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Reduced heart rate variability and lower cerebral blood flow associated with poor cognition during recovery following concussion

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ABSTRACT

Although physiological deficits such as altered cerebral blood flow (CBF), and autonomic nervous system (ANS) dysregulation have been reported following a concussion, the relationship between CBF and ANS with functional outcome post-injury remains unclear. Our present study was designed to examine heart-rate variability (HRV) using percentage of successive NN intervals (pNN50) and CBF on day-3 (T1), day-21 (T2), and day-90 (T3) following a concussion in collegiate athletes (N = 31) in comparison to non-injured controls (N = 31). Continuous RR-interval (3-lead electrocardiogram), middle cerebral artery blood velocity (MCAV; transcranial Doppler ultrasonography), mean arterial pressure (MAP; finger photoplethysmography) were obtained at rest. Cerebrovascular conductance index (CVCi) was estimated as a ratio of MCAV to MAP. Cognition was evaluated with standard assessment of concussion (SAC), and Trails A & B. Compared to the controls, lower HRV (43 ± 15 vs. 27 ± 20%; $p < 0.0001$) was observed at T1 with normalization at T2 and T3. No difference in MCAV between the control and the concussed groups across the three time points were observed. However, post-hoc analyses indicated a positive relationship between MCAV at T1 phase with HRV and CVCi during T2, and T3 phases. Higher MCAV at T1 was also associated with better cognition scores during the asymptomatic T2 phase in the concussed athletes. Therefore, our results indicate ANS dysregulation during the acute recovery phase after a concussion. Differences in CBF may be one of the underlying causes behind heterogeneity in clinical symptoms and functional outcomes after a concussion and future studies are warranted to validate this finding.

1. Introduction

Concussion is recognized as a major public health issue in the United States with 1.6 to 3.8 million incidences occurring annually in sports and recreational activities (Daneshvar et al., 2011). Concussion is considered a functional rather than a structural disturbance due to the absence of gross macrostructural abnormalities in neuroimaging (Leddy et al., 2017; MacFarlane and Glenn, 2015). It is a complex pathophysiological process affecting the brain and the related signs and symptoms are considered as surrogate clinical measures of physiological dysfunction post-injury (Giza et al., 2018). However, the clinical symptoms may not always coincide with physiological recovery resulting in a potential window of cerebral vulnerability and risk of exposure to secondary injuries (Giza et al., 2018; Wang et al., 2016). Nevertheless, the current concussion management options are mainly focused on symptom resolution rather than examining the underlying pathophysiology associated with the injury (Giza et al., 2018; Wang et al., 2016).

Autonomic nervous system (ANS) dysfunction is implicated in early and later stages of mild traumatic brain injury (mTBI) (Hilz et al., 2015; Hilz et al., 2011; La Fountaine et al., 2016; Senthinathan et al., 2017). Augmented sympathetic neural activity measured as transient increases in peripheral artery stiffness, utilizing arterial pulse wave analysis, was reported within 48 h of a concussion and the impairment was more prominent in athletes with longer duration until return-to-play (La Fountaine et al., 2016). Altered ANS control during Valsalva maneuver

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and orthostatic challenges were observed during the acute phase following concussion (Dobson et al., 2017). On the other hand, reduced parasympathetic neural modulation during eyeball pressure stimulation, and blunted baroreflex sensitivity reflecting poor beat-to-beat blood pressure control was reported in individuals with a history of mTBI compared to control (Hilz et al., 2011).

Heart rate variability (HRV) derived from electrocardiogram is commonly used as an index of ANS function reflecting cardiovascular health (Draghici and Taylor, 2016). Modulations between the sympathetic and parasympathetic branches of the ANS at rest and during physiologic stimuli are key determinants of HRV (Camm et al., 1996). Low HRV is associated with impaired cardiovascular response during stress and perceived threats, whereas increased HRV promotes behavioral adaptation and cognitive flexibility (Quintana et al., 2016). Low HRV at rest was reported during the acute recovery phase following a concussion and persisted beyond the sub-acute return-to-play phase (Senthinathan et al., 2017). In addition, low HRV during physical exertion was observed during acute and sub-acute phases after a concussion when compared to the controls (Abaji et al., 2016; Gall et al., 2004).

According to the neurovisceral integration theory proposed by Thayer et al., a flexible interplay between cognitive function and the ANS controlling cardiac activity exist; with higher HRV linked to greater cognitive effectiveness (Thayer and Lane, 2009; Thayer et al., 2009). Individuals with higher HRV at rest performed better on a cognitive test than those with lower HRV (Kemp et al., 2017; Kemp et al., 2016). In addition, individuals with enhanced executive function on and off the field perform better in real-life environment (Saus et al., 2006). Increased prevalence of cognitive impairment in community dwelling elderly women have been implicated to reduced HRV (Kim et al., 2006). Furthermore, epidemiological studies have reported an association between poor cardiovascular health and cognitive impairment in the future (Kemp et al., 2017).

Global and regional cerebral blood flow (CBF) is also altered following a concussion (Meier et al., 2015; Wang et al., 2016). In football athletes, CBF was abnormally reduced 24 h after a concussion with further decrement in CBF 8 day post-injury despite symptom resolution (Wang et al., 2016). In another study in collegiate athletes, regional CBF, specifically in the dorsal-mid-insular cortex, was markedly reduced among concussed athletes compared to the controls (Meier et al., 2015). The decrease in CBF in that region was associated with reduced cognition and the longer time until return-to-play suggesting a link between CBF and functional outcome. The insular cortex, a part of the central autonomic network, is the primary location for integration of the sympathetic and parasympathetic neural activity (La Fountaine, 2017; Thayer et al., 2009). Therefore, hypoperfusion of the insular cortex post-injury as reported by Meier et al. is postulated to manifest the uncoupling of the sympathetic and parasympathetic branches of the ANS resulting in alterations in HRV (La Fountaine, 2017). Deficits in the ANS are also suggested to be correlated to abnormal cerebrovascular response and subsequent reduction in CBF (Zhang et al., 2002).

Although physiological deficits such as impairments in CBF and ANS dysfunction have been confirmed separately in several studies, these physiological functions have not been examined simultaneously over time during recovery in sports-related concussion (Hilz et al., 2011; La Fountaine et al., 2016; Meier et al., 2015; Wang et al., 2016). Therefore, in the present study we examined ANS modulation utilizing HRV and middle cerebral artery blood flow velocity (MCAV) as a measure of CBF, during acute (approximately day-3; [T1]) and sub-acute phases (day-21; [T2], and day-90; [T3]) following a sports-related concussion and compared them with non-injured age and sports matched control athletes. Based on previous studies we hypothesized that MCAV and HRV would be blunted during the acute (T1) and sub-acute phases (T2, T3) following injury. The three time points chosen were in accordance with the National Institute of Neurological Disorders and Stroke (NINDS) recommendation for sports-related concussion that coincided with acute injury phase (day-3), sub-acute phase with typical symptom resolution (day-21) and chronic phase (day-90).

During the acute injury phase, hypermetabolism is followed by an energy crisis and simultaneous uncoupling of CBF regulation resulting in reduction in CBF (MacFarlane and Glenn, 2015). Heterogeneity in symptoms and different recovery trajectory following mTBI is likely related to this alteration in CBF (Meier et al., 2015; Metting et al., 2014). In mTBI patients, impairment in executive function at follow-up approximately 110 day post-injury, was related to reduced CBF at the acute phase of injury (Metting et al., 2014). Therefore, to further examine this pathophysiology, post-hoc analyses were performed to examine the association between MCAV during the acute injury phase and cognition during acute and sub-acute phases following concussion. The correlation between MCAV during the acute phase with HRV and CVCi, a measure of cerebral hemodynamic was also performed in the study.

2. Methods

2.1. Participants

Both men and women collegiate athletes participating in Division 1 and recreational contact-collision sports at our institution volunteered to participate in the study. Sports medicine physicians diagnosed the concussion in compliance with the recent concussion consensus statement (McCrory et al., 2017). A priori power analysis utilizing the findings from a study conducted on collegiate athletes were performed using G*Power statistical software (University of Düsseldorf, Germany) (Abaji et al., 2016). With an alpha level for error probability set at 0.05 for a 2-tailed test and with 80% power to detect a difference between power spectral metrics of HRV, a minimum of 15 athletes were determined to be required. Taking into account the longitudinal study design and anticipating subject attrition during follow-up, a total of sixty-two athletes were enrolled in the study, which included thirty-one athletes diagnosed with a concussion and thirty-one non-injured control athletes. Thirty-one athletes were assessed on day-3 (T1) post-concussion. Twenty-eight athletes from that group returned for a second visit on day-21 (T2) post-concussion and twenty-one athletes completed the final follow-up visit on day-90 (T3) post-concussion. All athletes were healthy, free of cardiovascular and respiratory diseases or any learning disabilities and were actively engaged in their sport at the time of entry into the study. All screenings and experimental procedures were approved by the Institutional Review Board at the Southern Methodist University (SMU), Dallas, Texas (Protocol # 2015-001-PURS) and were in accordance with the guidelines of the *Declaration of Helsinki*.

2.2. Clinical assessments

All experiments were performed in the Cerebrovascular Research Laboratory in the Department of Applied Physiology & Wellness at SMU. On the day of the laboratory visit, the participants were informed verbally about the study objectives and protocol prior to providing written consent. The subjects abstained from exercise, alcohol or caffeinated beverages 24 h prior to the laboratory visit. All follow-up visits were scheduled at the same time of the day. Both the concussed and the control athletes completed a health history questionnaire. Symptoms were evaluated at each visit with the sport concussion assessment tool 3rd edition (SCAT-3). Cognition was assessed with the standardized assessment of concussion (SAC), a component of SCAT-3. Higher SAC score is associated with better cognition. In addition, Trails making Tests A & B were administered to assess cognition, which includes executive function, attention, concentration and psychomotor speed (Bowie and Harvey, 2006). Adjusted Trails B score was derived as Trails B minus Trails A. The scores achieved from Trails making Tests A & B is the total time for completion of the tasks and a lower score is associated with higher level of cognitive skills.

2.3. Hemodynamics

All experiments were conducted in a quiet thermo-neutral environment of ~72 °F. The subjects were seated upright with arms rested on side tables for at least 30 min prior to data collection to account for fluid shift stabilization and to assure physiological steady state (Smith et al., 1994). Continuous RR interval recording was acquired with a standard 3-lead electrocardiogram (ECG) (Solar 8000i patient monitor, GE Healthcare, IL, USA). Continuous beat-to-beat mean arterial blood pressure (MAP) was recorded using finger photoplethysmography (Finometer Pro, Finapres Medical Systems, Amsterdam, Netherlands). Intermittent blood pressure recordings were also obtained using an automated ambulatory arm cuff (Tango, SunTech Medical, NC, USA) to ensure proper placement of finger cuff and accuracy of measurement throughout data collection. Transcranial Doppler ultrasonography (TCD) (Doppler BoxX, DWL USA, CA) was used to measure beat-to-beat middle cerebral artery blood flow velocity (MCAV). A 2 MHz probe was placed bilaterally over the temporal bone just above the zygomatic arch between the frontal process and the front of the ear to insonate the middle cerebral artery (MCA) at the M1 segment. An adjustable silicon headband was used to stabilize the Doppler probe for the duration of the study. MCAV was identified according to Aaslid et al.'s criteria and recording was made at a depth between 50 and 65 mm (Aaslid et al., 1984; Purkayastha and Sorond, 2012). The recording depth was kept constant for each subject during his/her follow-up visits. Expired CO_2 was continuously recorded with an infrared CO_2 analyzer (Capnocheck Plus, Smith Medical PM Inc, WI) connected to a nasal cannula to estimate end tidal CO_2 ($EtCO_2$). Subjects were instructed to breathe at a normal pace through the nose for the entire duration of the study. Rest data were collected for six-minutes while subjects sat upright and were instructed to sit still, remain quiet and relax with their eyes open. Data were collected in accordance with the guidelines provided for HRV (Camm et al., 1996; Quintana et al., 2016).

2.4. Data analysis

Analog ECG signals were sampled at 500 Hz and subsequently stored on a personal computer using the Windaq data acquisition system (Windaq DI720, DATAQ Instruments, OH, USA) for off-line analyses. The peak detection method inbuilt in the Windaq software was used for QRS detection. The peaks were visually inspected for ectopic beats and if found, the entire sample was excluded from the analysis. The resulting normal-to-normal RR intervals were included for the HRV analysis.

HRV was analyzed in the time and frequency domain utilizing Kubios HRV software, version 2.2 software (Biosignal Analysis and Medical Imaging Group, Kuopio, Finland) (Tarvainen et al., 2014). pNN50 was reported as the percentage of successive NN intervals differing by > 50 milliseconds to the total number of NN intervals in the sample. The square root of the mean squared differences (RMSSD) of successive NN intervals was also calculated. Both pNN50 and RMSSD provide cardiac vagal tone modulation in the time domain (Laborde et al., 2017). Prior to the analysis, the RR interval series was converted to equidistant sampled series by cubic spline interpolation and power spectrum was estimated from the Welch's periodogram. The method is explained in detail by the software programmer elsewhere (Tarvainen et al., 2014). The power spectrum estimate was obtained by integrating the fast Fourier transformation spectra and was divided into very low (VLF; 0–0.04 Hz), low (LF; 0.04–0.15 Hz) and high (HF; 0.15–0.4 Hz) frequency bands. Total power was calculated from the integration of the whole spectrum. Based on the guidelines of reporting one main HRV metric, pNN50 was utilized as the primary metric for assessment of cardiac vagal tone in the study (Laborde et al., 2017; Quintana et al., 2016).

Hemodynamic variables were obtained by averaging 6 min of steady state data. Mean arterial pressure (MAP) was determined from mean beat-to-beat blood pressure. Mean MCAV was determined and utilized as an index of CBF. Cerebrovascular conductance index (CVCi) was estimated by dividing beat-to-beat MCAV by MAP and average values were obtained from the six-minute data. CVCi is an estimate of cerebrovascular conductance resulting from changes in cerebral perfusion pressure and reflects changes in vascular tone during spontaneous fluctuations in blood pressure (Lautt, 1989; O'Leary, 1991).

2.5. Statistics

Mean and standard deviation are used to describe the clinical symptoms and physiological variables. Clinical symptoms, HRV, and cerebrovascular hemodynamics are compared between the controls and the concussed athletes at three time points (T1, T2, T3) using a non-parametric Mann-Whitney *U* test if the data are not normally distributed, and a *t*-test if the data are normally distributed. The level of significance for these pairwise comparisons was set at $\alpha \leq 0.0167$ (0.05/3) to account for possible errors due to the three comparisons performed per variable. In addition, the same testing procedures are used to examine differences in HRV, clinical symptoms, and cerebrovascular hemodynamics between the concussed athletes at each time point (T1, T2, T3).

In a separate post-hoc analyses, to assess if CBF during the acute phase is associated with recovery, cognition (SAC, Trails B, adjusted Trails B), HRV, and CVCi from the concussed subjects are modeled as functions of MCAV at T1 phase using linear regression. The regression analyses allow investigation of the relationship between MCAV at T1 on cognition, HRV and CVCi at the three time points during recovery. The reported p-value is associated with the linear regression coefficient, and thus a $p \leq 0.05$ implies a linear relationship between the cognition variable and MCAV at T1 exists. The statistical software R is used for these analyses.

3. Results

3.1. Demographics and baseline physiological data

For concussed subjects, assessments were made on 4 ± 1 day for T1, 22 ± 4 day for T2, and 95 ± 11 day for T3 visit. The characteristics of the control and the concussed athletes are summarized in Table 1. No differences in age, level of education, height, weight, BMI, and previous number of concussions ($p > 0.05$) were observed between the concussed and the control athletes. Symptoms, cognition scores and baseline physiological measurements between the control and the concussed athletes across the three time points are presented in Table 2. As anticipated, the concussed athletes on T1 reported higher symptom number ($p < 0.0001$) and higher symptom severity ($p < 0.0001$) on the SCAT-3 when compared to the control athletes. Symptom number and severity was comparable to the control during the T2 phase. Significant differences in Trails A and B were observed

Table 1
Demographics & subject characteristics.

	Control (N = 31)	Concussed (N = 31)
Demographics		
Age (years)	20 ± 1.2	20 ± 1.5
Female (N)	12	9
Caucasian (N)	18	13
Characteristics		
Height (m)	1.8 ± 0.1	1.8 ± 0.1
Weight (kg)	78 ± 17	86 ± 23
BMI (kg/m^2)	25 ± 3.09	26 ± 4.7
Education	15 ± 0.9	15 ± 1.1
Previous concussions	1 ± 1	1 ± 1

Values are means ± standard deviation.

Table 2
Symptoms & hemodynamic data.

	Control (N = 31)	Concussion		
		T1 (N = 31)	T2 (N = 28)	T3 (N = 21)
Symptoms (SCAT-3rd edition)				
Total symptom number	2.1 ± 3	11.7 ± 6.5*	2.8 ± 4†	1.5 ± 2.2†
Symptom severity	3.2 ± 5	28 ± 23*	3.7 ± 6†	2.3 ± 4†
Cognition				
SAC (SCAT-3rd edition)	28 ± 1.5	26 ± 2.2*	27 ± 2	27 ± 2.4†
Trails A (s)	22.6 ± 6.7	24.5 ± 8.1*	18.3 ± 4.8*,†	18.1 ± 4.0*,†
Trails B (s)	52.0 ± 11.4	55.8 ± 11.7	45.7 ± 10.2*,†	42.9 ± 11.1*,†
Adjusted trails B (B-A)	30.2 ± 10.3	31.3 ± 12.3	27.3 ± 8.7	24.8 ± 10.3*,†
Hemodynamic				
Heart rate (bpm)	65 ± 7	68 ± 9	69 ± 11	69 ± 10
Mean arterial pressure (mmHg)	84 ± 7	85 ± 8	88 ± 9	86 ± 7
Middle cerebral artery velocity (cm/s)	64 ± 14	64 ± 16	68 ± 15	66 ± 14
Respiratory rate (BPM)	16 ± 4	16 ± 3	15 ± 3	15 ± 3
End tidal CO_2 (mmHg)	39.5 ± 3.1	39.6 ± 2.4	38.9 ± 2.2	38.9 ± 2.4
CVCi (cm/s/mmHg)	0.75 ± 0.23	0.76 ± 0.19	0.77 ± 0.16	0.77 ± 0.17

Values are means ± standard deviation.
SCAT, sport concussion assessment tool 3rd edition; SAC, standard assessment of concussion; CVCi, cerebrovascular conductance index.
* $P < 0.05$ significant difference between control and T1.
† $P < 0.05$ within concussed group, significant difference from T1.

between the control and subjects during T2, and T3 phases, which may have been a result of training effect in the concussed group over time. No differences in heart rate, MAP, MCAV, respiratory rate, $EtCO_2$ or CVCi were observed between the control and the concussed athletes across the three time points.

3.2. Heart rate variability

HRV data is presented in Fig. 1. Compared to the controls (43 ± 15%), pNN50 was significantly lower at T1 (27 ± 20%; $p = 0.0012$) phase following concussion. pNN50 value was comparable to the controls during T2 (38 ± 20%), and T3 (36 ± 24%) phases. A significant difference in pNN50 ($p = 0.035$) within the concussed group was observed between T1 and T2 phases. The other time and frequency domain HRV metrics for the control and concussed athletes are presented in Table 3.

The relationship between HRV and CBF was further examined within the different time points following a concussion. MCAV at T1 phase was positively associated with pNN50 during sub-acute phases T2

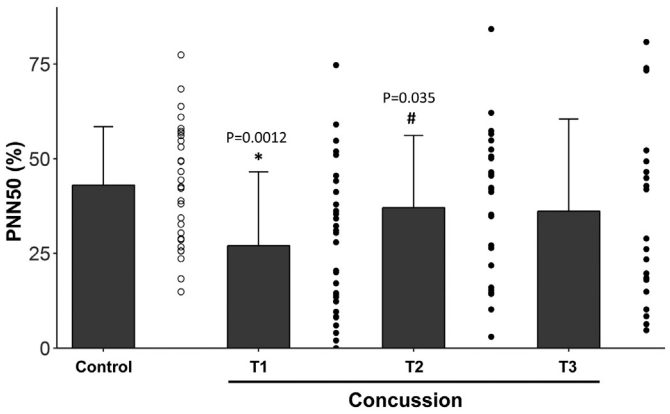

Fig. 1. Group (bar) and individual percentage of successive NN intervals (pNN50) in non-injured controls and concussed athletes at three time points (T1, day-3; T2, day-21, and T3, day-90) post-injury. Values are expressed as means ± standard deviation with stacked individual data. *Significantly different from the controls. #Within the concussed groups, significantly different from T1.

Table 3
Time & frequency domain HRV data.

	Control	Concussion		
		T1	T2	T3
Time domain				
RMSSD*	73 ± 31	53 ± 29*	63 ± 42	80 ± 45†
Frequency domain				
LF power (ms^2)	2051 ± 1555	2330 ± 2663	2007 ± 2320	2023 ± 1614
HF power (ms^2)	2356 ± 2700	1367 ± 1556*	1915 ± 2383	2912 ± 3606†
Total power (ms^2)	6757 ± 5766	5289 ± 4457	5515 ± 4350	7580 ± 7079

Time and frequency domain heart rate variability data in and controls and concussed at 3 time points.
Values are reported as means ± standard deviation.
RMSSD, root mean square of successive differences; LF, absolute low frequency power; HF, absolute high frequency power.
* $P < 0.05$ significant difference from control.
† $P < 0.05$ within concussed group, significant difference from T1.

($\beta = 0.55$, $p = 0.018$) and T3 ($\beta = 0.73$, $p = 0.03$) despite no association during the symptomatic T1 phase (Fig. 2). Furthermore, a positive association between MCAV during T1 phase was observed with CVCi during sub-acute phases T2 ($\beta = 0.004$, $p = 0.03$) and T3 ($\beta = 0.005$, $p = 0.04$) post-injury.

The relationship between MCAV and cognition within the concussed group was also examined. Overall, a strong positive relationship between MCAV and SAC ($\beta = 0.045$, $p = 0.009$) score was observed across the three time points. In addition, MCAV values during T1 phase were positively correlated to SAC scores during T1 ($\beta = 0.05$, $p = 0.03$) and T2 ($\beta = 0.08$, $p = 0.002$) phases post-injury (Fig. 3). Overall, a negative relationship between MCAV and Trails B ($\beta = -0.06$, $p = 0.002$) scores was observed across the three time points. In addition, MCAV values during the acute T1 phase were negatively correlated to Trails B scores during T1 ($\beta = -0.31$, $p = 0.02$) and T2 ($\beta = -0.35$, $p = 0.004$) phases post-injury. MCAV at T1 was also negatively correlated to adjusted Trails B during T2 phase ($\beta = -0.23$, $p = 0.032$) after concussion.

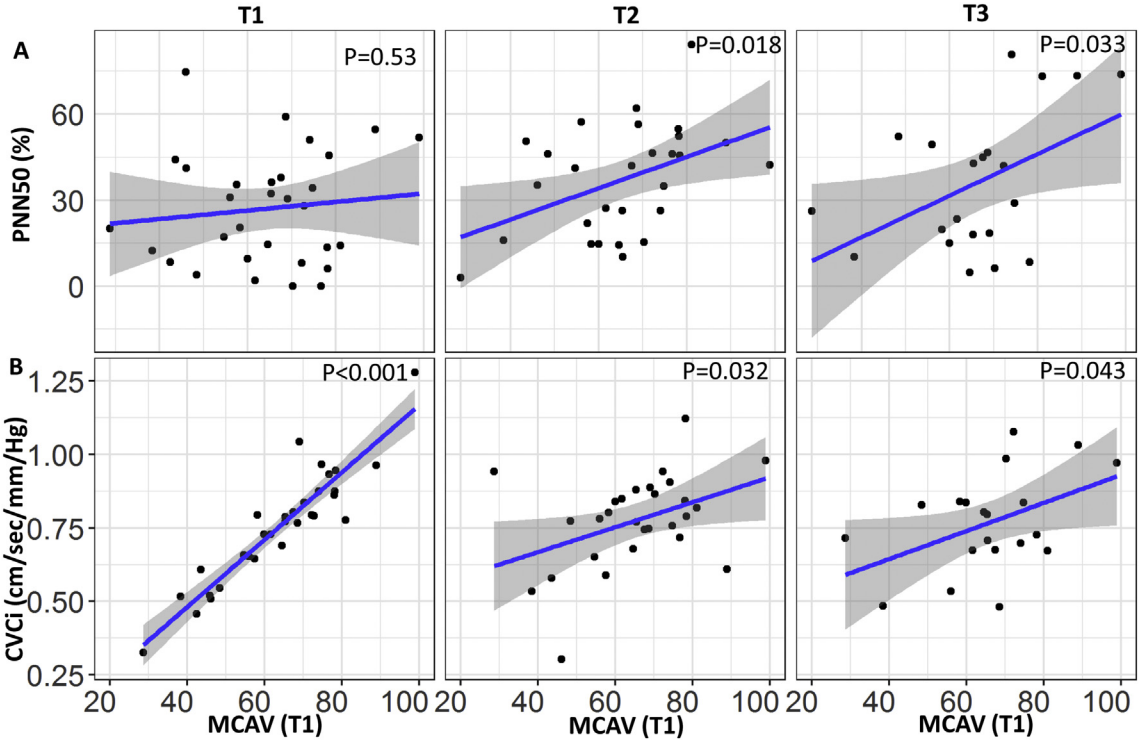

Fig. 2. Scatterplots indicating the relationship between (A) percentage of successive NN intervals (PNN50) and (B) cerebrovascular conductance index (CVCi) with middle cerebral artery blood velocity on day-3 [(MCAV) (T1)] in concussed athletes across three time points (T1, day-3; T2, day-21, and T3, day-90). The shaded region in each graph represents the 95% confidence intervals of the linear prediction line. p = level of significance.

4. Discussion

The major findings of this longitudinal study examining HRV during acute (day-3; [T1]) and sub-acute (day-21; [T2], and day-90; [T3]) phases after a concussion as are as follows; i) HRV measured as pNN50, was lower during the acute phase after a concussion compared to the non-injured control however; HRV was comparable to the control during T2, and T3 sub-acute phases, ii) no difference in MCAV between

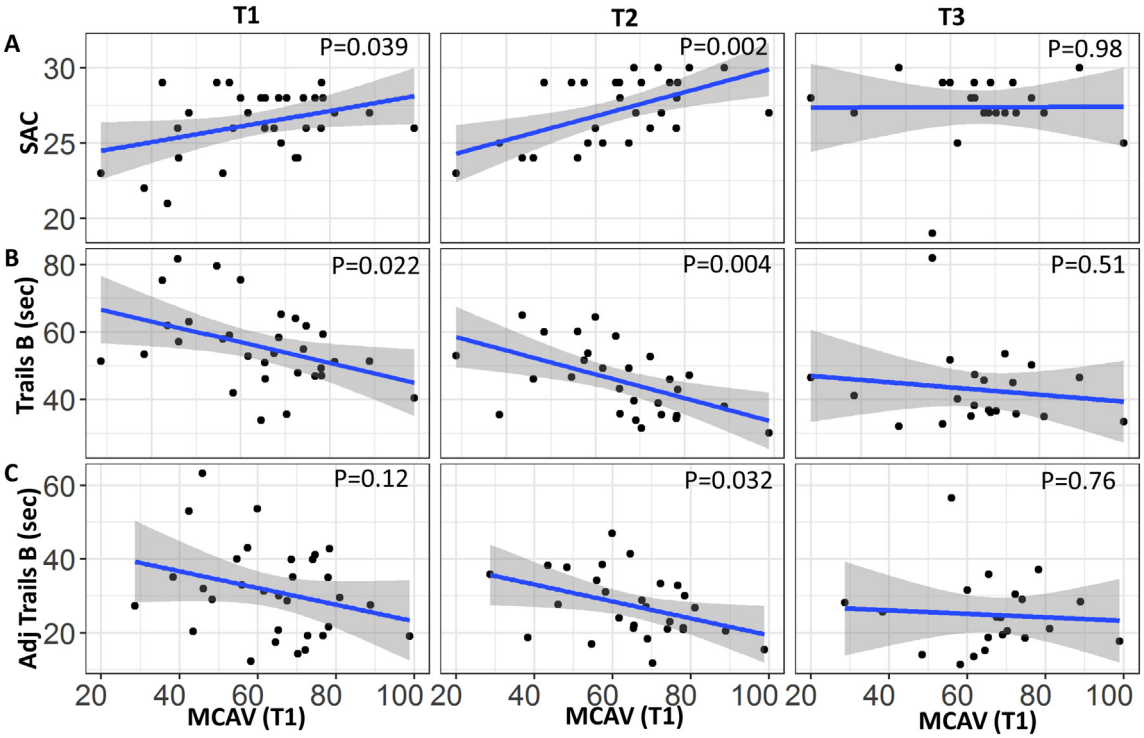

Fig. 3. Scatterplots indicating the relationship between cognition outcomes (A) standard assessment of concussion (SAC), (B) Trails B, and (C) adjusted Trails B with middle cerebral artery blood velocity on day-3 [(MCAV) (T1)] in concussed athletes across three time points (T1, day-3; T2, day-21, and T3, day-90). The shaded region in each graph represents the 95% confidence intervals of the linear prediction line. P = alpha level of significance.

control and concussion groups across the three time points were observed, iii) however, a positive relationship between MCAV at T1 phase with pNN50 and CVCi during T2, and T3 phases were present, iv) higher MCAV at T1 was also associated with better cognition scores (SAC, Trails B, and adjusted Trails B) during the asymptomatic T2 recovery phase within the concussed subjects. Although heterogeneity in cognition recovery across various domains are reported, in young adults overall recovery occurs approximately 7 day post-injury (Karr et al., 2014). In summary, our findings demonstrate recovery of HRV metrics within 3-weeks of a concussion. In addition, our results also support an association between CBF, HRV and functional outcome in a prospective cohort of collegiate athletes with a concussion.

No differences in mean MCAV and CVCi were observed between the control and the concussed athletes across the three time points. However, within the concussed athletes, higher MCAV was positively associated with higher HRV. Our results corroborate previous findings that demonstrated that higher HRV at rest is associated with greater CBF (Allen et al., 2015). Differences in MCAV within the concussed athletes may be one of the underlying causes behind heterogeneity in clinical symptoms and functional outcomes post injury (Jordan, 2013). The low CVCi following the injury could explain the lower MCAV within the concussed group.

There is extensive literature confirming the role of the ANS in the cerebral vasculature in humans (Ogoh et al., 2008; Purkayastha et al., 2013). During acute hypotension following a selective alpha-1 adrenergic blockade mediated inhibition of sympathetic neural activity, resulted in alterations in CVCi in healthy adults (Ogoh et al., 2008). In another study, blockade of alpha-1 adrenergic receptors resulted in augmentation of CVCi in at rest in healthy individuals confirming the role of sympathetic activity in CVCi (Purkayastha et al., 2013). Although in the present study, sympathetic activity was not examined, exaggerated sympathetic response is consistently reported following mTBI (Hilz et al., 2011; Leddy et al., 2017). Therefore, in the present study decreases in CVCi and simultaneous reductions in MCAV may have resulted from exaggerated sympathetic activity as a result of mTBI.

Concussion is associated with reduced global and regional CBF (Meier et al., 2015; Wang et al., 2016). Reduced CBF and subsequent impairments in clinical assessments were evident up to a month post-injury. Of particular interest, hypoperfusion of the dorsal mid-insular cortex has been observed at 1 day and 1 week after a concussion (Meier et al., 2015). The dorsal mid-insular cortex is part of the central autonomic network and plays an important role in the integration of sympathetic and parasympathetic neural activity within the ANS. Similar findings of alterations in regional CBF and functional connectivity in several regions of the brain, including the insular cortex, during the acute recovery phase post-concussion has been reported (Churchill et al., 2017). The insular cortex is perfused by the middle cerebral artery and therefore, MCAV measured in our study is reflects blood flow to the insular cortex (La Fountaine, 2017; Türe et al., 2000). Lower CBF, specifically hypoperfusion of the ANS integration center may have resulted in subsequent manifestations of the clinical symptoms (Giza and Hovda, 2014). Our present findings corroborate the association between MCAV and poor HRV in the collegiate athletes during the sub-acute recovery phases. In mTBI patients, impairment in executive function during sub-acute recovery phase approximately 110 day post-injury, was related to reduced CBF at the acute phase of injury (Metting et al., 2014). Therefore, our study provides further evidence that cognitive deficits may be related to impairment in CBF and ANS dysregulation following a sport-related concussion.

Conflicting results on HRV at rest, assessed from 48 h up to 43 months, i.e. acute concussion to post-concussion syndrome phase have been previously reported (Abaji et al., 2016; Gall et al., 2004; Hilz et al., 2011). No differences in HRV at rest were reported between concussed and control athletes acutely (2 days) and sub-acutely (95 days) following concussion (Abaji et al., 2016; Gall et al., 2004). On the other hand, HRV disturbances were observed at rest 7 days following concussion and after the athletes returned to play, suggesting persistent ANS disturbances beyond symptom resolution (Senthinathan et al., 2017). Our results corroborate the latter findings with lower HRV observed in the concussed group as early as 4 days after a concussion. The discrepancy in prior findings between the studies may have resulted from the differences in the time points of measurement following a concussion, the use of HR monitors instead of ECG for data acquisition; the latter is required for identifying ectopic beats and therefore accurate analysis and interpretation of HRV (Bishop et al., 2018; Quintana et al., 2016). In addition, HRV could also be confounded by differences in physiological state during data acquisition or anticipatory response to exercise, which are some of the known factors influencing HRV (Quintana et al., 2016).

Although the physiological recovery window for concussion is not yet established, Vagnozzi et al. documented that metabolic disturbance persists beyond symptoms resolution and can last up to 30 days (Vagnozzi et al., 2008). A recent systematic review incorporating multiple modalities to evaluate physiological changes post-concussion concluded that physiological recovery surpasses clinical recovery with disturbances lasting for > 15 days but < 30 days after injury (Kamins et al., 2017). Our results reflect a similar trend with physiological function deficits such as blunted HRV, lower MCAV, and reduced CVCi persisted for up to three week post-injury. Physiological recovery was evident bat the three-month time-point when the measurements were obtained.

In this study we refrained from utilizing LF power and LF/HF ratio to infer sympathetic modulation because of the complex non-linear reciprocal interaction between the sympathetic and parasympathetic nervous system (Billman, 2013). The LF power is not a reflection of sympathetic activity. Studies have suggested that parasympathetic activity contributes at least 50% of HRV in the LF range and the sympathetic activity accounts for 25% of LF HRV and the remaining results from unidentified factors (Billman, 2013). In the present study pNN50, a time domain metric was utilized as a surrogate measure of cardiac vagal modulation (Laborde et al., 2017).

4.1. Study limitations

To analyze HRV during the acute phase following concussion, it was pertinent to enroll volunteers early in their post-injury phase. However, due to academic commitments and a wide range of symptom burden, the athletes were not able to visit the laboratory on one specified day following injury. On average athletes visited the laboratory within 4 ± 1 day post-injury. Respiratory rate is a factor known to influence HRV in individuals (Draghici and Taylor, 2016). In the present study respiratory rate was not paced anticipating a distraction while subjects were at rest. However, no difference in respiratory rate was observed between the concussed and control athletes indicating that HRV findings were not influenced by respiratory rate. To eliminate any differences in ANS modulation due to disparities in physical fitness, the control athletes were sports matched and actively participating in their team at the time of the study. Therefore, the difference in HRV at rest due to differences in physical conditioning is very unlikely. In the present study, MCAV was measured using TCD ultrasonography. Changes in blood flow velocity (MCAV) reflect volumetric blood flow (CBF) only if the diameter of the insonated vessel remains constant (Serrador et al., 2000). The change in MCA diameter between subjects at rest is very improbable and therefore, MCAV was an indicator of CBF.

5. Conclusion

In summary, the longitudinal study designed to examine acute and sub-acute phases in sports-related concussion confirms deficits in physiological function and associated cognition impairment during the recovery phase following a concussion. HRV was lower as early as 4 day

post-injury compared to non-injured control athletes. A positive relationship between MCAV during the acute phase and HRV was observed during the sub-acute recovery phases despite no difference in the group average of MCAV across the three time points. In addition MCAV during the acute phase was also tightly correlated to cognition during the sub-acute recovery phase. Our findings suggest that disparities in CBF during the recovery phase following a concussion may be the underlying cause for poor cognition. Future studies in a larger sample size are warranted to validate our finding.

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Author contribution

Conception and design of research: SP, and KRB. Data collection and analyses: SP, BW, MM, & SL. Manuscript was drafted by SP, BW, MM, SL, TS and KRB. All authors contributed to data interpretation, editing, and revision of the manuscript. All authors approved the final version of the manuscript.

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