

Biomechanics and neurochemical changes to predict the effect of traumatic brain injury

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ABSTRACT

Traumatic Brain Injury (TBI) can occur when the head suddenly hits an object and the internal forces produce damage to the brain, disrupting its normal function, with or without structural changes. TBI causes disability and death to almost all age groups. This review aimed to describe the biomechanics that were involved in brain injury of varying severity degrees and summarizes the neurochemical and metabolic changes to predict the effect of brain injury. There are various methods in biomechanics measurements for TBI, as well as computational models to understand several pathophysiology and effects of TBI that are very important to find better TBI treatments. Moreover, several neurochemical and metabolic changes in brain may explain the short and long-term effect of TBI to the brain. The various methods in biomechanics measurements for TBI are very important to find better treatments.

Keywords: Traumatic brain injury, concussion, biomechanics

INTRODUCTION

TBI is a non-degenerative, non-congenital brain injury due to external mechanical

forces, namely when the head hits an object suddenly and violently, which can cause permanent or temporary disruption to cognitive, physical, and psychosocial functions, accompanied by a decrease or

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change in state of consciousness [1,2]. TBI is a consequence of variations in spatiotemporal pressure on the brain [3] and is the cause of death for 40 % of all acute injuries in the US, where annually as many as 200,000 Traumatic Brain Injury (TBI) victims require hospital care and 1.74 million people with mild TBI still need further control at outpatient clinic or experience temporary disability for at least 1 day [1]. In children and adolescents, TBI of varying degrees of severity in the developing brain may cause complication in ongoing brain maturation [4].

The brain is the most important organ that should be protected against trauma, as injuries to its structures are irreversible, and the consequences of injury can be devastating. Victims of TBI may experience deleterious effects on overall neurological function and even death or permanent disability [2,5]. It is also increasingly recognized as a key environmental factor of neurodegeneration worldwide [5–7]. More than 30 clinical trials have been conducted in TBI without success. Better diagnostic tools and protective measures can help reduce the incidence and serious effects of injuries, therefore, better understanding of TBI pathology is needed [2]. This awareness, however, also points to the need of

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clarification on many issues as there are many questions on the definition of exposure to at risk populations [8]. The human brain is a very complex organ, the center of supreme intellectual egocentrism and a source of ongoing scientific challenges. At a basic functional level, we need to understand the various functions that result from the interaction of eighty six billion neurons with one hundred trillion connections. From this perspective, the problem lies in how to relate the biochemical and electrophysiological properties of brain cells and the overall network properties of the interconnected cells [9].

Over the last 3 decades, a number of experimental models of TBI have been developed to explore and understand various aspects of TBI in the human brain to predict its effects [4]. However, some of the pathophysiology and treatment of TBI differ between human and animal models [6]. With TBI biomechanics, we can explore phenomena that mechanically contribute to early craniocerebral lesions that may provide a starting point for an overall understanding of the pathophysiology of TBI [3].

Therefore, this review aimed to describe the biomechanics that were involved in brain injury of varying severity degrees,

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summarizes the neurochemical and metabolic changes in the brain to predict the effect of brain injury, and clinical application of biomechanics in TBI.

Biomechanics of TBI

TBI biomechanics is the relationship between the impact of forces that are experienced during head and neck movements, the stiffness of the tissues that frame the head and neck complex, structural deformation at the macroscopic and microscopic levels, and the biological responses to numerous conditions of stress that are imposed on the head (Figure 1). Biological responses can be structural (tearing of vessels and axons) or functional (changes in blood flow or neurological status), and may be immediate or delayed [4].

Brain damage after TBI is classified as focal (e.g. contusions, lacerations, hematomas [extradural or intradural], and tentorial/tonsillar herniation) and diffuse (Diffuse Axonal Injury [DAI], cerebral swelling, cerebral ischemia), or alternatively classified as primary (direct) and secondary, which is based on the process of the neuronal damage after injury [10]. The focal lesions often coexist with variable degrees of diffuse lesions (as occurs in DAI), which are more often concentrated in deep brain areas and are

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often not visible on radiological examination [3]. Forces can be exerted, or loaded, on the head in several different ways. Forces that are applied relatively slowly are termed static or quasi-static (timespans greater than 200 ms), while those applied rapidly are termed dynamic forces (less than 50 ms). Dynamic loading causes injury the most, and can be classified into 3 types: impact, impulsive, and blast overpressure loading. Impact loading happens when the head strikes or is struck by an object. In contrast, the head does not strike an object during impulsive loading, and instead is set in motion due to another part of the body moving, while in blast overpressure or shock wave loading, rapidly moving, very short (less than 5 ms) pressure waves travel through the brain [11].

Researchers can use human field data during sporting events to help understand the processes that occur in TBI. Usually, a helmet or mouthpiece is attached to a sensor to measure the amount, direction, and type of head movement (linear, rotational, centroidal, non-centroidal) [4]. Camarillo and colleagues [12] in their study used an instrumented mouth guard for measuring linear and angular head impact kinematics in American Football, which concluded that peak linear acceleration,

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peak angular acceleration, and peak angular velocity measurements were highly correlated between the instrumented mouth guard and anthropomorphic test device. This study showed the potential of an instrumented mouth guard as a research tool for measuring in vivo impacts and showed the relationship between head impact kinematics and TBI on American football. A brain injury prediction study that assessed the combined probability of concussion using linear and rotational head acceleration by Rowson and Duma [13], which introduced a new injury metric, computed the overall risk of concussion based on the peak linear and rotational acceleration that were experienced by the head during impact, and showed that all parameters were good predictors of injury for the datasets analysed. However, combination probability of concussion by linear and rotational acceleration was a significantly better predictor than rotational acceleration alone, though they were not different from each other. These kinds of sensors do not measure forces' impact directly, but rather they measure the movement of the head, either acceleration or velocity, as a response to an impact, and the recorded data are correlated with clinical assessment of injuries on the sport field. Nevertheless, such data are mostly

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affected by equipment design limitations [4].

For more controlled kinematic information, human-like anthropomorphic surrogates and laboratory-based studies are used to relive film reports and watch sports-related events to estimate impact strength and head movement (kinematics), as well as to document kinematics that are associated with non-detrimental activities, so they can be used to identify both tolerable and injurious kinematic conditions. Surrogates only measure kinematic response, and currently, they cannot be used to predict or measure concussion or tissue distortion, but conversely, the results should be correlated with animal studies, autopsy reports, and patients records to infer biological responses to kinematic loading conditions or with computational models to infer tissue deformation due to head impact or rotation [4].

Computational models are valuable for understanding mechanics especially when they use life-like tissue stiffness [4]. Computational head models can provide valuable insight into the multi-length scale complexity that is associated with the main nature of DAI. These models involve understanding how trauma to the head (at the centimeter length scale) translates to white matter tissue (at the millimeter length

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scale), and even further to the axonal length scale, where physical injury to the axon (e.g., axon splitting) can occur. Therefore, to accurately show the development of TBI, the bio-fidelity, which represents lifelike appearance and responses, of this computational model is very important [14]. Therefore, recent computational studies have incorporated structural anisotropy in both the material definition of the white matter and the injury criterion as a means to improve the predictive capabilities of computational models for TBI [2,14]. El Sayed *et al* [10] dealt with biomechanical modeling of the brain tissue response to traveling wave impact and the computational stimulation of TBI using a constitutive model for brain tissue components, in which the material response was split into elastoplastic and viscoelastic components, including rate effects, shear and porous plasticity, and finite viscoelasticity. This modeling was also reported by Zhang *et al.* [15,16]. Computational models can also simulate head response to an impact and provide additional data for estimating tissue distortions that are associated with TBI [4]. Kimpara *et al* [17] proposed two criteria based on angular acceleration for TBI such as Rotational Injury Criterion (RIC) and Power Rotational Head Injury Criterion

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(PRHIC), for assessing head injuries caused by rotational kinematics, and concluded that the RIC was significantly correlated with Cumulative strain damage measure (CSDM) with strain threshold less than 15 %, which might predict mild TBI, while PRHIC was strongly correlated with the CSDMs with the strain thresholds equal to or more than 20 %, which might predict more severe TBI. Post *et al.* [18] reported that using computer simulations of TBI events from falling, many of the impacts were pooled to the occipital region of the head (as expected from backward falls or from slipping from ladders), and resulted in low rotational acceleration values and high linear accelerations, which suggested that linear acceleration may be an important characteristic of this injury mechanism, and that the Head Injury Criterion (HIC15) values did not consistently predict injury when the kinematic output was lower than 300 g (suggests that HIC15 may have limited value as a predictor for high energy of short duration direct impacts to the head). The results supported a relationship between fall height and duration of loss of consciousness, with the higher fall heights produced longer times of unconsciousness. The multi-scale computational model of blast-induced TBI (bTBI) as used by Przekwas *et al* [19] showed that the micro-

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mechanical responses of neuroaxonal structures occurred sequentially in time with “damage” and “relaxation” periods in different parts of the brain. A new integrated computational framework described the coupling of brain-scale biomechanics with micro-mechanical damage to axonal and synaptic structures.

Computational models have been used to investigate brain tissue biomechanics after high impact loading and to simulate brain deformations in the surgical settings [10,20,21]. TBI caused brain edema leads to increased intracranial pressure and decrease cerebral perfusion. One of treatment recommendation is a decompression craniectomy with controversies regarding proper location and the size of the decompression craniectomy. With mathematical and computational (in silico) models, Lambride et al [22] presented a finite element model of post TBI and decompression craniectomy, which combined biphasic and nonlinear biomechanical models of the brain, and concluded that the herniated volume of brain tissue as a function of intracranial pressure load under a specific craniectomy geometry and size was particularly relevant for planning a decompression craniectomy.

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Neurochemical and metabolic changes in the brain after TBI

TBI may cause sudden changes in brain neurochemistry, in the form of unchecked ionic fluxes that leads to metabolic changes, and impaired cerebral blood flow, impaired magnesium level, and abrupt release of neurotransmitters, which causes neurotransmitter alteration [4,23]. In normal condition, certain cellular energy is used to keep ion distribution across the plasma membranes to maintain membrane potential between -40 and -80 mV [4].

Ionic Flux, Metabolic changes, and Cerebral Blood Flow

In normal condition, excess extracellular K⁺ is taken up by surrounding glial cells, so the brain can maintain physiologic potassium levels after mild disruption. Nevertheless, greater insults as brain trauma or ischemia, may overcome this compensation ability. Disruption of neuronal membranes, axonal stretching, and opening of voltage-dependent K⁺ channels may occur after biomechanical brain injury, and lead to significant increase in extracellular K⁺. Increase in extracellular K⁺ triggers neuronal depolarization that results in Excitatory Amino Acid (EAA) release, and opening of EAA receptor channels i.e. N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

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(AMPA), and kainate, which leads to greater K⁺ flux, followed by neuronal suppression (spreading depression). This depression can be manifested as early loss of consciousness, amnesia, or other cognitive disturbance [23]. The magnitude of the rise in extracellular K⁺ increases with the severity of the injury, with a fivefold increase observed at 1.5 min post-injury, and resolved after about 2.5 min in minor injuries and within 6 min after more severe injuries [4]. Studies in rat models reported that as compensation for restoring ionic homeostasis, some energy-requiring membrane pumps were activated that lead to an immediate increase in glucose use (cerebral metabolic rate of glucose/CMR_{glc}), which persisted for up to 30 minutes in the ipsilateral cortex and hippocampus [4,23]. This abrupt increase in energy requisite was compensated by an

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increase in glycolysis, that might lead to increased lactate production [23]. Studies in humans showed a negative association between CMR_{glc} that was measured with positron emission tomography (PET) and global cerebral metabolic rate of oxygen (CMRO₂), which supported the evidence of hyperglycolysis [24,25].

Normally, Cerebral Blood Flow (CBF) is coupled to neuronal activity and cerebral glucose metabolism. An experimental fluid percussion injury showed reduced CBF to 50 % of normal level [23]. However, Richards *et al* [24] reported some discrete areas of uncoupling of CBF and glucose metabolism after head injury within 2 hours of cerebral contusion in the rat that could not be explained by changes in cerebral glucose content on most animals.

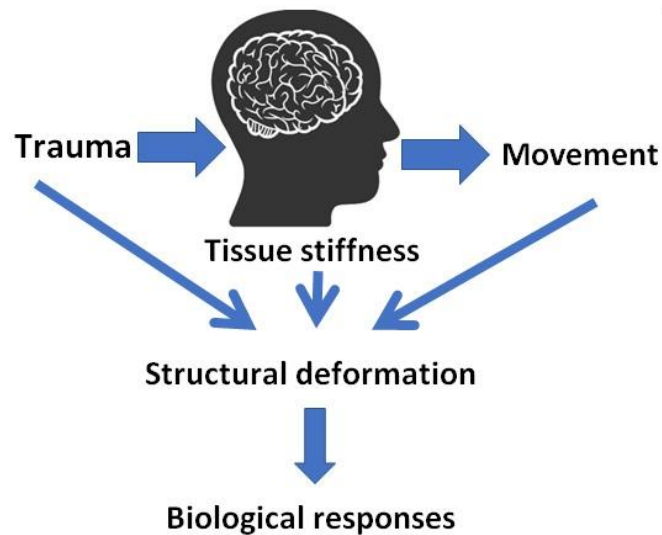


Figure 1. Biomechanics of traumatic brain injury.

Reduction in magnesium level

Reduction in intracellular magnesium levels occurs immediately after TBI, and suggests some correlation with neurologic deficits, whereas magnesium pretreatment leads in improvement of motor function in experimental animals. Low magnesium levels may cause neuronal perturbation through several mechanisms, such as glycolytic and oxidative generation of ATP, as well as unblocking the NMDA receptor channels that results in greater influx of Ca^{2+} leading to potential deleterious intracellular effects [23]. Hypomagnesemia appears to be an independent prognostic marker in patients with severe TBI [26].

Neurotransmitter alterations

After a concussion dysfunctional excitatory neurotransmission may occur that cause long-term deficits in memory and cognition, even in a setting of minimal structural brain damage. After a TBI, changes in glutamatergic, adrenergic and cholinergic system have been reported [23,27]. Rise in extracellular glutamate concentration occurred following TBI in adult rats. In human, the release of EAA after severe TBI has been observed with micro-dialysis probes [4]. Early changes in choline acetyltransferase activity followed by loss of forebrain cholinergic neurons also have been reported [23,27]. TBI may cause alteration in inhibitory neurotransmission. Loss of inhibitory neurons may occurred after TBI, and

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associated with predisposition to the development of seizures [23]. Some studies reported the involvement of dopamine level alteration after TBI that lead to oxidative stress and cellular dysfunction. Therapeutic targeting of dopamine pathways may provide benefits in neural survival and functional outcome after TBI [28].

Medical application of biomechanics in TBI

Medical applications of biomechanics in TBI have been used for clinical assessment of tissue damage due to blunt impact loading in two cases that corresponded well with Magnetic Resonance Imaging (MRI) (Table 1) [29].

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In case-1, a road traffic accident caused a blunt impact loading from a small solid object, which caused a skull indentation when visualized by MRI, and corresponded well with an effective strain rate that was higher than 250 per second. In case-2, an occipital collision due to a fall from height caused a coup–contrecoup injury, which caused no noticeable skull indentation, with contusion and edema when visualized by MRI, and corresponded well with a negative pressure of -90 kPa or more [29].

Table 1. Medical assessment of TBI using biomechanics and MRI

Case	Cause of injury	Type of injury	MRI findings	GCS score at ER	Biomechanics parameter
1	Road traffic accident	Blunt impact loading injury from a small solid object	Skull indentation	13	Effective strain rate > 250 per sec
2	Fall from height	Occipital collision, <i>coup–contrecoup</i> injury	Contusion and edema	15	Negative pressure \geq -90 kPa

MRI= Magnetic Resonance Imaging, GCS= Glasgow Coma Scale, ER= Emergency Room

CONCLUSION

There are various methods in biomechanics measurements for TBI such as sensor in a helmet or mouthpiece, or more controlled kinematic information e.g. human-like anthropomorphic surrogates and laboratory based studies, as well as computational models to understand several pathophysiology of TBI. These methods are very important to find better treatments for TBI. Moreover, several neurochemical and glucose metabolic changes in brain may explain the short and long-term effect of TBI to the brain.

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