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A Clinician's Guide to the Pathophysiology of Traumatic Brain Injury

Andranik Madikians M D**, Christopher C Giza** M D*
Divisions of Critical Care & Neurosurgery and Pediatric Neurology*
Department of Pediatrics and Division of Neurosurgery
UCLA Brain Injury Research Center
David Geffen School of Medicine at UCLA, Los Angeles, CA

Abstract: Traumatic brain injury induces a complex pathophysiological cascade of cellular events. Central components of this response include increases in cerebral glucose uptake, reductions in cerebral blood flow, indiscriminate excitatory neurotransmitter release, ionic disequilibrium, and intracellular calcium accumulation. Acute glutamate release and nonspecific neuronal depolarization induce threatening perturbations in neuronal function. Restoration of homeostasis requires significant increases in glucose metabolism; however, there is often a concomitant reduction in cerebral blood flow, resulting in an uncoupling of supply and demand. Understanding the nature and timing of these processes provides the practicing clinician with a mechanistic rationale for acute physiological monitoring, aggressive interventions to address and minimize secondary injuries, implementation of advanced neuroimaging techniques, and careful monitoring return to normal activity in head injured patients.

Keywords: cerebral blood flow, glucose metabolism, glutamate, monitoring, positron emission tomography (pet)

INTRODUCTION

Traumatic brain injury (TBI) is a major cause of death and disability in children and young adults and has been identified as an important public health problem in the United States and worldwide [1-6]. When head injuries of all severities are included, the age-related incidence has been estimated to be as high as 670/100,000[7]. Over the past 15-20 years the reported incidence of TBI resulting from motor vehicle accidents has been declining steadily in the United States; whereas brain injury resulting from firearms has been on the rise, somewhat negating the benefits of better public education and improved motor vehicle safety[8]. Worldwide, motor vehicle accidents remain a major cause of TBI, and this problem is actually increasing, particularly in developing nations. TBI remains a major cause of trauma-related death and hospitalization. Approximately 2 million persons suffer TBI in the United States annually and of these about 70,000 to 90,000 will have permanent long-term disability, creating a significant socioeconomic and emotional burden on the families and society. The most commonly affected group is males 15-24 years of age, but children under the age of five and adults above the age of 65 also tend to be at increased risk[6]. In the U.S., pediatric TBI (under 14 years of age) is responsible for an estimated 3000 deaths, 29,000 hospitalizations and 400,000 emergency department visits annually[4].

The etiology of TBI varies with age. The elderly experience an increased proportion of TBIs as a result of falls. Motor vehicle accidents, and, to a lesser degree, assaults, are predominant injury mechanism in adults and adolescents. Adolescents may also experience a higher rate of sports-related concussions. Preadolescent children are also frequent victims of motor vehicle accidents, but more often as a pedestrian or while riding a bicycle. Those under the age of 5 years are more prone to falls[4], while infants are particularly vulnerable to repeated severe TBI in the form of nonaccidental trauma (child abuse). Boys are more likely than girls to sustain TBI, and this gender difference becomes increasingly apparent in the older pediatric and young adult population[9,10].

Over the past 20 years, basic science studies have provided significant insight into the underlying pathophysiological changes associated with TBI, making it distinct from other types of brain injury such as ischemia and seizures[11,12,13]. First and foremost, TBI causes neural dysfunction and cell death as the result of a biomechanical load being imparted to the brain. This force results in indiscriminate neurotransmitter release and ionic flux shortly after the injury. Subsequently, there are significant alterations of cerebral metabolism and blood flow that result in cellular dysfunction and vulnerability to secondary

Corresponding author address: Room 18-235 NPI, Mail code 703919, Division of Neurosurgery, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095 USA
Phone: 1-310-206-3480 Fax: 1-310-794-2147
Email: cgiza@mednet.ucla.edu

injuries (such as hypoxia, hypotension, seizures or repeated TBI). Using advanced monitoring techniques in the neuro-ICU, many of the pathophysiological changes originally described in animal models have now been reported following severe human TBI[9-17]. Better understanding of these underlying perturbations should result in improved ICU care and lead they way for future clinical and translational research to develop effective guidelines and brain-specific therapy following TBI.

In this paper we will provide an overview of neurometabolic changes that take place following TBI (Figure 1). Furthermore, we will discuss the clinical relevance of these basic pathophysiological mechanisms from the standpoint of ICU management.

BIOMECHANICAL FACTORS

The biomechanics of traumatic brain injury involve both linear and rotational forces. Linear forces result from straight ahead acceleration-deceleration and can be associated with coup injury (at the site of contact) and contra-coup injury (distant, usually opposite the site of contact). While most high-speed head injuries involve some linear component, rotational forces will almost always also play a role. It is these rotational forces that lead to twisting and shearing injuries in the brain parenchyma, particularly in the white matter fiber tracts (resulting in diffuse axonal injury). Rotational forces of lower magnitude are also present in milder forms of TBI such as sports-related concussion.

Biomechanical forces in the pediatric population can be distinct from those in the adults. Some of these differences result from the relatively large head size, reduced muscular strength, and increased flexibility in the neck, which may allow larger forces to be transmitted to the brain. On the other hand, there is there is less CSF space around the younger brain, and the prominent bony ridges of the anterior and middle cranial fossae are less developed. These factors may contribute to the lower occurrence of focal lesions in pediatric TBI[18-21]. The developing skull is thinner as compared to an adult skull and therefore, more vulnerable to diffuse deformation[22]. The open fontanelles and the flexibility of the sutures may help dampen the traumatic forces; where the adult skull is lacking this luxury. The open fontanelles and sutures also help accommodate slower growing space-occupying lesions (such as chronic subdurals). On the other hand, the lower water content of the adult brain renders it more compliant[23-24]. Clearly, the biomechanics of the injury should be carefully considered in the evaluation of any TBI patient, and the etiology of trauma as well as the patient's age are important factors in the understanding these forces.

PATHOPHYSIOLOGY
GLUCOSE METABOLISM

Experimental models have shown that TBI results in a significant increase of glucose utilization within the first 30 minutes post-injury, after which glucose uptake diminishes and then remains low for about 5-10 days [25,13]. Clinical studies in humans using Positron Emission Tomography (PET) have demonstrated comparable results. Although it is difficult to capture the acute period of hyperglycolysis in a critically ill TBI patient, globally decreased glucose metabolism has been demonstrated persisting chronically for weeks to months post-injury in human patients[15]. In the subacute phase, another study showed no correlation between the level of consciousness as measured by Glasgow Coma Scale (GCS) and glucose metabolism[26]. Diminished cerebral glucose metabolism was seen in both comatose (severe) and relatively intact (mild) TBI patients, implying marked global neurometabolic abnormalities may be present with or without significant clinical symptoms[26]. Importantly, a follow-up study revealed that reduced glucose uptake in subcortical structures (including brainstem) did correlate with the presence of coma, suggesting that regional differences in physiology are relevant to clinical exam measures[27].

The initial hyperglycolysis described above results from disruption of ionic gradients across the neuronal cell membrane, activating energy-dependent ionic pumps[28-32]. In experimental animal models the increase in glucose utilization is almost instantaneous following injury and lasts up to 30 minutes in the ipsilateral cortex and hippocampus[25,33]. In more severe types of injury such as cortical contusion, the rise in glucose metabolism may last up to 4 hours in the outlying areas of the contused segment[34]. As cerebral oxidative metabolism at baseline is already near or at maximum levels, this increased energy demand may be dealt with by augmenting glycolysis[35,36] which in turn increases lactate production[37]. Increased lactate levels are seen after both ischemic and concussive brain injuries[38-44]. However, the mechanism of lactate accumulation has traditionally been ascribed to reduced oxidative metabolism after ischemia, while, at least acutely after trauma, increased glycolysis may play a more prominent role. More recently, a mechanism of alternative metabolic substrate production has been proposed, whereby lactate originates from astrocytes and is shuttled to the neuron to facilitate energy production at a time of need [45-47]. This idea has received further support from experimental TBI studies utilizing ketone bodies as an alternative substrate[48] and clinical studies that show increased brain uptake of lactate following TBI[49].

In addition to the glycolytic disturbances mentioned above, there is also increasing evidence for impairment of oxidative metabolism following brain trauma[50-53]. This may lead to depletion of high-energy phosphates (adenosine triphosphate, ATP)[54-56], with a subsequent rise in anaerobic metabolism, and yet further accumulation of lactate[41, 57-59]. Increased lactate may generate neuronal dysfunction as a result of acidosis, membrane damage, disruption of the blood brain barrier and cerebral edema[60-63]. There is also some evidence suggesting lactate accumulation post-injury may render the neurons more susceptible to secondary ischemic insults[64].

Severely head injured patients frequently show cerebral lactic acidosis[65, 66]. Post-injury cerebral lactate production is marked by an acute and extended increase in cerebrospinal fluid, and a negative arteriovenous difference in lactate content (higher jugular venous than arterial concentration)[65-67]. Several investigators[41, 68] have shown a rise in lactate concentration in cerebrospinal fluid and in brain tissue within the initial 60 minutes following mild to moderate fluid percussion injury in rat models. Nilsson, et al., using a weight drop model of injury, showed a 4-to 5 fold increase in the dialysate concentration of lactate for about 80 minutes post injury; they also demonstrated a significantly higher elevation of lactate (7 fold) as injury severity increased[69, 70]. The rise in extracellular lactate is partially presumed to be as a result of decreased cerebral blood flow in the face of increased energy demand from injury- induced ionic changes. However, as mentioned earlier, recent studies have suggested that the lactate story is not all bad. Lactate appears to serve as an alternative oxidative fuel in states of physiological stress or activation[45-47]. Furthermore, at least in patients with relatively preserved oxidative metabolism, brain uptake of lactate has been associated with improved outcome[49].

CEREBRAL BLOOD FLOW (CBF)

Cerebral hemodynamics change significantly post injury, and the pattern of these changes depends upon the type of injury and its severity[71, 72]. Dietrich, in experimental animal models using mild to moderate TBI, showed a significant drop off in blood flow (70-80% of normal)[73] , and with more severe injury the drop off neared ischemic levels[71]. Currently, there is an ongoing debate as to whether these low flow events are a contributing cause of cell injury, a consequence of the injured and dying tissue[74,75], or a manifestation of a non-ischemic physiological perturbation. While studies after TBI have shown histopathological or neuroimaging changes compatible with hypoxia/ischemia[72,76] as well as marked acute reductions in CBF[74,76,77], the presence of true ischemia following clinical TBI has been difficult to demonstrate. Diringer, et al., in clinical studies, has shown flow reduction to levels classically defined as "ischemic" following hyperventilation in severely head-injured patients; however, these flow reductions were not associated with a concomitant decrease of the cerebral metabolic rate for oxygen ($CMRO_2$) beyond that induced by TBI itself[75]. Using a voxel-based method to identify a noncontiguous, physiological region of interest, Coles, et al., reported an ischemic brain volume of approximately 6%[78]. In a different set of patients, Vespa, et al., reported an ischemic brain volume of only about 1.5%. They did find, however, that metabolic crisis, as defined by a lactate/pyruvate ratio (LPR) of >40, was present in 7/19 patients and this parameter (LPR) correlated negatively with $CMRO_2$, leading them to conclude that a "metabolic crisis without ischemia" was present after TBI[79].

In the pediatric population, increased blood flow (hyperemia) was once felt to be a common complication of TBI, resulting in increased intracranial pressure and cerebral edema. Current studies point out that post-injury hyperemia is not as common as once thought[80]. Earlier studies of cerebral blood flow were done comparing brain-injured children to normal young adult values. It is now known that CBF undergoes significant changes through development and is significantly higher in children than adults[81-83]. The newer studies, by comparing to age-appropriate controls, have not shown marked hyperemia[84,85].

Kelly in 1996 and Vavilala in 2004 showed an association between outcome and cerebral blood flow that is dependent on the autoregulation. Intact autoregulation in the face of hyperemia is linked to better perfusion and subsequently a better outcome[86, 87], while hyperemia in a setting of impaired autoregulation is generally associated with intractable increases in intracranial pressure and ultimately, poorer cerebral perfusion and worse outcome. Thus, it appears that it is not only the magnitude of cerebral blood flow, but also the reactivity of the cerebral vasculature that determines tissue viability and prognosis.

IONIC FLUX AND GLUTAMATE

Acute injury to the brain causes a rapid release of glutamate[88, 89], the predominant excitatory neurotransmitter in the central nervous system. This indiscriminate release occurs as a result of extensive triggering of action potentials, synaptic neurotransmitter release, and membrane disruption. This massive release of glutamate is a major source of potassium efflux into the extracellular space[70, 89]. The rise in the extracellular concentration of potassium also results from nonspecific breakdown of the plasma

membrane, especially in areas of the brain damaged by localized contusion[90, 91] or intracerebral hemorrhages[92].

It is well known that experimental TBI triggers a rise in the extracellular potassium concentration[89, 90]. Both the fluid percussion and weight drop models of experimental brain injury transmit a substantial force to wide areas of the brain, resulting in diffuse dysfunction. This rise in the extracellular concentration of potassium occurs as the result of opening voltage-gated potassium channels by neuronal depolarization. Julian and Goldman demonstrated that deformation of neural tissue alone could produce enough depolarization to lead to neuronal firing[93]. Importantly, glial cells play a prominent role in the re-uptake of extracellular potassium[94-96] and are able maintain the concentration below the physiological ceiling in mildly abnormal states such as brief seizures or mild concussion[89, 97, 98]. Nonetheless, some have shown that more severe concussive injury causes increases in extracellular potassium concentration up to 70 percent of the maximum level reached in ischemia (80 mM)[99-101]. This significantly exceeds the physiological ceiling of 6-10 mM[67, 97, 98, 102], and indicates that the normal glial uptake mechanisms have either been overwhelmed or somehow impaired[94, 103]. This increase in extracellular potassium, in turn, may lead to increased energy demand, causing greater rates of glycolysis with a parallel rise and accumulation of lactate.

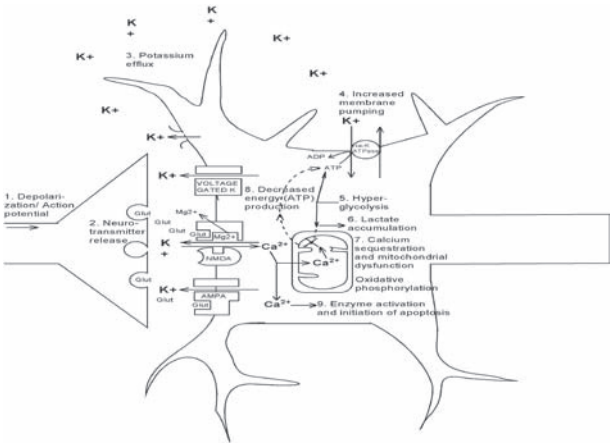

Fig 1: Neurometabolic cascade following traumatic injury. CELLULAR EVENTS 1) Nonspecific depolarization and initiation of action potentials. 2) Release of excitatory neurotransmitters (EAAs). 3) Massive efflux of potassium. 4) Increased activity of membrane ionic pumps to restore homeostasis. 5) Hyperglycolysis to generate more ATP. 6) Lactate accumulation.7) Calcium influx and sequestration in mitochondria leading to impaired oxidative metabolism. 8) Decreased energy (ATP) production. 9) Calpain activation and initiation of apoptosis (modified from Giza and Hovda[134]).

Glutamate also induces opening of ligand-gated channels that are permeable to calcium. A number of studies have shown an increase in intracellular calcium concentration following various experimental traumatic brain injury models[52, 104-107]. Fineman and colleagues have described a significant calcium accumulation for up to four days post fluid percussion injury in the ipsilateral cortex, hippocampus, striatum, and thalamus of the injured adult rat[104, 107]. Accumulation of calcium intracellularly has been an indicator for impending cell death. There are multiple means by which calcium exerts its apoptotic properties[108, 109]. For example, increased intracellular calcium can cause overstimulation of phospholipases[110], plasmalogenase, caplains[111, 112] protein kinases[108], guanylate cyclase[113], nitric oxide synthetase, calcineurins, and endonucleases. As a result of these cellular changes there is overproduction of toxic reaction products, such as free radicals[114, 115], significant disruption of the cytoskeletal organization[116, 117], and activation of apoptotic genetic signals[118]. Accumulation of intracellular calcium does not always result in cell death, but affects the metabolic machinery of the mitochondria to such an extent that any secondary metabolic demand cannot be met, subsequently rendering the cell vulnerable to energy failure[119]. This becomes a significant issue in TBI patients, as in their initial phase of the injury they fight an uphill battle against secondary insults such as increased body temperature, seizures, hypotension and hypoxia. The need for meticulous monitoring to prevent or at least minimize the occurrence and/or repetition of the secondary injuries is clear.

Magnesium is one of the electrolytes that play a significant role in maintaining ionic balance within the injured cell. Several studies in experimental models of traumatic brain injury have shown a marked decrease in brain intracellular free and total magnesium concentration that lasts up to 4 days post injury[120-122]. Vink and colleagues have shown in animal models that the decrease in free intracellular magnesium correlates with severity of injury[122]. Memon and colleagues demonstrated this finding in humans, where they showed a graded decrease in serum magnesium, correlating with severity of injury based on the CT scan and other diagnostic parameters[123].

Magnesium plays a pivotal role in maintaining the integrity of the mitochondrial inner membrane[124] and the functional reliability of the ATPase pump[125]. Additionally, magnesium has a significant role in influencing the degree of excitotoxic damage as a result of TBI, as intra- and extracellular magnesium concentration affects the opening and closing of sodium and calcium ion channels, as well as

their ionic transporters[126]. There is significant evidence pointing to a marked correlation between decreased magnesium levels and the outcome of TBI, such as cerebral edema, behavioral abnormalities, and impaired cognitive performance[127-129].

Thus, ionic flux represents a fundamental cellular change induced by biomechanical injury. Direct potassium efflux and indiscriminate release of glutamate with subsequent neuronal depolarization may serve as the triggers for subsequent metabolic perturbation. Cellular metabolism and functional outcome also appear to be impaired by concomitant reductions in intracellular magnesium.

SUMMARY

Multiple physiological processes characterize the neurometabolic cascade of TBI. These include alterations in glucose metabolism, changes in blood flow and neurovascular coupling, release of excitatory neurotransmitters, efflux of potassium and accumulation of intracellular calcium. Attempts to restore ionic equilibrium require activation of energy-dependent membrane pumps. Increases in energy demand post-TBI may occur at a time of diminished cerebral blood flow and thus, a time of limited substrate availability. Using advanced monitoring and imaging techniques, many of the physiological processes originally described in experimental animals can now be detected and even followed in head-injured patients. These investigations have led to a more nuanced understanding of cerebral metabolism after brain injury. Conditions once felt to be associated with bad outcome (such as increased cerebral lactate and reduced cerebral blood flow) are not black-or-white indicators of cerebral distress. Increasingly, it appears that it is the relationship between these parameters that is more important in determining treatment response or outcome than the physiological values in isolation. Thus, being able to reliably monitor cerebral physiological changes in the intensive care setting is only the first step; understanding the complexity of post-injury pathophysiology is also critical for optimal management of head-injured patients.

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