maintains a relatively constant CBF despite variable cerebral perfusion pressures (CPPs) (See Table 1 for the terminology used in cerebral physiology). CPP is defined as the difference between the mean arterial pressure and ICP. Autoregulation is achieved through tight control of cerebral vascular resistance and is dependent on an intact and functional BBB. CPP below 50 mm Hg leads to brain tissue ischemia and autoregulation failure. When this happens, the brain becomes dependent on the mean arterial pressure for perfusion. Although the brain can compensate for decreased CBF by increasing oxygen extraction, this compensation has finite limits. Therefore, low CPP directly translates into ischemic injury risk.

The brain is very susceptible to ischemic injury, and in the setting of TBI, it is vital for cerebral perfusion and oxygenation to be maintained. Among the recommendations of the Brain Trauma Foundation, the first priority is rapid physiological resuscitation. Hypotension and hypoxia are seen in more than a third of TBI patients and are 2 of the 5 most potent predictors of mortality. Ninety percent of patients who die from TBI demonstrate ischemic cell changes, and cerebral ischemia may be the most important secondary event affecting outcome following TBI.

CBF is typically low following TBI and is often half of normal in the first 24 hours following injury. In some patients, there is a paradoxical increase in CBF (luxury perfusion) due to a loss of autoregulation. There are a number of factors that contribute to the decrease in CBF following TBI, not only globally but also focally in the brain. CBF is highly dependent on blood pressure, oxygenation, and blood carbon dioxide concentrations. Interventions such as hyperventilation and pharmacological agents can markedly decrease CBF. A mass effect caused by intracranial lesions on cerebral blood vessels, traumatic vasospasm, and decreased metabolism may also play roles. There is a direct correlation between CBF and the Glasgow Coma Scale score in the first 24 hours post-injury, and low CBF is associated with poor outcome and death. By injury type, CBF tends to be the lowest with diffuse injury accompanied by significant edema, with large subdural hematomas, and when the patient has experienced hypotension. TBI patients with normal computed tomography scans and those who have isolated epidural hematoma usually have normal or increased CBF.

The brain is housed in a rigid cavity and has a very limited ability to compensate for hemorrhage, swelling, edema, or mass effects (see Figure 2). Although these pathological processes can often be characterized by diagnostic imaging, clinical examinations are unreliable unless the patient has progressed to brainstem herniation. The most accurate way of assessing ICP is to insert a monitor. ICP in the intact cranium is determined by the brain parenchyma tissue pressure, presence of mass lesions, cerebral blood volume, and intracranial CSF volume. Any threshold value for ICP monitoring must take into account that it is the location of intracerebral masses that most directly affects the risk of herniation.

**Table 1. Terminology of Traumatic Brain Injury.**

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
</tr>
<tr>
<td>ICP</td>
<td>Intracranial pressure</td>
</tr>
<tr>
<td>CPP</td>
<td>Cerebral perfusion pressure (mean arterial pressure − intracranial pressure)</td>
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<tr>
<td>CVR</td>
<td>Cardiovascular resistance</td>
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<tr>
<td>CBF</td>
<td>Cerebral blood flow (cerebral perfusion pressure/cardiovascular resistance)</td>
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Increased ICPs (intracranial hypertension) can be reduced by the shrinkage of the volume of brain tissue (mannitol or other hypertonic substances), the reduction of CSF (drainage), the reduction of blood (hyperventilation-induced vasoconstriction), or the surgical removal of the pathological process. Alternatively, one may open the skull to allow expansion of the structures (decompressive craniectomy). Although ICP monitoring has been a cornerstone of neurosurgical management for decades, it must be always considered in its clinical setting.

Two types of brain edema have been described: interstitial (vasogenic) and intracellular (cytotoxic.). Both types occur following TBI, and both can contribute to secondary injury. Brain edema is usually worst at 24 to 48 hours post-injury. Vasogenic edema can result from failure of the BBB or from reflex vasodilation of vessels. This dilatation can occur the partial pressure of carbon dioxide in the arterial blood increases as a result of ventilatory failure. The increase in cerebral volume that results from vasogenic edema may initially be offset by changes in brain tissue compliance. Compliance may be achieved through the shunting of CSF to the spinal subarachnoid space, an increase in CSF absorption, a decrease in CSF production, or the shunting of venous blood out of the cranium. Although generally linked to ICP, brain edema can often occur without a corresponding increase in ICP.

Cytotoxic edema is the result of changes in cellular osmolality with resultant failure of the cell’s ability to regulate its ionic gradients. Alterations in cell membrane function and ion transport can ultimately lead to failure of ATP production and cell death. In areas of the brain with an impaired BBB and ischemia, restoration of blood flow can cause cytotoxic brain injury as well. Neurons and glial cells are particularly susceptible to cytotoxic cell injury. Cytotoxic edema, if widespread, can be associated with increased ICPs, impeded blood flow, and ischemia, yet not independently with permanent neurological impairment.

Hemorrhage in TBI can be from the initial insult or the product of secondary injuries, such as cytotoxic edema, ischemia, or intracranial hypertension. Apart from its effect in increasing ICP, blood is also a rich source of iron, which can catalyze free-radical formation. Larger amounts of bleeding in the epidural or subdural spaces increase intracranial blood volume and pressures. Intraparenchymal and subarachnoid bleeding occurs in the setting of endothelial and BBB disruptions and may exacerbate secondary injury by stimulating the release of excitatory amino acids (glutamate), free radicals, and nitric oxide. Blood within the interstitial space is also proinflammatory.

CONCLUSION

TBI is characterized first by physical forces leading to brain tissue destruction and alteration of function. Although many cells may be rendered dysfunctional during this phase, they are not necessarily irreversibly damaged or disrupted (Table 2). The state of the postinjury cerebral environment and resultant
secondary responses to TBI are what ultimately determine the final outcome. If a favorable milieu is created, brain cells and tissues may recover; if it is unfavorable, they may die. The great challenge is to identify what constitutes a damaging environment versus a healing environment and then how to mediate that environment.

An understanding of the biomolecular and physiological responses to TBI is essential to developing future therapies. Much has been learned in this area, but our knowledge is still relatively unsophisticated and incomplete. In the clinical setting, we are currently limited by what we can do on a macroscopic scale. Although there is great promise in the future of secondary interventions, it is unlikely that these will be solitary, standardized therapies; more likely, therapies will need to be tailored to the individual patients, taking into account mechanistic, genetic, cellular, anatomical, and pharmacological differences. With increased understanding of the pathophysiology of brain injury, there is great promise for future therapies; however, to date there have been far more failures than successes.

**DISCLOSURES**

**Potential conflict of interest:** Nothing to report.

**REFERENCES**

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