

REVIEW ARTICLE

Cerebrovascular pathophysiology following mild traumatic brain injury

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Summary

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Mild traumatic brain injury (mTBI) or sport-induced concussion has recently become a prominent concern not only in the athletic setting (i.e. sports venue) but also in the general population. The majority of research to date has aimed at understanding the neurological and neuropsychological outcomes of injury as well as return-to-play guidelines. Remaining relatively unexamined has been the pathophysiological aspect of mTBI. Recent technological advances including transcranial Doppler ultrasound and near infrared spectroscopy have allowed researchers to examine the systemic effects of mTBI from rest to exercise, and during both asymptomatic and symptomatic conditions. In this review, we focus on the current research available from both human and experimental (animal) studies surrounding the pathophysiology of mTBI. First, the quest for a unified definition of mTBI, its historical development and implications for future research is discussed. Finally, the impact of mTBI on the control and regulation of cerebral blood flow, cerebrovascular reactivity, cerebral oxygenation and neuroautonomic cardiovascular regulation, all of which may be compromised with mTBI, is discussed.

Introduction

Mild traumatic brain injury (mTBI) is a growing area of concern in society today and is quickly evolving from a typically sport-related injury to one of epidemic proportions (Elleberg et al., 2009). Aside from the sporting context, mTBI is becoming increasingly linked with other situations including blast-related injuries and motor vehicle accidents (Jaffee et al., 2009; Wright et al., 2009). Research into understanding the underlying physiological mechanisms responsible for the neurological and/or cardiovascular disruption associated with mTBI is limited and a need for more has been expressed (McCrorry et al., 2009). Understanding the relationship between mTBI and these mechanisms will assist professionals working in the field to help protect and rehabilitate not only athletes but also other individuals who have suffered a mTBI by other means (Wilberger et al., 2006).

Evolving areas of mTBI research include the study of relationships between cerebral autoregulatory function and changes that occur post-mTBI as well as cerebrovascular reactivity and neurovascular changes. Evolution of diagnostic technology now allows researchers to effectively and efficiently monitor mTBI subjects non-invasively. This will contribute to our understanding of the pathophysiology of mTBI. Previous

reviews have been limited to predominantly more severely brain-injured subjects; however, as the research into mTBI continues to increase, the information gap remains.

This review focuses on the current research surrounding the pathophysiology of mTBI and in particular the impact on the cerebrovascular and cardiovascular systems, both of which are compromised during mTBI. In addition, the lack of a definitive set of diagnostic criteria for mTBI and the associated problems is discussed as well. Information included is primarily drawn from clinical studies on humans alongside a small number of animal studies. Particular emphasis is placed on the effect of mTBI on cerebral blood flow (CBF) and autoregulation, cerebrovascular reactivity, cerebral oxygenation, and neuroautonomic cardiovascular regulation.

Defining mild traumatic brain injury

The search for a unified definition of mTBI has been an ongoing process for decades and is an important consideration for not only medical professionals but also clinicians involved in sport and athletics. By implementing a definitive standard of characterizing mTBI, researchers can aid in facilitating the development of treatment and rehabilitation strategies as well as in increasing the understanding of the mechanistic properties of

these injuries. Differing opinions and beliefs have contributed to this struggle of a consensus agreement as to how mTBI should be characterized. The quest to define mTBI began in 1966 when the Congress of Neurological Surgeons proposed a description of mild head injury. Since then, researchers, physicians and clinicians have continued to develop various definitions that have progressively evolved to recognize the shifting paradigms surrounding mTBI.

When first introduced, the idea of mTBI was centred around generalized symptoms including altered mental state, vision problems and balance disturbances (Congress of Neurological Surgeons, 1966). Although providing neurological analyses, this explanation did not account for the underlying physiological and psychological processes affected by mTBI. Prominent symptoms such as headaches and nausea were not included and while generally accepted by physicians and researchers, the definition was the focus of much criticism. However, no other definition of mTBI was available at that time. For nearly 30 years, the definition of mTBI remained as proposed in 1966. In 1993, the American College of Rehabilitative Medicine revamped the accepted definition to include more specific symptoms. Loss of consciousness (LOC), amnesia, and the well-established Glasgow Coma Scale were introduced as defining characteristics of mTBI (Kay *et al.*, 1993). Alongside the previously acknowledged altered mental state and neurological deficits, this was the first definition of mTBI to outline objective criteria for diagnosis specifically.

Through the late 1990s, several operational definitions of mTBI were suggested (Alexander, 1995; American Academy of Neurology, 1997; Centers for Disease Control and Prevention, 1997; Kutner & Barth, 1998). For the most part, the defining characteristics put forward by the respective authors were in agreement regarding LOC, amnesia and Glasgow Coma Scale score. However, the Centers for Disease Control and Prevention (1997) in the United States proposed that mTBI may or may not involve LOC. Since this suggestion, the lowered significance of LOC in defining mTBI has been noted in the majority of recommended definitions (American Academy of Neurology, 1997; Centers for Disease Control and Prevention, 1997; Johnston *et al.*, 2001; Aubry *et al.*, 2002; Guskiewicz *et al.*, 2004; McCrory *et al.*, 2005; American College of Sports Medicine, 2006; Defense and Veterans Brain Injury Center Working Group, 2006).

Beginning with a generalized description and evolving into specific list of diagnosis criteria, mTBI has come full circle and returned to a generalized definition that outlines the non-specific symptoms that occur with injury. Since 2001, the suggested definition of mTBI is quite similar. This is partly due to the formation of the Concussion in Sport Group (CISG). The CISG comprises some of the foremost medical practitioners and researchers of mTBI in the world as it relates to sport-induced concussion. Most of the previously published definitions outlined included one, if not several, of the authors involved with this group. A landmark paper released by the CISG in 2002 outlined the basis of the consensus definition on sport

concussion which has been proposed to be synonymous with mTBI used throughout the world today (Aubry *et al.*, 2002). In 2005, the CISG released an updated position statement (McCrory *et al.*, 2005) following the 2nd International Conference on Concussion in Sport in Prague which maintained the previous definition as proposed in 2001 by Aubry *et al.* (2002). However, they added that in some cases, post-concussive symptoms may be prolonged or persistent. At this time, the Sport Concussion Assessment Tool (SCAT) was developed (McCrory *et al.*, 2005). Following the 2005 definition, the Centers for Disease Control and Prevention (2007) in the USA suggested a comprehensive definition of mTBI. The definition attempted to provide information to clinicians and medical practitioners regarding the individualized nature of mTBI.

In early 2009, the CISG (McCrory *et al.*, 2009) released the most recent proposed definition for mTBI that read:

‘Concussion is defined as a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces. Several common features that incorporate clinical, pathologic and biomechanical injury constructs that may be utilized in defining the nature of a concussive head injury include:

- 1 Concussion may be caused either by a direct blow to the head, face, neck or elsewhere on the body with an “impulsive” force transmitted to the head.
- 2 Concussion typically results in the rapid onset of short-lived impairment of neurologic function that resolves spontaneously.
- 3 Concussion may result in neuropathological changes but the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury.
- 4 Concussion results in a graded set of clinical symptoms that may or may not involve LOC. Resolution of the clinical and cognitive symptoms typically follows a sequential course however it is important to note that in a small percentage of cases, post-concussive symptoms may be prolonged.
- 5 No abnormality on standard structural neuroimaging studies is seen in concussion’

It is apparent that the current definition lacks objective diagnostic criteria and to date, no single definition of mTBI has encompassed the entire spectrum of diagnostic considerations surrounding mTBI. The quest for a unified, consensus definition of mTBI is an ongoing process and until the injury is further understood pathophysiologically, it may prove difficult to suggest an empirically sound description. A clearer definition will increase the accuracy of incidence rates and help shed light on a more definitive number of mTBIs that occur each year and may play a vital role in developing new injury prevention and rehabilitation strategies, and a potential means of diagnosis.

Incidence and epidemiology

In a recent review by the World Health Organization Collaborating Centre for Neurotrauma Task Force, it was estimated that up to 90% of all traumatic brain injuries are treated as mTBI

(Cassidy et al., 2004). Langlois et al. (2006) suggested that upwards of 3.8 million sports-related traumatic brain injuries occur in the United States each year and this number may still be underestimating the actual number of injuries. Furthermore, it is estimated that sport-related mTBI in the USA alone costs their health care system \$56 billion annually (Mihalik et al., 2005).

Due to the absence of a clear and accepted definition of mTBI, it is difficult to establish prevalence and incidence rates. The majority of studies use different inclusion and exclusion criteria and some do not list any criteria used in determining if the injury was in fact a mTBI. Regardless, the incidence of mTBI is continually increasing and remains an issue that needs to be addressed. While observing published incidence rates for mTBI, it also becomes clear that a consensus decision as to how to measure participation (athlete exposures, exercise hours, etc.) needs to be made. The first step in the process of understanding and conclusively defining mTBI is understanding the physiological mechanism(s) associated with these types of injuries.

General pathophysiology of mTBI

Previous research has provided excellent summaries of the neurometabolic and neuromechanical physiological changes following mTBI and will not be discussed in great detail in this review (Hovda et al., 1995; Giza & Hovda, 2001; Biasca & Maxwell, 2007). Werner & Engelhard (2007), Wilberger et al. (2006), and DeWitt & Prough (2003) have provided useful reviews on the pathophysiology of severe TBI. However, knowledge regarding the functional physiological deficits following mTBI remains relatively unknown. In fact, sport-induced concussion or mTBI is one of the least understood injuries facing the neuroscience and sports medicine community today (Thompson et al., 2005). This lack of information regarding pathophysiology of mTBI has been recognized, and furthermore, it has been suggested that the current research focus be directed toward the cerebrovascular response (Wilberger et al., 2006; McCrory et al., 2009).

Moderate and severe TBI results in autoregulatory and vascular reactivity impairment (DeWitt et al., 1992; Davis et al., 1998; DeWitt & Prough, 2003). Studies have shown that these responses following mTBI are similar (Junger et al., 1997; Strebel et al., 1997; Becelewski & Pierzchala, 2003). However, confounding results have shown these responses to actually be heightened, or in some cases nil, following mTBI (Becelewski & Pierzchala, 2003). It is suggested that the injured brain is more vulnerable to ischemic conditions that could lead to increased neurological damage (Junger et al., 1997). There is also emerging evidence that neural control of other physiological systems in the body is affected by mTBI. Greater resting heart rates as well as increases in heart rate following physiological and cognitive stress have recently been observed (Hanna-Pladdy et al., 2001; Gall et al., 2004a,b). Altered heart rate variability at rest and exercise has been witnessed along with increased sympathetic and lowered parasympathetic activity (Gall et al., 2004a,b). In addition, electrophysiological abnormalities found

using event-related potentials have been noted following mTBI (Gaetz et al., 2000).

There remains a great deal of 'unknowns' in the area of mTBI research and as physiological research on human subjects remains limited in the cerebrovascular area, this review will primarily consider the results of human studies, but when animal studies can add to the research, they will be included as well. The following information will discuss specific pathophysiological effects of mTBI related to CBF and oxygenation, cerebral autoregulation, cerebrovascular reactivity and neuro-autonomic cardiovascular dysregulation in an attempt to contribute to our understanding of the physiological mechanisms implicated with mTBI and appear to influence recovery from injury.

Specific pathophysiology of mTBI

Cerebral blood flow

Regulated control of CBF is essential in the fact that ischemia of the brain lasting 4–5 min results in irreversible brain damage and ultimately, brain death. The control of blood flow in the brain is accomplished by alterations in cerebral perfusion pressure (CPP) and cerebrovascular resistance (Golding et al., 1999a). CBF is defined as the ratio of CPP to cerebrovascular resistance. CPP is the difference between arterial and venous pressure in the brain and can be defined as: mean arterial blood pressure (MAP) minus venous pressure. Thus, CPP can be expressed as MAP minus intracranial pressure and subsequently, CBF can be considered a function of these variables. There are a number of mediating factors of CBF. For the purpose of this review, special attention will be focused on the effect of CPP and carbon dioxide production on CBF as both are influential factors in cerebrovascular pathophysiology.

CBF is known to decrease immediately following both TBI and mTBI and can remain lowered for extended periods of time dependent on severity (McQuire et al., 1998; Golding et al., 1999b; Giza & Hovda, 2001; Bonne et al., 2003; Grindel, 2003; Werner & Engelhard, 2007). In paediatric studies, CBF increased following mTBI on the day of the injury in younger subjects (<30 years old) and was then followed by a subsequent decrease in the following days (Mandera et al., 2002; Becelewski & Pierzchala, 2003). On the other hand, there were no significant differences observed in older subjects (>30 years) following mTBI suggesting that age may play a role in the moderation of CBF. Another study demonstrated that following mTBI, CBF remained elevated in injured subjects for an average of 1 day post-injury (Chan et al., 1992).

An interesting observation was made by Lang et al. (2003b) when they observed changes in blood flow velocity in response to changes in CPP and cerebrovascular reactivity. They found that blood flow velocity in the middle cerebral artery remained stable when CPP varied with preserved cerebrovascular reactivity. When cerebrovascular reactivity was impaired, it was found that blood flow velocity was increasingly dependent on CPP.

This indicates the importance of maintaining cerebrovascular reactivity following mTBI and also the idea that carbon dioxide plays a more important role in the regulation of CBF than previously thought.

Animal studies have shown mTBI to elicit a significant decrease in regional CBF 1 h after mild brain injury (Golding et al., 1999b). However, the researchers did not follow the rats longer than 1 h post-injury leaving the long-term physiological responses unmentioned.

Cerebral autoregulation

Cerebral autoregulation is the intrinsic ability of the brain to maintain a constant CBF in response to variations in systemic blood pressure (Junger et al., 1997; Strebel et al., 1997; Golding et al., 1999a; Czosnyka et al., 2001; Leddy et al., 2007; Werner & Engelhard, 2007). This phenomenon is typically observed in CPP between 50 and 150 mmHg (Junger et al., 1997; Golding et al., 1999a). As systemic arterial blood pressure is reduced, the cerebral vasculature will react by dilating, maintaining CBF and vice versa. The constriction and dilation of the cerebral blood vessels occurs primarily in the cerebral arteriolar and capillary beds (Edvinsson & Krause, 2002). Once the lower limit of autoregulation is reached, CBF will decrease passively in response to any further reduction in CPP. Likewise, as CPP increases past the upper limit of autoregulation, CBF increases. Figure 1 illustrates the traditional concept of cerebral autoregulation (Golding et al., 1999a). However, recent data has suggested that this relationship could be influenced by other variables including carbon dioxide and cardiac output (Ainslie & Duffin, 2009).

Traumatic injuries to the head can cause significant changes in intracranial blood pressure dependent on the severity of the injury. As cerebral trauma has the potential to cause intracranial haemorrhaging influencing intracranial blood pressure, changes

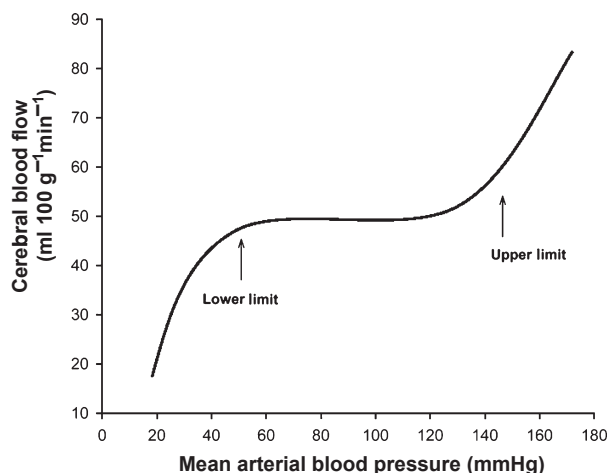


Figure 1 Concept of cerebral autoregulation. Cerebral blood flow values as a function of mean arterial blood pressure. Lower and upper limits of autoregulation are indicated.

in both CPP and arterial blood pressures occur as well (Ainslie & Duffin, 2009). Thus, the autoregulatory mechanism is very sensitive to any trauma or damage, from mild to severe, occurring to the brain or head (Junger et al., 1997; Strebel et al., 1997).

Following severe TBI, cerebral autoregulation is either lost or impaired (DeWitt et al., 1992; Junger et al., 1997; Strebel et al., 1997; DeWitt & Prough, 2003; Vavilala et al., 2006; Rangel-Castilla et al., 2008). The lowering of CPP as discussed above in response to traumatic injury is thought to contribute to this impaired autoregulatory response (Junger et al., 1997). Arterial hypotension often occurs following trauma and if cerebral autoregulation is impaired, the detrimental effects of this situation may be increased (Strebel et al., 1997) indicating the need for continued monitoring following even mild trauma (McCrory et al., 2005, 2009).

It is suggested that following TBI, the lower shoulder of the autoregulatory curve shifts to the right leaving subjects less able to deal with a lower CPP which could lead to ischemic injury (Lewelt et al., 1980). These changes gradually resolve and improve in the days following TBI (Lang et al., 2003b). Similar to TBI, autoregulation has been found to be lost or impaired following mTBI for up to 14 days (Junger et al., 1997; Strebel et al., 1997; Rangel-Castilla et al., 2008). If cerebrovascular reactivity is impaired, autoregulation seems to be less preserved following injury suggesting that cerebrovascular reactivity plays a more important role than the autoregulatory process (Lang et al., 2003b). As with TBI subjects, vulnerability to ischemic damage following mTBI may elicit a decrease in CPP (Junger et al., 1997) and is a primary concern in returning to activity following injury as second impact syndrome, a fatal result of repeated head trauma, may occur. Conceptually, cerebrovascular reactivity has been shown to operate similar to autoregulation, but it is not identical and is discussed below (Lang et al., 2003b).

Cerebrovascular reactivity

Carbon dioxide is a potent cerebral vasomotor agent indicated by the typical rapid increase or decrease in CBF in response to increases or decreases in the partial pressure of arterial carbon dioxide (PaCO_2) and thus is a significant mediator of cerebrovascular reactivity. Cerebrovascular responses to PaCO_2 are typically greater than the autoregulatory response to CPP (Panerai et al., 2000) suggesting that it may be a more sensitive mediator of CBF regulation. Up to a 5% increase in CBF following a 1 mmHg increase in PaCO_2 has been cited in the literature demonstrating the sensitivity of the brain to blood flow changes with minimal biochemical change (Ide et al., 2003; Akca, 2006; Rangel-Castilla et al., 2008). The normal range of PaCO_2 is 35–45 mmHg with hypocapnia being defined as a $\text{PaCO}_2 < 35$ mmHg and with hypercapnia being >45 mmHg (Akca, 2006). PaCO_2 changes will affect the cerebrovascular constriction mechanisms and possibly lead to decreased CBF. As shown in Fig. 2, Ainslie & Duffin (2009)

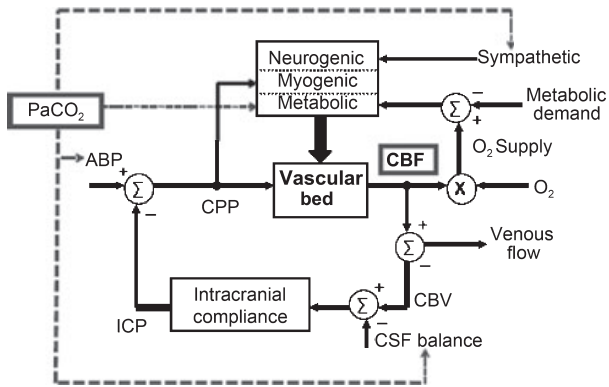


Figure 2 Main mechanisms responsible for control of cerebral blood flow (CBF). Hyphenated lines indicate areas, direct and indirect, in which arterial PaCO_2 (PaCO_2) may influence CBF. ABP, arterial blood pressure; ICP, intracranial pressure; CSF, cerebrospinal fluid; CPP, cerebral perfusion pressure; CBV, cerebral blood volume. Reprinted from *Med Eng Phys*, 25(8), Panerai, The critical closing pressure of the cerebral circulation, 621–632, Copyright (2003), with permission from Elsevier as modified in *Am J Physiol Regul Integr Comp Physiol*, 296(5), Ainslie and Duffin, Integration of cerebrovascular CO_2 reactivity and chemoreflex control of breathing: Mechanisms of regulation, measurement, and interpretation, 1473–1495, Copyright (2009).

outline the primary mechanisms responsible for the control of CBF with emphasis on areas in which PaCO_2 has a major influence on CBF. As PaCO_2 is a potent moderator of vasoconstriction and dilation, it has a seemingly more direct impact on the cerebral vasculature as do changes in CPP. Considering this, one can understand why autoregulation and cerebrovascular reactivity operate seemingly independent of each other, but yet both are affected by head trauma.

Recently, studies have shown that cerebral autoregulation is not correlated with cerebrovascular reactivity in normal and diseased (i.e. TBI, stroke, hemorrhage) subjects (Singhal & Markus, 2005; Gommer et al., 2008; Carrera et al., 2009). However, as with cerebral autoregulation, there are conflicting results regarding the effect of mTBI on cerebrovascular reactivity. Differences between younger and older subjects have been indicated. A recent study indicated that cerebrovascular reactivity is decreased in younger subjects (<30 years old) following mTBI (Becelewski & Pierzchala, 2003). However, the same study observed that there was no change post-injury in older subjects (>30 years old). Although not discussed in detail, the authors suggested that the changes in younger patients seemed to be connected with the altered activity of the autonomic nervous system. This line of reasoning warrants further investigation.

Enevoldsen & Jensen (1978) also suggested that preserved autoregulation associated with impaired cerebrovascular reactivity indicated very severe brain damage and that impaired autoregulation associated with preserved cerebrovascular reactivity suggested moderate or severe brain damage during recovery. Also, complete absence of cerebrovascular reactivity has been shown to carry a poor prognosis and usually accompanies a terminal event. The associated factors related to

this loss of cerebrovascular reactivity seem to be relatively unknown. The idea that the loss of cerebrovascular reactivity following mTBI is a result of metabolic factors (ions, neurotransmitters, hormones, etc.) rather than direct injury to blood vessels which has also been suggested (Golding et al., 1999b), but research into the actual causes remains very limited. As shown in Fig. 2, the numbers of pathways PaCO_2 can take to influence CBF ultimately as compared with changes in CPP coupled with the effect of PaCO_2 on CPP indicate that CO_2 plays a key role in CBF regulation. These findings, along with those mentioned above by Lang et al. (2003b), affirm the idea that cerebrovascular reactivity is, more so than cerebral autoregulation, a crucial indicator of not only CBF regulation but also injury severity.

It is interesting to note that in animal studies, it has been demonstrated that mTBI impairs CBF response to carbon dioxide, whereas moderate-to-severe TBI abolishes any such response to carbon dioxide in acute stages (Enevoldsen & Jensen, 1978; Golding et al., 1999a). Enevoldsen & Jensen (1978) suggested that this abolition with TBI may be due to the disconnection between the brain stem and cortex, leading to a 'false' autoregulatory response. In a study involving mild brain-injured rats, it was observed that 30 min following injury, responses to hypercapnia were significantly blunted as were responses to hypocapnia (Golding et al., 1999b). Similar findings in humans have also shown abnormalities in CBF velocity response in the middle cerebral artery following physiological stress in the concussed state (Len et al., 2009). Figure 3a,b illustrate CBF velocity response to hypercapnic and hypocapnic challenges in varsity hockey players suffering a recent mTBI (unpublished data from our laboratory). Responses to both physiological challenges are diminished in mTBI-injured subjects in comparison with non-injured matched control subjects.

It is apparent from the literature that cerebrovascular reactivity is affected following mTBI, but still not totally understood. Commonly observed in more severe brain injuries, response to changes in PaCO_2 levels can provide future researchers with additional information regarding the physiological changes associated with mTBI. This information would be invaluable as cerebrovascular reactivity is easily monitored in a non-invasive manner.

Cerebral oxygenation

The available literature on the effects of mTBI on cerebral oxygenation levels is very limited. However, there is research available that has observed cerebral oxygenation changes following moderate-to-severe TBI (Bhambhani et al., 2006). It is known that metabolic and neural activity escalate following mTBI which leaves the injured brain in a state of increased oxygen demand (Giza & Hovda, 2001; Jantzen et al., 2004). Some research has used fMRI to record the blood oxygenation level-dependent (BOLD) signal to show that mTBI-injured athletes have different brain activation responses than control

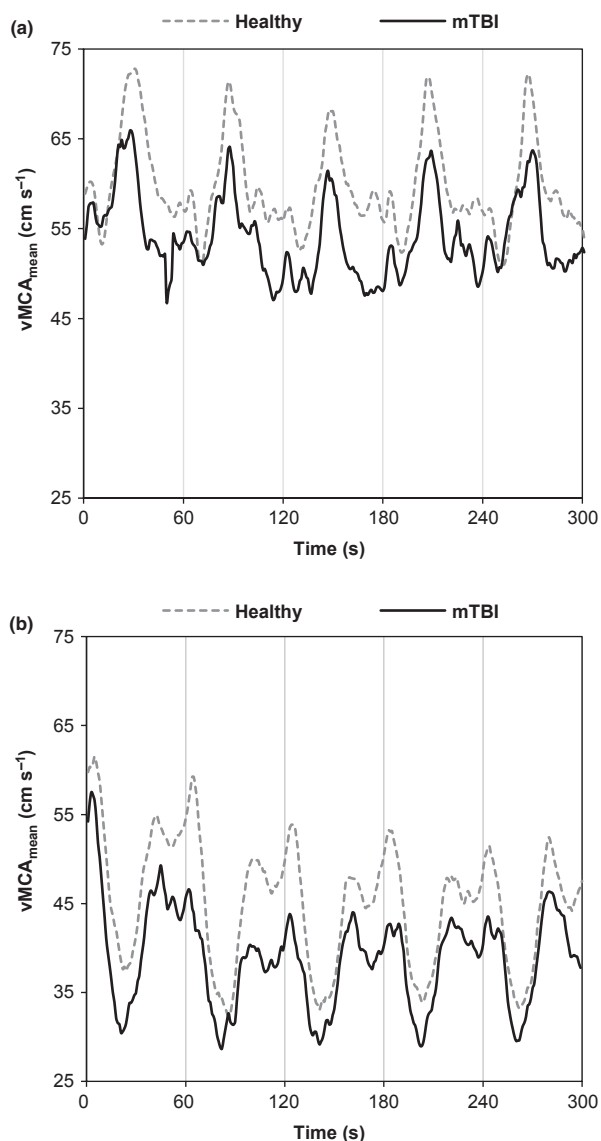


Figure 3 (a) Hypercapnic and (b) hypocapnic responses in healthy and mild traumatic brain injury (mTBI)-injured subjects. Data illustrate cerebral blood velocity response to five consecutive 20 s (a) breath holds and (b) hyperventilations in healthy ($n = 10$) and mTBI-injured ($n = 3$) subjects. 40 s of normal breathing occurred between each repetition. Note the diminished response in mean middle cerebral artery blood velocity ($vMCA_{\text{mean}}$) in the mTBI-injured subjects (unpublished data from our laboratory).

subjects (Chen et al., 2004; Jantzen et al., 2004; Davis et al., 2009). Concussed athletes displaying a higher activation pattern using fMRI imaging have been shown to have an increased recovery time (up to 25 days longer) than those demonstrating normal activation (Lovell et al., 2007).

Brain activation is dependent upon changes in blood haemoglobin concentration and as such, utilizing near infrared spectroscopy (NIRS) has been effective in monitoring changes following mTBI. Previous research has also shown that the fMRI BOLD signal is well correlated with the deoxygenated-haemoglobin of the NIRS suggesting that NIRS can be used to monitor

oxygenation changes in mTBI (Kleinschmidt et al., 1996). It is not possible to perform this type of physical exercise during MRI assessment.

Results using NIRS indicate that cerebral oxygenation is significantly reduced (up to a 35% decrease) on day one following mTBI, and appears to be unresolved up to 7 days following the injury (Cote et al., 2006). It was also observed that there was up to a 20% reduction in oxygen saturation 1 day post-mTBI during moderate-to-intense exercise (HR = approximately 155 bpm). This study provides important information on two aspects of mTBI. First, it demonstrates that tissue oxygenation changes can be monitored during mild-to-moderate aerobic exercise following mTBI. Second, the results indicate that the injured brain has not recovered within 24 h of injury and exercise following mTBI needs to be implemented in a step-wise progression as suggested by the CISG (Aubry et al., 2002; McCrory et al., 2005, 2009).

With little research available on the effects of mTBI on cerebral oxygenation, one can consider the effects of TBI. Cerebral oxygenation is typically reduced following TBI (Dings et al., 1996; Daugherty et al., 2004). A transient increase in cerebral haemoglobin saturation (27%) followed by a profound decrease (45%) was observed 30 s post-injury in young rats (Armstead & Kurth, 1994). In the same study, juvenile rats showed a modest increase of 10% followed by a mild decrease of 4%. Although found in the rat model, these results are similar in concept to those found in the cerebrovascular study by Becelewski & Pierzchala (2003) where they showed that younger subjects seem to be more affected by injury than older subjects. This reduction in cerebral oxygenation may lead to the development of a disproportionate oxygen consumption – demand relationship. This mismatch can lead to ischemic or hypoxic situations resulting in secondary brain tissue damage (Werner & Engelhard, 2007).

A link between CBF and oxygen consumption has been observed in TBI patients and it is suggested that it becomes temporarily uncoupled post-injury (Obrist et al., 1984). A critical cerebral oxygenation threshold of 10–15 mmHg has been established, below which neuronal cell death occurs (Werner & Engelhard, 2007). When combining the decrease in cerebral oxygenation with the associated decrease in CBF post-injury, profound hypoperfusion of brain tissue may occur (Buchner et al., 2000). The increased oxygen demands of the TBI-injured brain stress the autoregulatory and cerebrovascular reactivity responses to physiological disturbances. Cerebral oxygenation and cerebral autoregulation have been shown to be mutually correlated and when autoregulation is preserved, smaller changes in cerebral oxygenation in response to CPP changes are observed (Lang et al., 2003a).

Neuroautonomic cardiovascular regulation

The cardiovascular system is under autonomic control. The coupling of the autonomic nervous system and cardiovascular system can then be referred to as neuroautonomic cardiovas-

cular regulation, and thus is the ability of the human body to coordinate dynamically these two body systems. Typical analysis involves monitoring heart rate variability, a measure of fluctuation around the mean heart rate, which reflects the activity of the sympathetic and parasympathetic divisions of the autonomic nervous system. The heart rate variability technique is widely accepted as an applicable method in evaluating autonomic function and balance between the sympathetic and parasympathetic nervous systems and has been used in many lines of research, including athletic training, critical care and other experimental research (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Zhang et al., 2002; Gall et al., 2004a). It has been proposed that there is a neuroautonomic cardiovascular dysregulation, an uncoupling between the autonomic nervous system and the cardiovascular system, following mTBI (Goldstein et al., 1998; Gall et al., 2004a,b).

Goldstein et al. (1998) illustrated that the autonomic and cardiovascular systems become uncoupled following acute brain injury. Furthermore, as the degree of injury increases, the level of neuroautonomic cardiovascular regulation impairment proportionally increased as well (Goldstein et al., 1993, 1998). Power spectral analysis of heart rate variability diminishes in proportion to the degree of neurological injury suffered and approaches zero during brain death. Autonomic impairment occurs on multiple levels stemming from the brain to the peripheral vasculature. As recovery from brain injury progresses, heart rate variability begins to return to near healthy levels (Goldstein et al., 1998).

The original hypothesis of Goldstein et al. (1998) was recently tested in an athletic group using heart rate variability. Gall et al. (2004a) examined heart rate variability of junior hockey players in British Columbia, Canada, suffering a recent mTBI. They observed that at rest there were no differences in any of the heart rate variability measures recorded between the mTBI-injured subjects and the healthy controls. However, once exercised, a perturbation to cellular homeostasis, the mTBI-injured group demonstrated a significant decrease in some of the heart rate variability measures in relation to the healthy control subjects. As mTBI typically involves a mild neurological disruption, the severity of the injury may not have been sufficient to warrant any significant changes at rest. Interestingly, once physiological stress was induced, significant changes began to occur. Abnormal heart rate variability has been observed in athletes suffering mTBI up to 10 days post-injury during submaximal exercise (Gall et al., 2004a). Unpublished data from our laboratory illustrated similar phenomena of physiological stress-induced changes in CBF response following mTBI as shown in Fig. 3a,b.

Another study of interest examined the effect of removing autonomic neural activity with ganglion blockade using trimethaphan on cerebral autoregulation (Zhang et al., 2002). It was suggested that by removing neural control, both dynamic (regulation of CBF in response to rapid changes in arterial blood pressure) (Paulson et al., 1990) and static (responsible for

maintaining CBF in response to gradual changes in cerebral perfusion (Zhang et al., 2002) cerebral autoregulation were altered, indicating that neuroautonomic cardiovascular regulation plays a major role in cardiovascular homeostasis in humans. If we consider impairment in neuroautonomic cardiovascular regulation to occur following mTBI, and this impairment to emulate removal of neural control, it can be suggested that deficits in neuroautonomic cardiovascular regulation will be correlated with abnormal cerebrovascular responses. Zhang et al. (2002) also suggested that the absence of neuroautonomic activity alters the beat-to-beat pressure-flow velocity relationship in humans indicating that the effects of neuroautonomic cardiovascular regulation impairment can affect the entire body. These findings form the basis for the notion that the effects of mTBI are more systemic than previously believed.

Summary

Over the last few decades, advancements in knowledge surrounding the short- and long-term pathophysiological consequences of mTBI have been exponentially increasing. Switching focus to understanding the physiological mechanisms involved in mTBI will aid in determining what factors are needed for consideration regarding recovery and to help evolve the management of these injuries. However, the lack of quality research in this area is still evident. As suggested by Ainslie & Duffin (2009), the tendency of researchers to examine each of the different aspects discussed in this review (CBF, autoregulation, etc.) as a separate entity rather than taking an integrative, systemic approach may be hindering the evolution of research in this area. It is apparent that there are observable changes in the physiological functioning of the brain and body following mTBI including the importance of CO₂ in the regulation of CBF and the independency of cerebral autoregulation and entire cardiovascular system. Although the current accepted return-to-activity guidelines are based largely on neuropsychological test results, the pathophysiological changes must be considered as well. Future research into mTBI should include an increased focus on the pathophysiological effects to aid in understanding not only these physiological symptoms but also the systemic effect of the injury. Further understanding of these mechanisms may provide some unique and distinctive perspectives as to the effective management of mTBI.

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