TRAUMATIC BRAIN INJURY CENTER OF EXCELLENCE

INFORMATION PAPER ON THE IMPACT OF MILD TRAUMATIC BRAIN INJURY ON THE AUTONOMIC NERVOUS SYSTEM

PURPOSE

The purpose of this information paper is to provide a general overview of the current evidence related to the impact of concussion/mild traumatic brain injury (mTBI) on the autonomic nervous system (ANS). This paper will focus on heart rate variability (HRV), pupillary light reflex (PLR), and hyperhidrosis within the military and civilian populations.

BACKGROUND

The impact of traumatic brain injury (TBI) on the ANS has been well documented in the literature for severe injuries. More recently, there is increasing evidence suggesting that ANS dysfunction may occur following mTBI.[1] The underlying pathophysiology of ANS dysfunction following a mTBI remains unknown; however, the literature postulates that ANS dysfunction may result from diffuse axonal injury during initial head impact, reduced cerebral blood flow (CBF) after mTBI, or deconditioning following the injury.[1] ANS dysfunction is becoming more apparent following mTBI, and many of the classic symptoms following concussion are, at least in part, likely a result of injury to the ANS.[2] Cognitive difficulties seen after mTBI may be related to ANS dysregulation, specifically impaired CBF.[3] Typically, disturbances in the ANS appear greatest in the earlier stages after injury[4], however, the literature remains inconsistent on when the resolution of ANS symptoms usually occurs. As the ANS is responsible for regulating responses to internal and external environmental factors[5], dysfunction of the ANS can impact heart rate (HR), lead to pupil abnormalities, and disrupt thermoregulation.

HEART RATE VARIABILITY (HRV)

Heart rate variability (HRV) is defined as the variation in time intervals between consecutive QRS complexes (‘R-R’ intervals) and is traditionally measured on an electrocardiogram (ECG).[6, 7] The degree between intervals can be used to gauge the balance between the parasympathetic nervous system (PNS) and sympathetic nervous system (SNS).[7] The SNS is thought to increase HR and decrease HRV, while the PNS decreases HR and increases HRV.[5] Along with the influence of the PNS and SNS, baroreceptor reflex activity, breathing rate, and hormones may also contribute to HRV.[7] HRV has been seen as a reflection on the ability of the cardiovascular system to adapt to stressors including environmental, physiological, and social factors.[8] Traditionally, a lack of HRV suggests cardiopathology, morbidity, and reduced quality of life, while optimal HRV has been associated with good cardiovascular health, ANS functioning, and emotional regulation.[9] A meta-analysis of 16 studies found that higher HRV is related to better neurological, emotional, and behavioral functions after acquired brain injury.[10]

Cerebral Blood Flow
Baroreflex sensitivity (BRS) and cerebral autoregulation (CA) play an important role in maintaining constant cerebral blood flow (CBF) during systemic changes in blood pressure (BP).[11] Those with chronic TBI often have impaired dynamic CA which may contribute to persistent cognitive impairment.[11] In a study of 31 collegiate athletes, lower HRV was observed at 3 days after a concussion with normalization in 21 days.[3] Associated differences in CBF were thought to be the underlying cause behind the heterogeneity in clinical symptoms and functional outcomes observed after the concussion.

Contributing Factors
HRV is affected by many variables including age, sex, level of physical fitness, body position, medication, time of the day, alcohol consumption, face cooling, and emotional stress.[8] Current evidence supports the association between emotional stress, including post-traumatic stress disorder (PTSD), and HRV, demonstrating that individuals with lower HRV may be more likely to develop PTSD.[12, 13] This is particularly relevant to the military population due to the high prevalence of PTSD and the possibility that an altered state of ANS functioning can contribute to PTSD vulnerability.[13] HRV also has the potential to be impacted by a prior history of concussion. In a study of 113 collegiate athletes months to years following a concussion, no differences in HRV were observed in female athletes with or without a history of concussion; however, in male athletes with a history of concussion there was a significantly lower mean HRV in the seated position compared to those with no history of concussion.[14]

HRV may also be mediated by important clinical factors including sex differences.[14] Sex differences in HRV are present even in a healthy human population.[15] A case-control study completed by Hutchinson et al. (2017) identified significant interactions between concussion status and sex difference with female athletes showing greater HRV suppression extending into the post return to play (RTP) phase.[16] Early dysautonomia following an mTBI, as measured with HRV, has also been associated with late depression in female mTBI patients.[17] Future studies need to account for sex differences in the analysis of data examining the impact of concussion on HRV.

Measuring HRV
A TBI of any severity, including mTBI, can have an adverse impact on HRV.[9] Therefore, HRV offers the possibility to serve as a means to gauge autonomic function and the interaction between the PNS and SNS.[8] Currently, HRV is one of the most commonly used methods to evaluate the functioning of the ANS in concussion-related studies.[5]

The gold standard for measuring HRV is by an electrography (ECG), however clinical multi-lead ECG systems (e.g., Holter ECGs) are expensive, involve sizeable researcher and participant burden, and therefore are not deemed particularly practical for field base monitoring in the active duty population.[18] A number of currently available wearable devices may be difficult to integrate into the active duty setting due to placement of sensors and wires, short battery life, insufficient or no internal memory, and/or the technology is not capable of dealing with harsh field conditions.[18] Wearable devices are available that can continuously measure heart rate, though the accuracy varies between different manufacturers.[19] Relatively new devices using single lead ECG or photoplethysmography (PPG) are more practical, less intrusive, simple to use, and have been integrated into wearable wrist and finger-worn devices[20] making it an attractive alternative to a multi-lead ECG system.[18] Motion artifact and inconsistencies in data have been noted as a limitation for PPG, [21] and currently due to the reduced accuracy in PPG devices during exercise they are only recommended for use during resting conditions or very mild exercise.[22] Additional options for wireless monitoring of HRV include chest straps that use ECG electrodes and these are currently the most accurate when compared to traditional methods.[18] The practicality of chest strap devices within the military setting is being investigated.[18]

Wearable HRV monitoring devices may eventually serve as a non-invasive way to monitor autonomic control of the cardiovascular system in concussion patients. HR monitors are Class II devices that are not generally exempt from 510k clearance requirements. A recent pilot study was completed by Uomoto et al. (2022) which assessed the feasibility and validity of using the Zeriscope platform system in a real-world clinical setting to measure HRV. Results of the study conclude that the Zeriscope system fell short of reaching acceptable accuracy when compared to standard ECG. However, the study did find user acceptability of wearing a device during clinical treatment sessions[13] The Polar H10 strap, another commercially available heart rate monitor, is currently one of the most practical and accurate wearable devices for collecting HRV data during exercise.[18] The reliability of the Polar H10 was evaluated using two clinically feasible exertional tasks that include HRV measures.[23] In healthy participants a 6-min step test and 2-min pushup test evoked the targeted physiological response, and the HRV measured with the Polar H10 was found comparable to the ECG.

HRV and Return to Play (RTP)
Resolution of mood disturbances, post-concussion symptoms, and sleep quality typically occur by the time an athlete is considered ready for return to play (RTP), but autonomic nervous system disturbances as measured by HRV can be seen beyond RTP, especially in female athletes.[16] Persistent long term changes in automatic dysfunction are most likely related to parasympathetic dysregulation.[16] Alterations in HRV have not only been noted to be present during physical exertion, which is known to stimulate the ANS[24], but also at rest in the post-RTP stage of injury.[16] Detection and monitoring of autonomic dysregulation after a sport-related concussion may require near-daily assessment of HRV.[25] There is evidence of elevated HR and reduced HRV with low-intensity, steady-state exercise up to 10 days following concussion.[26] A meta-analysis of 18 studies found persistence of significant changes in HRV even 4 weeks to 6 months after mTBI.[27] A study of 30 concussed athletes found significant changes in HRV, spontaneous baroreflex sensitivity (BRS), and systolic blood pressure variability during the first 5 days after a concussion.[28] HRV and baroreceptor sensitivity recovers from moderate-intensity exercise within 60 minutes in healthy adults.[29]

Monitoring HRV potentially may aid diagnosis and provide insight into a safe return to play. In some University Athletic programs HRV is included as baseline concussion testing.[30] The overall significance of HRV data is not fully understood and usefulness currently seems individualized to the level of athlete, age, and sex; therefore, it cannot be generalizable.[31] In order to be more clinically meaningful and to assist with current clinical decision making regarding RTP, a preinjury baseline assessment could be beneficial as an individualized reference for post-concussion comparison.[31] However, the exact relationship between ANS regulation and poor prognosis after injury has yet to be fully elucidated. Further research into the value of HRV as an indicator of ANS dysfunction is warranted prior to guiding mTBI assessment and management.

Treatment and Interventions
Along with serving as a potential biomarker, HRV may be a valuable asset for treatment and rehabilitation. HRV training via biofeedback has the potential to serve as a treatment tool allowing service members real-time awareness of the physiological impact of concussion and assist with managing autonomic dysregulation.[9] Heart rate variability biofeedback may be an effective, safe, and easy-to-learn and apply method for both athletes and coaches in order to improve sports performance.[32] A systematic review evaluating the effect of heart rate variability biofeedback (HRV BFB) on performance of athletes supported HRV BFB as a potential intervention to improve fine and gross motor function in athletes,[33] and HRV BFB also was found useful to improve their respiratory mechanics.[34] However, a systematic review to summarize and critically assess the effects of yoga on HRV found no convincing evidence for its effectiveness in modulating HRV in patients or healthy subjects.[35] HRV can also be used to screen mTBI patients for poor sleep quality and post-TBI sleep disorders. [36] There has also been preliminary

evidence on the use of HRV biofeedback training to enhance neurocognitive performance, particularly executive functioning and working memory.[9] Performing a mild cognitive task during the early stages of recovery may help improve ANS functioning.[37] This could support participation in cognitive rehabilitation for service members presenting with cognitive complaints to assist with return to duty.

PUPILLARY LIGHT REFLEX (PLR)

It is well known that head impacts and concussions can result in measurable changes in the pupillary light reflex (PLR),[38, 39] likely the result of impairment of the autonomic nervous system caused by the concussion.[40] Therefore, PLR has been widely utilized to evaluate the activity of the ANS.[41] The change in pupil size in response to variation in ambient light is known as the PLR.[41] Constriction and dilation of the pupil is thought to be one of the most sensitive measures of autonomic dysfunction with constriction controlled by the PNS and pupillary dilation controlled by the SNS.[41] PLR function is known to be correlated with other measures of ANS function including HRV, specifically evaluating PNS activity.[41] The differences in PLR metrics are modulated not only by concussion history but also by gender, age, and whether or not the person has symptoms associated with a head injury.[41]

Pupillometry can provide a means to detect subtle changes in pupil abnormalities that may be present after a concussion, potentially serving as an objective biomarker for the clinical setting.[42, 43] Modern pupillometers are able to provide clinicians with information on pupil baseline size, constriction latency, constriction velocity, contraction percentage, minimum size, and dilation velocity.[44] Pupillometers are Class 1 510(k) exempt medical devices by the US Food and Drug Administration (FDA), with NeurOptics NPi-200 or 300 being the most common in the clinic/hospital and research settings. The durability, objectivity, and portability of pupilometers lends to clinical feasibility and implementation, however at this time, future research is needed for standardization and evaluation protocols in the mTBI population.

The PLR variables of latency, maximum pupil diameter (MaxPD), minimum pupil diameter (MinPD), maximum constriction velocity (MCV), and the 75% recovery time (75% PRT) are associated with significant differences between subjects who have sustained a concussion and those who have not.[41] Following a mild TBI, pupillary responsivity may be significantly delayed, slowed and reduced, but is usually symmetrical in nature, and with a smaller baseline diameter, as compared with normal.[42] The slowed dilation dynamics and reduced maximum pupillary diameter in mTBI suggest deficiency primarily of the sympathetic nervous system.[45] The reduced peak velocities and related amplitudes suggest subtle parasympathetic involvement. In 17 adults with chronic, non-blast mTBI, maximum (or peak) constriction velocity, average constriction velocity, average dilation velocity, maximum diameter and amplitude of constriction were significantly reduced in the mTBI group as compared to controls.[45] There is also a potential use for pupillary dynamics to identify the presence of photosensitivity after mTBI, which is defined as pain or discomfort in the presence of normal lighting conditions.[46]

HYPERHIDROSIS

Hyperhidrosis is characterized as an abnormal increase in sweating, defined as sweating in excess of what is needed to regulate body temperature.[47] Hyperhidrosis is a clinical feature of paroxysmal sympathetic hyperactivity (PSH) which is a syndrome that leads to increased SNS activity in patients with acquired brain injury.[48, 49] TBI is the most common condition associated with PSH, and has been primarily reported in severe injuries with little reported about PSH or hyperhidrosis in mTBI patients.[47] Injury to the hypothalamus has been suggested as the pathological basis for hyperhidrosis in patients with TBI.[47] A small study completed by Jang et al. (2022) used diffuse tensor imaging (DTI) to correlate hypothalamic injury with hyperhidrosis in mTBI patients. [47] Participants were recruited within the civilian population and included seven patients with hyperhidrosis and 21 healthy sex-matched control subjects between 39-60 years of age. The results suggested that hyperhidrosis present in patients with mTBI could also be related to a hypothalamic injury.[47]

EXERCISE AND ANS FUNCTION

Exercise intolerance has been seen in athletes after sports-related concussions (SRCs) and may be related to abnormal regulation of cerebral blood flow (CBF).[50] Exercise intolerance can present clinically as an abnormal heart rate or blood pressure for a given workload and may be considered a symptom of cardiovascular autonomic nervous system dysfunction.[4, 51] Due to the working relationship between the cardiovascular system and ANS, concussed athletes whose injuries have not fully resolved can experience intolerance with physical exertion.[4]

Asymptomatic athletes still may exhibit modifications in cardiac autonomic modulation weeks to months following a concussion, and these modifications may sometimes only become apparent during physical exertion.[24, 52] Exercise following a concussion typically exposes changes in HRV, though reports on the relation between HRV and both acute and prolonged concussion recovery are conflicting. During endurance exercise HRV has been used to monitor responses to different exercise intensities, movement frequencies, and exercise duration.[53] While some authors report on differences in the low-frequency component of HRV during postural manipulations and post-exercise conditions, others have found no significant differences in various HRV measures.[7] A systematic review of impairment of HRV during exercise for individuals with concussion found that available studies lack control over confounding factors, and only less than half of the results show a significant difference between individuals with concussion and controls.[8]

Monitoring ANS sensitivity to changes in training load may indicate an individual's capability to adapt or tolerate exercise.[54] Increases in vagal-related indices of resting and post-exercise HRV, post-exercise heart rate recovery (HRR), and HR acceleration are evident when positive adaptation to training has occurred, allowing for increases in athletic performance.[54] However, increases in post-exercise HRV and HRR also occur in response to overreaching, demonstrating that additional measures of training tolerance may be required to determine whether training-induced changes in these parameters are related to positive or negative adaptations. Negative adaptations to endurance training refers to a period of overreaching leading to attenuated exercise performance.[54] Resting HRV is largely unaffected by overreaching. HR acceleration appears to decrease in response to overreaching training, and thus may be a potential indicator of training-induced fatigue.

Aerobic exercise is a recognized, non-invasive, and non-pharmacological treatment approach that could potentially improve ANS functioning in mTBI patients.[50] Exercise enhances ANS function and can serve as an effective method for treatment in the acute stage of mTBI and for those patients who present with post-concussive syndrome (PCS).[2] A graded exercise treatment regimen beginning in the first week following concussion has the potential to improve symptoms and biomarkers of ANS function.[2] The military health system has adopted this strategy with the use of the Progressive Return to Activity Following Acute Concussion/Mild Traumatic Brain Injury Clinical Recommendation (2021) to allow service members to gradually increase activities, within symptom tolerance, until they receive full clearance for return to duty (RTD) by their primary care manager.

DISCUSSION

Due to the current variation in studies and the unknown timeline for the resolution of ANS dysfunction, it is difficult to reach a robust consensus on the full impact of ANS impairment following a concussion/mTBI.[8] As the literature represents, ANS biomarkers may have the potential to demonstrate the continued physiological impacts of concussion despite reported symptom resolution. However, further studies are warranted to provide insight into the physiological basis and implications of persistent abnormal ANS dysfunction beyond symptom resolution and the impact on clinical outcomes.[16] Future studies need to account for and address confounding factors (e.g., age, level of physical activity, sex) in their analysis and methodology prior to clinical usuage.[8, 16] Continued research to understand the impact of mTBI on the ANS could offer additional diagnostic and treatment strategies for the evaluating and managing concussion/mTBI patients[55], including return to duty protocols.

CONCLUSIONS/RECOMMENDATIONS

- Post-traumatic autonomic dysfunction can be measured with HRV monitoring and pupillometry; however, confounding factors (e.g., age, level of physical activity, sex, drugs/ supplements use) and co- morbid conditions need to be considered when reviewing and analyzing the data
- HRV does not correlate with presence of TBI nor severity of TBI
- HRV cannot be used at this time for RTD/RTP decision making
- HRV cannot be used to predict outcomes
- For military clinical and/or research considerations, continuous monitoring of HRV is expensive, bulky, involves sizeable researcher and participant burden ,
- Developing technology that supports less invasive wearable HRV monitors have not yet shown validity. Additionally, they are not particularly practical for military field base monitoring due to placement of sensors and wires, short battery life, insufficient or no internal memory, and/or the technology is not capable of dealing with harsh field conditions. Future military research and use will need to address above factors and limitations

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