

Autonomic, cerebrovascular and mild traumatic brain injury physiology: Linkages and future applications

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Approximately 250,000 youth sustain a sport-related concussion annually; however, practical and cost-effective methods of assessment have yet to be established. Recent research shows that cerebrovascular measures, which are pervasive with traumatic brain injuries, have successfully been applied to concussions, and have enhanced the understanding of

Despite the hyper-awareness of brain injury, particularly in contact sports, there is still no 'gold standard' for tracking recovery, let alone a physiological benchmark. This is surprising, especially considering that more than one million individuals will sustain a traumatic brain injury (TBI) this year in North America alone, and that an additional 1.6 to 3.8 million will sustain a mild TBI (mTBI). This is particularly startling, considering the National Collegiate Athletic Association in the United States, and high school injury surveillance systems both indicate that popular North American contact sports have high incidences of concussion when reported as rates of injury per number of athlete exposures (1,2). Even more alarming is that these numbers only represent the documented sport-related injuries. This is likely a conservative figure for total mTBIs sustained because these injuries are also acquired through other means, such as motor vehicle collisions, military operations and recreational activities (1-4).

To complicate matters, the physiological gold standard being sought is inherently part of complex physiological systems, and often leaves more questions regarding what the biomarker represents than how such biomarkers can further be used to index recovery. Recently, several review articles have suggested that monitoring cerebrovascular indexes may hold promise as a means to examine the potential mechanisms of mTBI (5,6). In particular, cerebrovascular reactivity (CVR) to carbon dioxide (CO₂) has been shown to be altered following concussion in a limited number of human studies (7-10). These articles highlight recent mTBI cerebrovascular measures (which will be re-addressed and updated in the present article), and also point to physiological mechanisms that may underpin the altered cardiovascular physiology. Generally, these articles focus on nitric oxide (NO)- and CO₂-induced changes in cardiovascular signals (5,6). What appears to be missing are the possible linkages between a frontal lobe injury and the regulation of blood flow in the medulla. To address this, the present review focuses first on the complex integration of autonomic and cardiorespiratory physiology, and will then explore overlapping mTBI physiology, with applications to mTBI-cerebrovascular measures.

AUTONOMIC NEURAL CIRCUITRY AND PHYSIOLOGY

The following paragraphs will discuss the neural circuitry that dictates the regulation of the autonomic nervous system's stress response. This is imperative for understanding the links among arousal, executive

mild traumatic brain injury pathophysiology. The present article reviews autonomic, cerebrovascular and concussion physiology, and attempts to address some potential linkages that explain why blood flow measures are impaired. Future applications for hemodynamic concussion research will also be suggested.

Key Words: *Autonomic regulation; Cerebrovascular physiology; Concussion; Near-infrared spectroscopy; Transcranial Doppler*

function and cerebrovascular physiology and, thus, its implication for mTBI. Specifically, cortisol and the regulation of its precursors will be discussed because cortisol synthesis and feedback mediate crucial junctures within the medullary and limbic network. In turn, this can influence arousal, executive function, neurovascular physiology (via medullary inputs) and, thus, could affect mTBI pathophysiology (and mTBI symptoms). The discussion of cortisol and the regulation of cortisol precursors will be followed by a brief overview of the nervous system from a 'global' perspective, which will highlight how afferent and efferent signals are integrated with autonomic regulation. Again, this is important for understanding how concussion-induced changes in the frontal lobe link psychological changes to cerebrovascular changes.

Cortisol synthesis: Cortical-limbic interactions and regulation

Cortisol is synthesized as a result of elevated levels of corticotropin-releasing factor (CRF), which stimulates the synthesis of pro-opiomelanocortin (POMC); POMC is cleaved to create adrenocorticotrophic hormone (ACTH) and pro-opiate factors (11-15). Once ACTH is released into systemic circulation, all three zones of the adrenal glands are stimulated to release cortisol (16-18). It is also noted that CRF, POMC-ACTH and cortisol all use cyclic (c)AMP as a second messenger system when binding to their respective receptors (11,12,19). It is noted that cAMP has previously been implicated in creating postsynaptic electrochemical variance and modifying cellular metabolism. Hence, CRF and cortisol have been classified as synaptic neuromodulators (that also regulate autonomic states). This is because numerous cellular homeostasis models have characterized cAMP to have regulatory properties that are both feed-forward (eg, protein kinase A/C activation) and feedback (eg, receptor density changes) in nature (20,21). It is also important to consider that disrupting cAMP's contribution to intracellular ion variance through injury does, in fact, have the potential to alter cellular processes and, more globally, alter input to other brain areas.

The CRF-cortisol synthesis pathway is regulated through various anatomical inputs that 'fine-tune' the intracellular ion and cAMP changes. Generally speaking, the anatomical locations whose inputs have been cited as having a significant effect on CRF release are areas with adequate levels of glucocorticoid (type II – 1× affinity) and mineralocorticoid (type I – 10× affinity) cortisol receptors (11). This is because these same cortisol receptor sites (along with secondary neural

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TABLE 1
Anatomical location of mineralocorticoid (type I) and glucocorticoid (type II) cortisol receptors in the rat brain

Region	Type I (10× affinity)	Type II (1× affinity)	Total	%
Hippocampus	414	305	719	45.19
Lateral septum	51	194	245	15.40
Nucleus of solitary tract	76	123	199	12.51
Amygdala	9	112	121	7.61
Locus coeruleus (LC)	41	75	116	7.29
Paraventricular nuclei	28	59	87	5.47
Supraoptic nuclei	0	60	60	3.77
Raphe nuclei	0	44	44	2.77

Type I and type II receptor densities are expressed in fmol/mg protein. Data adapted from reference 13

inputs), will exert their cAMP-protein kinase A/C alterations onto sites that promote and suppress CRF synthesis. As shown in Table 1, sites within the rat brain associated with detection (and direct regulation) of cortisol have type I and II receptor densities (in fmol/mg protein) that are similar to humans (13). This research points to the hippocampus as the primary detector of cortisol, and is in agreement with the hippocampus' role as a tonic negative feedback influence on CRF-cortisol production (21,22).

While knowing the hippocampus has a tonic role in the regulation of the CRF-cortisol synthesis pathway, it is still only one neural site among many that influence CRF production. In fact, the anterior cingulate cortex (ACC), the amygdala, the bed nucleus of stria terminalis (BNST), the locus coeruleus (LC) and the paraventricular nucleus' (PVN) magnocellular and parvocellular projections, are also integral to CRF regulation (13,21). While these areas are all inter-related, it is noted that the magnocellular and parvocellular nuclei are the main sites of CRF production, with the magnocellular division also cosynthesizing arginine vasopressin (12).

With the PVN produces the majority of CRF, it is implied that the remaining structures (ACC, hippocampus, amygdala, BNST and LC) act as mediators of this synthesis pathway, although this is an oversimplification of an inherently complex model. Although all of the aforementioned structures do have some innervations to the PVN, the majority innervate the BNST, which subsequently stimulates the PVN (23-26).

What is interesting is that retrograde immunolabelling from the PVN to the BNST indicates gamma-aminobutyric acid (GABA) inhibitory neurotransmitter release (21-23,27). However, site-specific research investigating the BNST has shown that only the posterior-medial sections (which are innervated by the hippocampus) are involved with inhibitory neurotransmission. In essence, excitatory stimulation from the hippocampus causes the BNST to release inhibitory neurotransmitters (such as GABA) from the BNST onto the PVN and, thus, inhibit CRF production. Conversely, the anterior-lateral portions of the BNST (which are innervated by the amygdala) are associated with inhibitory (GABA) stimulation, from the amygdala onto the BNST. This suppresses/competes with the hippocampus' CRF inhibitory drive (through excitation of the BNST) and leaves the paraventricular nuclei 'more open' to other inputs, such as the LC, which can increase cAMP through norepinephrine (NE) neurotransmission. Thus, the amygdala 'primes' a sympathetic response by disinhibition of the BNST. This leaves the paraventricular nuclei with less GABA stimulation and more opportunity to be influenced by other sources (22,25).

As a side note, the neurotransmitters at play within the amygdala and hippocampus were confirmed using messenger RNA expression. It revealed large GABA (inhibitory) and glutamate (excitatory) expression profiles within the amygdala and hippocampus, respectively (23). Again, this has furthered the understanding of how the BNST innervations from higher limbic structures can influence the BNST's GABA

release on the PVN and, thus, CRF synthesis. Furthermore, while the main findings were that a large portion of genetic expression from the amygdala is GABAergic, and that the hippocampus utilizes excitatory processes, it was also noted that the ACC's genetic profiles were largely glutamergic (excitatory). Again, this links the amygdala's role in CRF production (and sympathetic shifts) to that of disinhibition, and the hippocampus/ACC to that of inhibition and suppression of CRF synthesis (23).

This leaves the LC's role in CRF regulation to be discussed, and its importance as part of the complex interaction with other neural pathways implicated in mTBI. These nuclei have other very important roles worth mentioning because it is the primary site of NE synthesis and projects to the anterior cingulate cortex, BNST, amygdala and the hippocampus, and has a higher mineralocorticoid receptor density in the rat brain than the amygdala (13). Interestingly, both NE and CRF second messengers rely on cAMP to exert feed-forward and intrinsic feedback modifications for electrochemical homeostasis. Furthermore, this nucleus is located in the medulla, thus implicating its activity with cerebrovascular responses.

Moreover, this same anatomical location also implies that the LC is part of a neural hub for efferent and afferent signal integration. Hence, it is also a site for maintaining current arousal states because the LC is impacted by global (ie, visceral and peripheral) arousal integration. Evidence for signal integration stems from the LC's neural activity, where NE neurotransmitters are released at both tonic and phasic frequencies (tonic: 2 Hz to 3 Hz when awake and <1 Hz when asleep; phasic: two to three bursts, followed by sustained activity of 200 ms to 300 ms). Tonic pulses are believed to be more related to current activity (and possibly metabolic state) of the body; hence, why observations are noted in sleep-wake cycles. Conversely, phasic firing rates are believed to be part of complex top-down and bottom-up psychophysiological efferent and afferent integration that is involved with vigilance and arousal (13,28,29).

Therefore, the LC is typically identified as a nucleus that is both maintaining current states of activity/metabolism, and is moderating emotional context found in top-down and bottom-up processes. Relating this to the regulation of autonomic function, it is because the LC projects NE to higher brain centres, which are also associated with autonomic regulation due to the feed-forward and intrinsic feedback mechanisms that are related to NE- and CRF-induced cAMP release. Based on the projections of the LC, the contributions to CRF synthesis can be direct (innervating the PVN), or can be through the contribution of electrochemical variance via the amygdala, hippocampus and other parts of the frontal lobe. Thus, the LC is not only involved with vigilance and metabolism for top-down and bottom-up integration, but is also directly and indirectly involved with a circadian-based tonic influence of cortisol's cAMP second messengers (13,28,29).

From a global neural network perspective, the processes of cellular homeostasis and autonomic homeostasis are integrated and give rise to healthy variance and complexity. This complexity and variance is further integrated as autonomic information is unified with environmental/psychological stimuli. An example of 'fused' autonomic and cognitive information is the identification of a perceived cognitive threat that stimulates a visceral response. This example sympathetically shifts the state of the nervous system (via frontal lobe withdrawal), thus priming sympathetic requirements (13). This example carries forth the concepts of highly variant and complex systems because a shift in sympathetic state indicates the global health of the dynamic system. Moreover, the health of the system can also be gauged by the regulatory variances that the subcomponents exert on one another. Should one system become unbalanced (ie, from a disease or brain injury), the parts of system's healthy variance can become dominated by the limits of a particular disease or injury. Hence, decreased variance and complexity (such as approximate entropy) are observed (30). In accordance with this concept, an 'executive homeostatic network' has been proposed (Figure 1), in which cortical, limbic and medullary structures are continuously using top-down and bottom-up

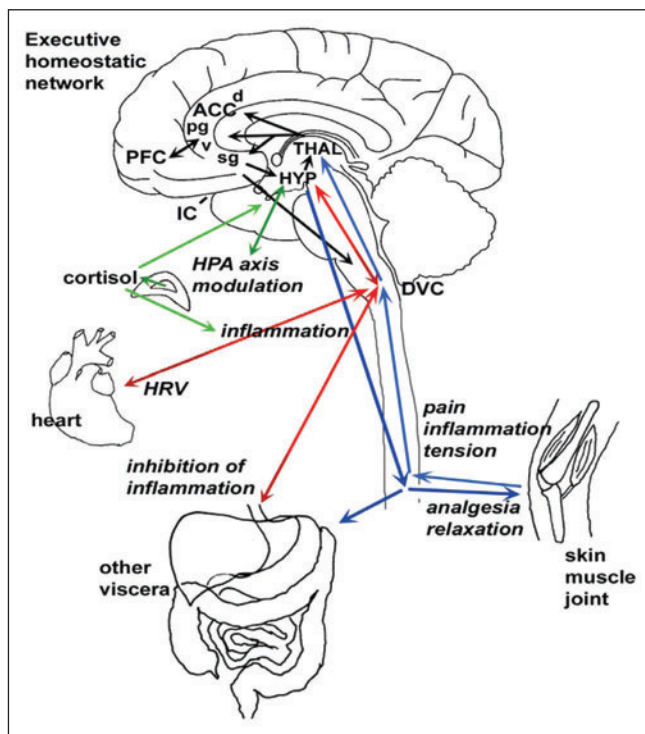


Figure 1) Diagram of the executive homeostatic network with some important cortical and subcortical relays, and the relation to the respective afferent and efferent pathways. ACC Anterior cingulate cortex; DVC Dorsal vagal complex; HPA Hypothalamic-pituitary-adrenal axis; HRV Heart rate variability; HYP Hypothalamus; IC Insular cortex; PFC Prefrontal cortex; pg Pregenuial; sg Subgenual; THAL Thalamus. Reproduced with permission from reference 31

psychophysiological efferent and afferent pathways (31). These interactions include hemodynamic measures (such as cerebral autoregulation and heart rate variability), and also encompass other peripheral variances such as training-induced musculoskeletal alterations and changes to immunity.

As previously mentioned, brain injury can limit the healthy variance of the global system. This is because the efferent and afferent potentials that are constantly being processed no longer have the luxury of the healthy cellular electrochemical (and metabolic) variance provided by synaptic modulators such as cAMP. Hence, this may explain why researchers have been able to find changes in post-mTBI cardiovascular measures in postexercise settings, during blood pressure stimulations and increased CO₂ build up (7-9,32,33).

To further understand how frontal lobe damage (which often accompanies mTBI during acceleration-deceleration injuries) and decreased healthy variance can contribute to altered cardiovascular measures, the following section discusses relevant anatomical locations and processes within the executive homeostatic network that relate to cerebrovascular physiology. Part of this discussion will focus on how the LC's neurotransmitter release of NE (and cAMP production) can potentially link frontal lobe damage to altered cardiovascular responses (30,31,34).

CHEMODETECTION PHYSIOLOGY

Metabolic status is monitored by central and peripheral chemodetection mechanisms. Specifically, central CO₂ (and thus pH) is monitored by a diffuse chemodetection network that exists within the medulla (Figure 2). In addition to the caudal and rostral ventral respiratory groups, the retrotrapezoid nucleus and the Bötzing complex, there exist previously mentioned nuclei that are crucial for autonomic regulation. This includes the LC, the raphe nucleus, the nucleus of the

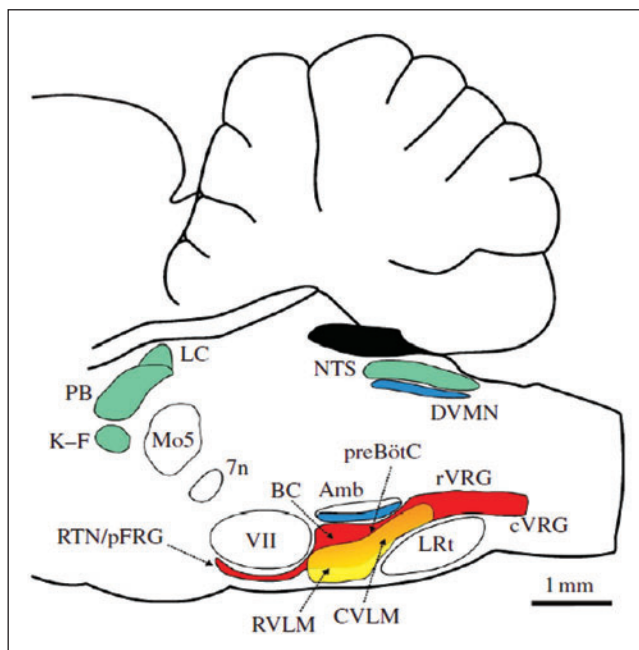


Figure 2) Saggital view of central chemodetection nuclei found within the medulla. Amb Nucleus ambiguus; BC Bötzing complex; cVRG Caudal ventral respiratory group; CVLM Caudal ventrolateralmedulla; DVMN Dorsal vagal motonucleus; K-F Kolliker-Fuse nucleus; LC locus coeruleus; LRt Lateral reticular nucleus; Mo5 Motor trigeminal nucleus; NTS Nucleus of the solitary tract; PB Parabrachial nucleus; preBötC Pre-Bötzing complex; RTN/pFRG Retro-trapezoid nucleus/parafacial respiratory group; RVLM Rostral ventrolateral medulla; rVRG Rostral ventral respiratory group; VII Facial nucleus. Reproduced with permission from reference 35

solitary tract and the dorsovagal motonucleus (35). Hence, it is apparent that autonomic regulation and chemodetection physiology are inherently linked, which can be evidenced by circadian-like rhythms found with CO₂ reactivity (36). This also means that arousal states and executive functioning can potentially modulate central chemodetection and, thus, ultimately affect symptoms during mTBI.

Peripheral metabolic monitoring uses chemoreceptors that are found on the carotid artery, which feed into the carotid sinus nerve (a branch of the glossopharyngeal nerve). A secondary source of peripheral chemodetection stems from chemoreceptors found on the aortic arch, which feeds into the vagus nerve. The glossopharyngeal nerve feeds into the nucleus of the solitary tract and the vagus nerve originates in the dorsal vagal motonucleus (35,37,38).

Because of the anatomical location of the peripheral and central detection sites, it has been proposed that peripheral chemodetection identifies the metabolic state of blood flowing toward the brain and electrochemically stimulates the central detection site. Thus, peripheral chemodetection allows for 'sampling' of the metabolic state of the body after external respiration, which is crucial for integrating responses with central chemodetection (36).

An important aspect of the mechanisms of chemodetection is that blood flow to the medulla must be inversely related to CO₂ detection and respiration (36,39). This is partially because needless increases in blood flow (with no change in metabolite concentration) can decrease CO₂ detection sensitivity, and give a 'false reading' of metabolic status. Thus, a needless increase in flow can 'dilute' the CO₂ concentration, which can negate the real need for vasodilation, vasoconstriction or altered respiration. Furthermore, the need for tight flow-metabolite detection coupling is very important during exercise because the central and peripheral signals must accurately infer when the amount of CO₂ detection is at capacity for the exercise-induced flow volume. At

this point, cardiorespiratory centres reach the neural threshold, thus causing ventilation and heart rate to exponentially increase to further increases in work (36). This aforementioned process occurs concomitantly with efferent and afferent signalling and, thus, requires a large amount of intracellular electrochemical variance; hence, why altered inputs from higher brain centres may contribute to false readings or altered cardiovascular outputs.

Regarding CO₂ sensitivity (outside of circadian patterns), research has indicated that the partial pressure of CO₂ between 35 mmHg and 55 mmHg is the range of physiological detection sensitivity. This sensitivity is believed to have the greatest effect on arterioles and precapillary sphincter radius. Specifically, increased levels of CO₂ (hypercapnia) causes the smooth muscle of smaller blood vessels to relax, whereas hypocapnia causes vasoconstriction across a significantly wider range of vessels and diameters. Moreover, research on the association of hypercapnia with increased vessel radius and higher metabolism indicates that increased CO₂ levels are associated with sympathetic nervous system shifts because increased peripheral muscle activity obviously increases aerobic respiration.

Despite observing flow changes in the presence of altered CO₂ levels, the mechanisms by which this occurs remain unclear. One of the main factors is believed to be regional pH decrements because a decrease in pH will activate ATP-potassium and voltage-gated potassium channels. It is noted that both CO₂ and lactate can decrease pH because both are important metabolites for blood flow signalling (40). Remembering that cells have higher intracellular concentrations of potassium, an influx will cause a hyperpolarization of cells. This hyperpolarization will cause intracellular calcium channels to deactivate, which will limit calcium-calmodulin activity and, thus, inhibit smooth muscle contraction (36,41-43). This mechanism may also be associated with other unknown events that characterize 'endothelium-derived hyperpolarization factor' (43).

NO is an additional mechanism that has an effect on hypercapnia; previous research has indicated that arteriovenous differences in surrogates for NO have increased with elevated CO₂ (44,45). It should be noted that NO production can be activated through cAMP and calcium-calmodulin pathways, which can be activated through the myriad autonomic pathways previously stated. Finally, astrocytes can cause vasoconstriction via glutamergic activation of arachidonic acid as well as vasodilation via prostaglandin release. The prostaglandin reduces myosin light-chain phosphorylation and can hyperpolarize smooth muscle, which in turn inhibits calcium-induced vasoconstriction (40).

To summarize chemodetection (and CO₂ reactivity), it is noted that detecting a metabolite that represents the current energy state of the body must be linked to the current arousal and the executive functioning status of the body. Where the physiology becomes cumbersome is trying to understand how a constant blood flow to the medulla is achieved so as to ensure as few 'false detections' of metabolic state as possible. More specifically, both NO and potassium can elicit changes to vessel radius, and are prone to calcium and cAMP activation. To make matters more complex, consider that the efferent and afferent stimuli will directly be modifying intracellular ion concentrations (thus altering the capacity for vasodilation by changing potassium concentration). These top-down and bottom-up integrations also stimulate the LC, which will modify cAMP levels and NO output. Naturally, these stimulations apply to altered inputs due to brain injury and, thus, contribute to altered cerebrovascular changes.

Neurovascular coupling physiology

Neurovascular coupling is characterized as the matching of localized blood flow to metabolic needs of the neural tissue in which the heightened cortical and subcortical areas have matched metabolite delivery and waste removal. It is important to reiterate that this local flow is best measured using functional magnetic resonance imaging (fMRI) (globally) or functional near-infrared spectroscopy (fNIRS) (at a cortical level), and that these tools can infer the regional changes described. Comparatively, transcranial Doppler ultrasound (TCD)

typically results in increased flow velocity of the middle cerebral artery (MCA) (an inferred global measure) and, sometimes, indicates a global lateralization of flow (46). It should be mentioned that as executive function increases, the stimulation frequency within the prefrontal cortex and LC also increases. Hence, the 'top-down' stimulation of cardiorespiratory centres in the medulla may underpin the general increase in flow velocity that is measured using TCD.

The combination of increased noradrenergic (and/or neurotrophic) modulators and intracellular calcium (both within the medulla and the active brain region) increase a variety of important cellular processes that have been previously mentioned. This includes increased cAMP-protein kinase A/C activity, which will increase levels of NO and arachidonic acid, both of which will elicit vasodilation (and in some cases vasoconstriction for arachidonic acid) (47). Additionally, as described above, lowered pH (via increased CO₂ levels) will also elicit vasodilation by activating voltage-gated potassium channels. The resultant hyperpolarization inhibits calcium-calmodulin activity, and decrease the chance of smooth muscle vasoconstriction (36,41-43). Again, this mechanism may also play a role in other unknown processes that have been described as the 'endothelium-derived hyperpolarization factor' (43). Moreover, these physiological processes (from the 'medulla up' and regionally) are likely underpinning some of the mTBI-cerebrovascular research that will be discussed in the following sections.

CONCUSSION MODELLING

It has been proposed that sport-related concussion is primarily a physiological injury, suggesting a pathophysiological basis (48). It has also been suggested that a continuum may exist for mTBI, spanning from 'uncomplicated' to 'complicated' (49), with each having a different time frame for recovery. Furthermore, loss of consciousness can accompany a concussion, as seen with 'complicated' concussions, but is not characteristic of 'uncomplicated' brain injury. It is also noted that loss of consciousness spans mTBI and TBI outcomes.

From a brain injury model perspective, combining two injuries (of opposite severity), which can both exhibit loss of consciousness – albeit for different time periods – is difficult to explain. This is especially true when considering that a severe infliction causes visible neuronal cell death, whereas mTBI typically shows only minimal damage in 10% of those injured (50-52).

To address this, brain injury models that incorporate the mechanism of injury and the associated neuroanatomical and neurophysiological consequences have been developed. Arguably the most prominent brain model to incorporate these transient changes in consciousness and concussion symptoms is the Ommaya-Gennarelli model (53). In previous years, this model has received a great deal of attention; however, more recent pathophysiology publications fail to cite their valuable contribution to the literature. The main predictions from this model are: when a trauma 'threshold' is surpassed and loss of consciousness is achieved, the cortical and subcortical areas will be far more affected than that of the brainstem; damage to the brainstem cannot occur without more severe damage to the subcortical and cortical areas; and cognitive symptoms can occur without loss of consciousness; however, the reverse cannot occur (ie, a loss of consciousness must present symptoms) (50,51,53).

In terms of the mechanism of injury, other research from Ommaya and Gennarelli's model indicated that the rotational inertia induced from an oblique force transfer (that results in transverse and coronal plane vectors), causes more harm than compressional injuries that occur in the sagittal plane alone. More specifically, sagittal compression resulted in good recovery, lateral injuries resulted in coma and/or severe disability, and the oblique injuries fell in between these two severities (51). This is why concussions are described as a blow that can be sustained directly to the head or can be kinetically transferred through the body (54). In fact, it is the inertia that perturbs normal function in the frontal lobe, often resulting in an acceleration-deceleration or coup-contrecoup injury.

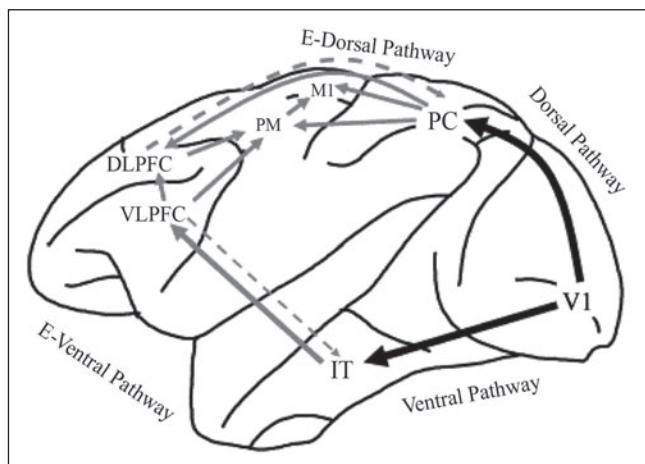


Figure 3) Pathways of activation commonly observed in visuospatial and visuomotor tasks. DLPFC Dorsolateral prefrontal cortex; IT Inferotemporal cortex; MI Primary motor cortex; PC Posterior parietal cortex; PM Premotor cortex; V1 Primary visual cortex; VLPFC Ventrolateral prefrontal cortex. Reproduced with permission from reference 55

Having identified the sagittal and/or transverse forces as strong indicators of the mechanism of injury, the Ommaya-Gennarelli model next sought to address mTBI outcomes (such as transient psychomotor deficits) and the potential for loss of consciousness. It should be noted that since their brain injury model was first proposed, neuroscience has refined and reinforced the potential mechanisms and neurocircuits that underpin these transient changes (discussed in the previous sections).

Regarding cognitive outcomes from mTBI, it is known that the frontal lobe is a moderator of executive functioning via interactions that occur at a cortical level, and is also a moderator of arousal via direct projections to the medulla and indirectly through limbic relays. Furthermore, frontal lobe injury has been associated with psychomotor changes. This anatomical location – and the cognitive deficits – are well aligned with motor learning research that focuses on the extended dorsal and the extended ventral neural circuits of visuospatial and visuomotor processing (55,56). It is also known that these cortical motor learning pathways are, in fact ‘overlapped’ onto subcortical structures, which modify arousal, which in turn places demand on cerebrovascular mechanisms to ensure arousal-matched blood flow. In addition to the relevant information regarding autonomic regulation network and chemodetection in the sections cited above, the reader is encouraged to review additional resources (13,21,22,35,36,51).

As shown in Figure 3, both of the dorsal and ventral circuits branch out of the primary visual cortex (V1). The V1-dorsal circuit stimulates the parietal cortex (including the primary somatosensory area), which is inherently linked to the primary motor cortex. Conversely, the V1-ventral pathway projects to the inferotemporal cortex. From the frontal lobe, the dorsolateral prefrontal cortex (DLPFC) and the ventrolateral prefrontal cortex (VLPFC) can influence the premotor and primary motor areas of the brain, and can also be influenced by the inferotemporal cortex (55). Generally speaking, the dorsal stream is designated as the ‘spatially oriented’ pathway and the ventral stream is known as the ‘identification and interpretation’ pathway (55,56). Moreover, visual processing through the posterior parietal cortex is used for immediate decision (ie, action plans) and is excellent with visual-spatial tasks; whereas the inferotemporal cortex is used more for identifying and inhibiting behaviours (56).

In relation to brain injury, the mechanism of impact (ie, oblique kinetic force transfer), will typically affect both the DLPFC and VLPFC. Consequently, inputs to the extended dorsal and extended ventral pathways will be altered, which likely manifest as a suppressed

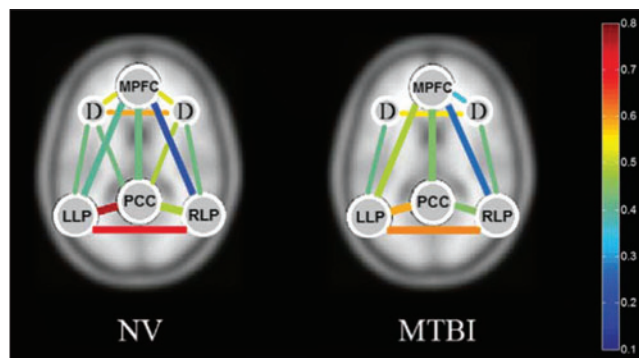


Figure 4) Normal volunteer (NV) and mild traumatic brain injury (mTBI) participant's resting state brain region correlations. The regions of interest were the medial prefrontal cortex (MPFC), the dorsolateral prefrontal cortex (D), the posterior cingulate cortex (PCC), the left lateral parietal area (LLP) and the right lateral parietal area (RLP). Usually, a connection is considered to be valid if $r > 0.3$. Reproduced with permission from reference 61

‘action plan(s)’ and inhibition processes. There is considerable evidence to support this because some of the initial concussion management strategies assessed executive function through a variety of visuospatial and motor tasks (57-60). These cognitive paradigms involved both simple reaction time (which primarily involve the dorsal pathway) and choice reaction time, which require the identification of a stimulus and the decision to inhibit or proceed (thus requiring the ventral pathway).

To further the notion of altered extended dorsal and extended ventral pathways, a recent review reported that inter- and intra-hemispheric functional connections are lowered during resting state fMRI recordings (61,62). As shown in Figure 4, the resting state fMRI neural connections were still significantly altered 24 h after the mTBI subjects were symptom free and were medically cleared (62). A similar study reconfirmed these findings in a postexercise setting, in which all scans occurred after being medically cleared and without neuropsychological deficits. However, this research group did not report any differences in a resting state, which may be explained by the previous cohort's increased number of previous concussions versus the postexercise group's null history (61,63).

Furthermore, a recent publication (10) reported that regional cerebral blood flow (rCBF) is reduced in specific brain regions following a sport-related concussion in National Collegiate Athletic Association football players. Using arterial spin labelling magnetic resonance imaging during longitudinal serial assessment, rCBF was significantly reduced in the right dorsal midinsular cortex and right superior temporal sulcus on day 1 and at week 1 postinjury compared with the one-month time period. Furthermore, compared with the control group, rCBF in these regions was significantly decreased at day 1 and week 1 in the concussed athletes but there were no differences at one-month postinjury. Based on the results, these authors suggested that rCBF provides a biomarker of concussion recovery, and also illustrated the importance (and damage) of these previously mentioned neural pathways during mTBI recovery (10).

In returning to mTBI outcomes and brain injury modelling, when Ommaya and Gennarelli initially proposed their brain injury model in 1974, the link between frontal lobe damage and loss of consciousness was mainly stemming from electroencephalography research, indicating that the reticular activating system (RAS) was the ‘driver’ of consciousness because influencing this area with lesions could lead to two electroencephalography outcomes: consciousness or incapacitation (50).

Since that time, researchers have shown that the RAS houses some nuclei that synthesize and project prominent neurotransmitters; however, it is still part of a diffuse network of nuclei within the brainstem that moderate efferent and afferent stimuli. Furthermore, the RAS has

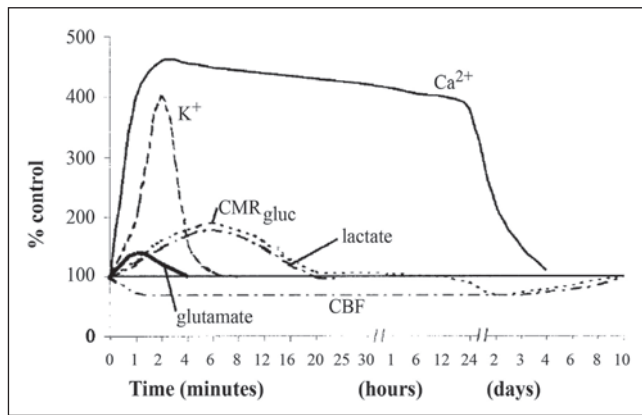


Figure 5) Time line and characteristics for some of the metabolic and electrochemical changes associated with mild traumatic brain injury. CBF Cerebral blood flow; CMRgluc Cerebral metabolic rate of glucose oxidation. Reproduced with permission from reference 70

thalamic and cortical relays, both of which can directly and indirectly contribute to consciousness and/or arousal by increasing or withdrawing neural inputs (51). However, the reverse is also true (ie, the RAS projects up to the cortex; thus, the frontal lobe can project down to the RAS/medulla). As a brief reminder, the frontal lobe can 'directly communicate' via efferent and afferent signalling with medullary nuclei such as the LC, and can also indirectly influence the hindbrain through amygdalar and hippocampal influence on the thalamus. Furthermore, the LC is responsible for the synthesis and secretion of NE and, thus, the direct and indirect influences of higher brain centres will influence both consciousness and arousal state (13,28,29). Nevertheless, the transient loss of the frontal lobe contribution to the medulla can also perturb cerebrovascular responses because central chemodetection is housed within the medulla (see 'chemodetection' and 'autonomic regulation' sections of the present review) (21,22,35,36).

To corroborate frontal lobe injuries and altered medullary control, studies of TBI and autoregulation (measured using TCD – an inferred global measure) have repeatedly shown that the medullary regions responsible for flow-pressure regulation are impaired. Moreover, the extent of impairment directly relates to injury severity (64-66). Recently, cerebral blood flow velocity assessed using TCD and heart rate variability metrics have been used with TBI, and have also been applied to concussion. These studies have shown that the autonomic controlled systems are impaired, and that impairment is related to the severity of injury (7,32,67-69). Some of these cardiovascular metrics will be discussed in the application of TCD and NIRS to concussion.

Concussion pathophysiology

Once the brain is set in motion during a head injury, both the neuronal membrane and mitochondrial membrane permeability will be disrupted. In characterizing these perturbed membranes, horseradish peroxidase (which is taken up by all parts of a neuron except an intact axon), indicated that the axon and soma could not initially be differentiated. By days 9 to 14, some degenerative and some regenerative processes were well underway (51). Thus, the axonal membrane can no longer effectively regulate intracellular ion concentration; however, as time progresses, there is the potential to recover.

As shown in Figure 5, there are metabolic and electrochemical consequences to having a disturbed membrane that can occur within minutes to hours of injury. As previously mentioned, one outcome is that voltage-gated proteins (among other ion channels) can be impaired, which allows for an indiscriminate flux of ions. Ultimately, this leads to increased extracellular potassium levels, and an intracellular increase in both calcium and sodium levels. This ion flux is further compounded by the widespread and excessive release of excitatory amino acids (eg, glutamate) at the site of injury and at 'downstream' neurons (70,71).

Given that these events are similar to that of TBIs, it is not surprising that the mass release of excitatory amino acids leads to a 'suppression of neurons', which is likely a mild version of a TBI's excitotoxicity (71). Moreover, an electrochemical suppression of neuronal activity directly plays into the previously mentioned psychomotor deficits that are mediated by the DLPFC (55,56,59,71).

Reversing the intracellular ion concentration requires the activation of mitochondria to produce energy. This is a transition point into longer-term consequences of mTBI because the rate of glucose oxidation and cerebral blood flow are immediately increased but are then decreased for a prolonged period. After seven to 10 days, intracellular calcium levels, cerebral glucose oxidation and cerebral blood flow typically return to baseline, which is consistent with the typical human timeline for return to play (52,70,71). During this time, alternative energy sources are recruited, as evidenced by lowered N-acetylaspartate (NAA) and NAA:creatinine ratios postinjury (72).

Furthermore, it has been postulated that there is a mismatch in energy requirement versus energy production. This area of research has shown that there are a multitude of factors that likely lead to this energy imbalance (52). One postulate is that the rate of glucose oxidation is altered because of increased mitochondrial calcium sequestration, which inhibits the ability to use oxygen as the final acceptor for ATP synthesis. This is also supported by the lowered NAA:creatinine ratio (52). Another area of research that has implications for altered glucose oxidation is decreased diameters of larger cerebral vessels (arterioles and venules) and microvasculature (73). This experiment did, however, use brain injury methods that were bordering between a high-risk mTBI and a more severe injury (52,73).

It should also be noted that despite the decrease in glucose oxidation, the heightened need for energy remains prevalent because calcium concentrations still need correcting. Hence, arachidonic acid and NO levels at the site of injury will likely be increased, and the ability of potassium to act as a local 'hyperpolarization factor' will be lowered. This clearly aids the physiological interpretation of the aforementioned decrements in rCBF within the midinsular and superior temporal sulcus (ie, the dorsal and extended dorsal pathways) (10). What is unknown is how the transient suppression of the frontal lobe (through increased intracellular calcium) affects the central site of chemodetection.

TCD applications to brain injury

One of the initial studies to examine blood flow changes in mTBI used laser Doppler flowmetry along with intracranial pressure (ICP) catheters in the rat model. During these studies, a 3 m/s impulse for 50 ms was administered to induce injury (74). Following this impact, a 10% inspired CO₂ reactivity test and a 10 mmHg stepwise hypotension challenge was administered (all while ICP was recorded). The force of the cortical impact increased ICP from 9.3 mmHg to 61.8 mmHg for the 50 ms duration, which then immediately returned ICP to baseline levels for the duration of the experiment. Thirty minutes following injury, the CO₂ reactivity produced a suppressed blood flow velocity response from a 68% increase in controls to 13% increase in the injured party. This was expressed as 3.1% increase per mmHg in controls and 0.5% increase per mmHg in injured rats, respectively. One hour after injury, it was revealed that the hypotension challenge elicited a significant difference in the slope of the mean arterial pressure (MAP) change for each stepwise reduction in pressure (74). This research suggested that mTBI damage does not affect ICP, which is a more classic sign of TBI damage, but does lend credence to altered cerebrovascular physiology in local areas of damage.

Recently, a cohort of World, European, Commonwealth and British champion boxers underwent cerebrovascular assessment. This is because of the nature of their chosen profession places them at risk for subconcussive damage (33). In addition to the collection of demographic information regarding their training regimens for volume, match knockouts, etc, these boxing champions were matched with age and physical fitness controls (measure of oxygen consumption via cycle ergometer) to examine neurovascular and cerebrovascular differences.

All subjects underwent neurocognitive tests, autoregulation tests (thigh cuff deflation and postural challenges) and CVR measures. The thigh cuff deflation was used to calculate the rate of regulation, the autoregulation index and baroreflex sensitivity. The rate of regulation from the thigh cuff release was calculated using the slope of the linear regression of the cerebral vascular conductance change from 1 s to 3.5 s following cuff release, divided by the subsequent change in MAP. Baroreflex sensitivity was similarly calculated as a change in heart rate divided by change in MAP. Resting data were assessed via transfer function analysis, and CO₂ reactivity indexes (change in flow velocity/change in CO₂) were also calculated.

The neurocognitive results for boxers were lower than for matched controls, as was the rate of regulation with the thigh cuff deflations. Moreover, the CO₂ reactivity was also impaired in boxers, and appeared to be more related to their sparring training volume and not the number of knockouts. It was also noted that while there were significant differences between controls and boxers, these results may be clinically insignificant because none of the boxers at any point were presyncopal and, thus, their brains were never challenged by oxygen deprivation. It is also noted that NIRS measures were used during the orthostatic challenges and no significant differences were reported. Again, even though the authors state that these findings were of 'low clinical significance', they did state that damaged neural tissue requires increased metabolic demand, which may become a challenge for neurovascular coupling, CO₂ reactivity and autoregulation after their boxing careers ended (33).

Another research group has focused on using a simple-to-apply technique with TCD by using repeated 20 s breathholds (BHs) and hyperventilations (HVs) (interspersed with 40 s normal breathing) to induce an acute hypercapnic or hypocapnic perturbation (7). As stated in previous sections, altered cerebral CO₂ is a well-known stimulus affecting cerebral blood flow velocity and the most potent physiological stimulus of arterial dilation (9,36). The initial results showed no significant impairments in 10 concussed individuals versus controls under resting baseline when insonating the MCA. However, it was shown that the mTBI group showed significantly less responsiveness in %MCA change during the HV test (hypocapnia) (P=0.034) despite similar changes in end-tidal CO₂ between groups (7). These results suggested an altered CVR in the concussed athlete.

In a follow-up study, and the first prospective study to use TCD and a CVR-CO₂ protocol with mTBI to monitor recovery – a similar protocol of BH- and HV-induced hyper- and hypocapnia, respectively (8). Using a larger sample of concussed athletes, analysis was conducted on day 2, day 4 and day 8 postinjury. Again, it was noted that there was no statistically significant impairment in resting CVR, but that significant changes occurred during both BH and HV. Specifically, the test day was significantly different from baseline and from day 2 versus day 8. It was also noted that the response to BH was increased on day 2, which then decreased on day 4 and day 8 (8). Finally, their results showed that impairment may resolve as early as four days postinjury in some subjects.

Interestingly, some researchers have also used other TCD indexes to monitor and assess mTBI. Specifically, peak systolic velocity and the resistive index were assessed during hypercapnia and a sit-to-stand orthostatic stress test, but reported no differences between concussed and control participants (75).

Collectively, the significance of these research endeavours demonstrate that there are potential TCD applications for monitoring mTBI because chemodetection and blood pressure regulation share the same anatomical locations within the medulla (5). Hence, future research could monitor pressure regulation serially to assess recovery in a similar fashion to serially monitoring CO₂ reactivity. Only one study has investigated dynamic cerebral autoregulation post-mTBI; however, the participant's injury's indicate that the brain injury was on the border between high-risk mTBI and low-risk TBI (76).

There are now more 'elaborate' imaging studies to support the first CVR recovery-tracking research, which again indicated that CVR is,

in fact, altered following concussion (7,8). As previously mentioned, a cohort of concussed athletes underwent rCBF measures using arterial spin labelling and reported significantly reduced flow in the right dorsal midinsular cortex and right superior temporal sulcus on day 1 and at week 1 postinjury compared with the one-month time period. These differences were also apparent when comparing the concussed groups with healthy controls (10). Another MRI study that supported the initial TCD-CVR research was conducted using a CO₂ stress test to confirm that CVR is, in fact, altered postinjury (9). This research group used a novel neuroimaging methodology that consisted of a RespirAct (Thornhill Research Inc, Canada) device to prospectively 'hold constant' end-tidal CO₂ while measuring regional blood oxygen-level-dependent responses as a result of the CO₂ stimulus. In that study, healthy control participants were compared with postconcussion syndrome patients who were symptomatic and/or recovered asymptomatic. From this, this research group developed an 'atlas' for the control subjects based on a voxel count ratio response to CO₂. Their results showed an abnormal CO₂ response that was dependent on severity (symptomatic or asymptomatic) when compared with the control atlas. Further research in this area will continue to advance diagnostic tools and methods for mTBI.

NIRS applications to brain injury

To our knowledge, only two studies have specifically investigated mTBI using NIRS measures (77,78). One study recruited 14 individuals who sustained a sport-related concussion within the past 15 to 45 days and were still symptomatic at the time of testing (78). A six-detector by 8-source (32-channel) fNIRS was positioned over the frontal lobe using the International 10-20 electrode system (79). This placement was designed to cover the bilateral areas of the inferior dorsolateral prefrontal and frontal regions. The fNIRS application was concomitantly used during a common neuropsychological test (ImPACT), in which each component of the test was treated as a new block, with 30 s of rest in between new trials. Collectively, the ImPACT test consists of a word memory task, a shapes memory task, a symbol match task, a colour match task, a three-letters memory task, and an Xs and Os spatial memory task. Results indicated that the injured cohort performed poorer on many of the neuropsychological components (78).

In the word memory task, concussed participants had poorer behavioural performance on the percent of correct word memory module, and the delayed word memory recall. The fNIRS measures during the recall showed a suppression of oxyhemoglobin in concussed individuals in the left dorsolateral region, with the delayed recall showing increased oxyhemoglobin in a concussed left dorsolateral region (78).

For the design memory task, the injured individual performed worse during the immediate recall phase at correctly identifying shapes that were not part of the task. During this time, concussed participants also had significantly less activation in the frontal area than controls. The delayed recall for designs did not show any significant differences for NIRS, although there was a trend toward increased activation in the concussed group. In part, this could have been related to the time period of testing postinjury. Once again, the delayed recall had significant behavioural differences with fewer correct 'no' responses for injured participants (78).

The symbol-match task had significantly higher oxyhemoglobin levels in the control group than the injured group. Behaviourally, the concussed group had fewer total correct responses.

Overall, these results show less activation during cognitive tasks than that observed in healthy controls. This is typically not observed in similar fMRI studies; increased activation has often been cited. However, these citations are based on 'simple' cognitive loads such as an n-back test of 1. More difficult tasks (ie, n-back tests of 2 or 3) have shown similar suppressions to the current study in activated areas compared with healthy individuals (78).

In another study that examined a concussed pediatric cohort, fNIRS was used to quantify functional coherence between the left and

right motor cortex as a marker of inter- and intrahemispheric communication (77). In this study, finger tapping was used to activate the motor cortex while monitoring the brain with multichannel fNIRS in an attempt to measure functional connectivity. A control group was compared with the mTBI (postconcussion) group with the results showing that the magnitude of the response in total hemoglobin and oxyhemoglobin was not different between groups during resting state or following task activation. However, the most significant finding was a reduction in total hemoglobin and oxyhemoglobin coherence during motor task activation in the contralateral hemisphere in the mTBI group compared with the control group. The authors suggested that their results showed an interhemispheric functional impairment in connectivity in the postconcussion subjects. Although the authors could not confirm the exact physiological mechanism(s) for this decrease in coherence, they suggested that cellular damage, metabolic dysfunction and focal axonal injury may be possibilities (77).

These studies demonstrate that NIRS technology can be used to assess mTBI, and that there are other NIRS-mTBI avenues that should be explored. For example, one avenue would be to replicate the acute bouts of hypercapnia because the changes reported during macrovascular measures with TCD will likely also be present in a microvascular setting. Based on this initial research, and both the arterial spin labelling-MRI study (10) and the fNIRS-cognition study (78), it appears to be highly plausible that oxyhemoglobin deficits will be found and will increase as the mild brain injury abates. Additionally, NIRS can also be applied when returning athletes to full contact (ie, during a return-to-play exercise trial). To briefly elaborate, it has been shown that cerebral oxygenation increases until the respiratory compensation threshold. After this point, oxygen levels decrease but metabolite extraction increases (80,81). Thus, it is plausible that NIRS could be used during the initial return-to-play cycle ergometer test and serve as an 'early warning system'. Specifically, compared with their baseline value/fitness level, the injured athlete's respiratory compensation threshold during incremental exercise may occur at an earlier workload (and may indicate symptom exacerbation). At this same time point, the injured party may also show increased oxygen extraction before symptom exacerbation.

SUMMARY

The present review focused on autonomic and cerebrovascular physiology, which was linked to mTBI pathophysiology and applications to cerebrovascular measures. In terms of autonomic function, it was noted that the frontal lobe and hippocampus promote inhibition of a sympathetic response via excitatory neurotransmitters. Comparatively, the amygdala promotes disinhibition via inhibitory neurotransmitters. The main nuclei these competitive processes integrate within is the BNST, which exerts an inhibitory influence onto the PVN – the main producer of CRF (11-13,21,23). Within the medulla, the LC not only influences CRF production through cAMP messengers, but it also projects up to the frontal lobe and moderates arousal, while simultaneously integrating with chemodetection centres. This is crucial to note because the postsynaptic release of NE will increase cAMP levels within the medulla, the amygdala, the hippocampus and other areas. This will contribute to the biochemical exertion on the BNST and, thus, will also contribute to the intracellular ion variance associated with chemodetection. This is why arousal state (such as that during exercise) and blood flow are linked, and that the cAMP pathway is engaged to increase NO production so as to ensure that metabolic status and metabolite delivery are matched (36,82). Thus, the LC (while being integrated with efferent exercise motor outputs from the frontal lobe) is also part of the 'diffuse network' of cardiorespiratory function and can, therefore, contribute to balancing the inverse relationship of CO₂ and blood flow through cAMP-NO production (31,34-36).

Having discussed healthy autonomic regulation and cerebrovascular physiology, it is clear that there are overlapping physiological mechanisms at work to restore damaged neurons, which will have a transient effect on chemodetection and autonomic regulation. However, the exact mechanism of how frontal lobe damage, which often occurs during

a concussion, can affect medullary (cerebrovascular) control is difficult to determine. However, there is reason to believe that this is, in fact, the case because CVR impairments assessed using TCD have shown this (8). Furthermore, as discussed above, two recent imaging studies have also supported this notion of impaired hemodynamics with mTBI. The first study used a RespirAct™ device to 'block' end-tidal CO₂ during fMRI scans, and showed that CO₂ reactivity was blunted in symptomatic postconcussion syndrome participants (9). Their results did not focus on the acute phases of concussion and were not separated into any specific brain regions of interest, but they did indicate that the frontal lobe and medulla show reductions in CO₂ reactivity. The second imaging study showed decrements in rCBF within the right dorsal midinsular cortex and right superior temporal sulcus on day 1 and at week 1 postinjury compared with the one-month time period (10).

Furthermore, NIRS-recorded frontal lobe impairments, and NIRS-recorded decrements for both inter- and intrahemispheric communication in the primary motor cortex, have also shown that cerebrovascular metabolite coupling is perturbed (77,78).

Although overlapping cognition, autonomic function and hemodynamics is physiologically cumbersome; having summarized these recent mTBI-cerebrovascular studies, it appears that medullary and frontal lobe cerebrovascular physiology is impaired during a concussion. Locally, changes in CVR are possibly accounted for by the heightened metabolism required for reversing intracellular calcium fluxes. This will increase cAMP and the production of NO, and will also enhance the release of arachidonic acid. Prolonged exposure of these messengers within microvasculature could result in an impairment. Identifying the physiology of medullary impairment, however, is more speculative. What is known through autonomic regulation is that the frontal lobe can influence hippocampal, BNST and medullary intracellular ion status. If these medullary innervations are 'muffled' through the inability to depolarize (due to high intracellular calcium levels in frontal lobe neurons), there may be a multitude of mild autonomic issues, including the potential for increased BNST disinhibition, altered CRF synthesis, cortisol feedback sensitivity, etc.

Having previously stated the cortical-limbic relationships present in CRF-cortisol regulation and knowing that CRF-cortisol production ultimately dictates the regulation of arousal, it is also possible that these mild autonomic regulation issues result in some of the circadian-like concussion symptoms, such as 'difficulty sleeping'. Conversely, other symptoms may be the result of the concussed participant's awareness that their reaction time is lower and, thus, feel 'slowed down' (54). There is some research to support this notion because a recent study showed that postexercise postconcussion headache symptom was highly correlated with a decreased postexercise cerebral perfusion volume as measured using TCD (83). Further research in this area is warranted.

As a final note, TCD-mTBI paradigms should also be used to serially track acute blood pressure challenges because the chemodetection and blood pressure regulation sites are anatomically overlapped. Moreover, NIRS could also be used in conjunction with transient hypercapnia and acute blood pressure models to assess recovery. Additionally, an fNIRS setup has been used to assess postinjury functional connectivity (77) and, because fNIRS is portable, this setup could also be used in the previously mentioned scenario to monitor submaximal graded exercise test postconcussion and before return to play.

CONCLUSION

A handful of research studies have now demonstrated that easy-to-measure physiological variables, including cerebral blood flow, CVR to CO₂, changes in both oxy- and deoxyhemoglobin, and heart rate variability, to name a few, have been used with mounting success to characterize sport-related concussion and track recovery (7-10,77,78). It is our contention that physiological data collection is the cornerstone of the objective diagnosis and management of concussion. Further research collecting such variables will help to advance this area of research and make return to play safer in the future.

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