

## Original Article

# Use of Mayer wave activity to demonstrate aberrant cardiovascular autonomic control following sports concussion injury

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**Dysregulation of cardiovascular autonomic control is gaining recognition as a prevailing consequence of concussion injury. Characterizing the presence of autonomic dysfunction in concussed persons is inconsistent and conventional metrics of autonomic function cannot differentiate the presence/absence of injury. Mayer wave (MW) activity originates through baroreflex adjustments to blood pressure (BP) oscillations that appear in the low-frequency (LF: 0.04–0.15 Hz) band of the BP and heart rate (HR) power spectrum after a fast Fourier transform. We prospectively explored MW activity (~0.1 Hz) in 19 concussed and 19 noninjured athletes for 5 min while seated at rest within 48 h and 1 week of injury. MW activity was derived from the LF band of continuous digital electrocardiogram and beat-to-beat BP signals (LFHR, LF-SBP, MWHR, and MW-SBP, respectively); a proportion between MWBP and MWHR was computed (cMW). At 48 h, the concussion group had a significantly lower MWBP and cMW than controls; these differences were gone by 1 week. MWHR, LFHR, and LF-SBP were not different between groups at either visit. Attenuated sympathetic vasomotor tone was present and the central autonomic mechanisms regulating MW activity to the heart and peripheral vasculature became transiently discordant early after concussion with apparent resolution by 1 week.**

**Keywords:** mild traumatic brain injury; sympathetic nervous system; arterial blood pressure regulation; baroreflex

## Introduction

The arterial baroreflex is the mechanism responsible for the regulation and buffering of acute perturbations to arterial blood pressure (ABP) in response to changing posture and physical or psychological demands that result in loading or unloading of the baroreceptors (i.e., rise or fall in ABP, respectively).<sup>1,2</sup> The baroreceptors are mechanosensitive nerve endings that innervate the adventitia of the carotid sinuses and aortic arch.<sup>2–4</sup> Upon mechanical deformation of the arterial wall

with each ejection of blood, an action potential is triggered within the baroreceptors and transmitted through cranial nerves IX and X to a synapse in the nucleus tractus solitarius (NTS). From the NTS, there are neuronal projections to the insular cortex<sup>5</sup> and caudal ventrolateral medulla, which provides tonic inhibition of the rostral ventrolateral medulla (RVLM).<sup>6</sup> The RVLM is the primary regulatory center of the sympathetic nervous system (SNS); efferent signals descend from here through the spinal cord to SNS preganglionic nerve fibers, the

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sympathetic chain ganglia, and then the post-ganglionic projections to the end organs, such as the heart and peripheral vasculature.<sup>6,7</sup> The arterial baroreflex has sensitivity and tolerance to ABP perturbations,<sup>8</sup> and baroreceptor sensitivity (BRS) serves as an important indicator of cardiovascular autonomic nervous system (CV-ANS) (dys)function in a range of health and disease conditions.<sup>8</sup>

CV-ANS dysfunction is becoming an increasingly recognized secondary consequence of concussion injuries. For reasons that are unclear and subject to speculation,<sup>9–11</sup> the pathophysiological consequences of concussion result in aberrant CV-ANS functions after injury. Numerous reports demonstrate the presence of altered heart rate or blood pressure variability (HRV and BPV, respectively),<sup>10</sup> changes to the arterial pulse wave contours,<sup>12</sup> baroreceptor dysfunction,<sup>13–16</sup> and case reports of anomalous electrocardiogram (ECG) findings<sup>17,18</sup> in concussed individuals who are often compared with a matched control group of noninjured athletes undergoing parallel observations. The dysfunction is most often present in observations that occur early after an injury, with a resolution to control group levels at some remote period after the incident.<sup>9,10</sup> In some cases, there is evidence for a persistent disparity of CV-ANS function from control group levels in those that are symptom-free and presumed to have recovered from the concussion injury.<sup>19,20</sup> Similar to other symptoms that may be experienced after a concussion (i.e., posttraumatic headache, cognitive impairment, photosensitivity, etc.), it is likely that CV-ANS dysfunction is not present in all individuals who experience an injury. Given the number of structures within the ANS involved in the regulation of beat-to-beat ABP, the complexities of their interactions, and the risk of influence by circadian rhythms or the psychophysiological state, conventional metrics of HRV or BPV may not be adequately capturing postinjury dysfunction and they have yet to identify those in whom CV-ANS dysfunction is present after a concussion injury.

Mayer waves (MWs)<sup>21</sup> are cyclical variations in ABP that arise through baroreflex-mediated adjustments to efferent sympathetic vasomotor tone.<sup>22,23</sup> The origin of MW activity is not fully agreed upon but is generally accepted to be a byproduct of changing efferent sympathetic outflow to vascular

tissues and vagal activity to the sinoatrial node as a function of the arterial baroreflex. Our current understanding of MW origins come from various experiments in animals and humans that have targeted different centers, receptors, and pathways via pharmacological blockade.<sup>22–24</sup> In humans, MW activity can be found at a frequency of  $\sim 0.1$  Hz and quantified by performing spectral decomposition of continuous digital ABP recordings<sup>25–27</sup> and the cardiac R-R interval as measured by an ECG.<sup>28–30</sup> A prior study by our group found that male athletes with a recent concussion injury had a marked reduction in BRS compared with a control group of male athletes without concussion.<sup>15</sup> The primary purpose of this report was to evaluate MW activity in the context of BRS among recently concussed athletes and noninjured controls during the first week following a concussion injury. A secondary aim was to discern if MW activity could provide objective evidence to identify those individuals with concussion in whom CV-ANS dysfunction was most likely present after injury.

## Methods

### Participants

The study procedures were approved by the institutional review board and all participants provided written informed consent before participating. As part of the clinical evaluation at the time of a suspected injury that occurred during practice or competition, the athletes were evaluated and diagnosed by the sports medicine staff using accepted clinical practices guidelines of concussion assessment for both immediate on-field and subsequent office-based follow-up evaluations that included symptom evaluation.<sup>31–33</sup> To determine the presence of a concussion, an injured athlete underwent a physical and neurological examination, an assessment of cognitive function and standing balance. These evaluations were aided by the use of the sport concussion assessment tool (SCAT), which is an industry standard in the evaluation of a suspected concussive head trauma.<sup>31–33</sup> If the injured party had positive signs and symptoms that were consistent with concussion, they were withheld from participation. In the event of a medical emergency (i.e., Glasgow Coma Scale  $< 13$ , prolonged loss of consciousness, or worsening somatic/cognitive or other neurological symptoms), the injured athlete was taken to the emergency department.

Otherwise, the injured party was reevaluated after a brief rest period to confirm the presence of symptoms. The final diagnosis of concussion was made by a physician trained in the care of mild traumatic brain injuries. Once the diagnosis was confirmed, the injured athlete was evaluated by sports medicine staff on a consistent daily basis over the subsequent days until the symptoms resolved. Clinical decision making on return-to-play (RTP) of concussed athletes was made by the sports medicine staff, and did not include any input from data collected in the research study. The number of days that an individual with concussion was symptomatic was tracked clinically and for this study were characterized as having symptoms for <7 days (i.e., RTP <1 week) or more than 1 week (i.e., RTP  $\geq$  1 week). Once the concussed athlete was free of symptoms, they began a five-stage clinically driven RTP protocol.

For the purposes of research participation, a candidate with a concussion injury was deemed by the principal investigator to have capacity to provide informed consent by demonstrating the ability to orient to person, place, time, and a current event. To be eligible for the research study, the athlete with a diagnosed concussion injury must have sustained their injury within the previous 48 h, be able to demonstrate capacity to provide written informed consent, not be taking medications with direct or indirect actions on the cardiovascular or central nervous systems, and be free of acute illness or trauma that would otherwise minimize their ability to complete the study procedures. Participants for the control group were recruited from in-season athletes with a goal of matching these individuals based on gender, sport, and when possible, sport position (attempt to account for fitness levels) with participants in the group with concussion. Control participants were enrolled based upon meeting the previously outlined guidelines, excepting for the presence of concussion. The number of diagnosed concussions that each participant sustained during their lifetime was obtained via self-report. As a result of their injury and the timing of enrollment in the first study visit, athletes with concussion were at least 24 h removed from their most recent bout of exercise. These individuals were also unlikely to engage in strenuous exercise for the week between study visits due to the participation restrictions arising from the presence and persistence of concussion symptoms. Similarly, because our testing

window occurred in the morning (details to follow), all control participants were at least 12 h removed from their most recent exercise bout before performing the study visits.

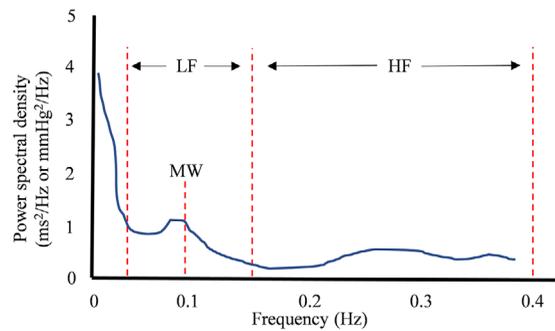
### *Data collection and signal processing*

The initial study observation occurred in a research laboratory within 48 h of injury (i.e., Visit 1) and was repeated 1 week later (i.e., Visit 2); participants in the control group completed two visits separated by 1 week. Data collection occurred between 8:00 a.m. and 12:30 p.m. for all study visits and the second study visit occurred within a  $\pm 30$ -min window of the start time from the initial visit to mitigate the impact from circadian variations. Similarly, participants were required to abstain from consuming alcohol-containing or caffeinated beverages for at least 12 h prior to data collection. The laboratory environment was thermoneutral (i.e.,  $\sim 70$  °F) and overhead lights were turned off; ambient lighting in the room came from exterior windows. At each study visit, a continuous 3-lead ECG (Lead II) and beat-to-beat finger ABP monitor using photoplethysmography was collected during 5 min of quiescent seating. The seated upright position was selected as a means to provoke the CV-ANS in a controlled and noneffort-dependent manner; this position requires accommodation by the ANS to buffer the hydrostatic gradient caused by the upright posture. ECG site preparation was performed according to clinical standards and the placement of three electrodes was standardized for continuous HR monitoring. Beat-to-beat ABP was obtained from the second and third finger of the right hand using a commercially available and FDA-approved photoplethysmography-based ABP monitor (CNAP Monitor 500, CNSystems Medizintechnik AG, Graz, Austria). Respiration rate was obtained using a respiration belt transducer (Biopac Systems Inc., Goleta, CA) that was placed distal to the xiphoid process and around the thorax.

After instrumentation and before data collection, participants remained seated in the upright position with their right arm elevated and resting on a foam pad at heart level and parallel to the surface of the floor with the elbow flexed to 90° at quiet rest for approximately 20 min to acclimate to the testing environment. After acclimation to the seated position, 5 min of continuous resting data were obtained during which the participants

breathed at a self-selected pace. Digital ECG, beat-to-beat ABP, and respiratory rate were collected at a sampling rate of 500 Hz with a commercially available data acquisition system (Biopac MP150, Biopac Systems Inc.) using proprietary software (Acknowledge v. 4.2, Biopac Systems Inc.). Data were archived for subsequent offline analysis. Finger ABP was calibrated by the device (CNAP Monitor 500, CNSystems Medizintechnik AG) for each data collection against the brachial artery pressure.

Offline data analysis was performed with customized programs created with LabVIEW software (National Instruments, Austin, TX). For each data file, the digital signals were visually inspected and ectopic beats, if present, were removed from the analysis using a customized LabVIEW program. Raw digital data files were filtered with a zero-lag fourth-order Butterworth filter with default cutoff frequencies of 6 Hz (high pass) and 100 Hz (low pass filter). Peak detection was performed on all QRS complexes and systolic blood pressure (SBP) peaks; the R-R intervals and beat-to-beat SBP were interpolated to create separate continuous time series signals. HRV and BPV variability were calculated by power spectral analyses using a discrete Fourier transform. The resulting power spectra were numerically integrated and the area of the power spectral density (PSD) curve in the corresponding bandwidths for oscillations in the low-frequency (LF; 0.04–0.15 Hz) and high-frequency (HF; 0.15–0.40 Hz) power spectra was calculated to reflect: cardiac parasympathetic modulation (HF-HRV); cardiac sympathetic and parasympathetic modulation (LF-HRV); and sympathetic modulation of peripheral vasomotor tone (LF-SBP).<sup>34–37</sup> The respiratory rate was confirmed by evaluating the corresponding spike and frequency in the HF band of the PSD curve at each visit. MW activity for ABP oscillations and heart period activity were obtained from the power spectrum density curves at  $\sim 0.1$  Hz (MW-SBP and MW-HR, respectively) by the analysis software. An example PSD curve is provided in Figure 1 to demonstrate the respective frequency bands and location of MW activity. To facilitate parametric statistical analyses, the respective HF-HRV, LF-HRV, LF-SBP, MW-HR, and MW-SBP values for each participant were log<sub>10</sub> transformed. The MW-HR and MW-SBP variables were also used to calculate the MW proportion ( $cMW = MW-HR/MW-SBP$ ). Spontaneous BRS was calculated from the R-R



**Figure 1.** Example power spectral density curve with high-frequency (HF) and low-frequency (LF) band ranges, and location of Mayer wave (MW) peak.

interval and beat-by-beat SBP using the bivariate phase rectified signal averaging technique.<sup>38</sup> The BRS was normalized (BRSn) to the corresponding mean directional SBP change for increasing (BRSn-UP) and decreasing SBP (BRSn-DN) within a participant's signal for each visit.<sup>39,40</sup> These values (e.g., BRSn-UP and BRSn-DN) were averaged to provide a single measure of BRS (BRSn-Avg) for each subject and visit. These computations were identical to those in our prior report on BRS after concussion.<sup>15</sup>

### Statistical analyses

Values are expressed as group mean  $\pm$  SD unless otherwise indicated. Pearson chi-square tests were performed to determine if the groups differed for the composition of gender and ethnicity within the cohort. Between-subjects analyses of variance (ANOVA) were performed to identify group differences (i.e., control and concussion) for demographic data (age, height, weight, and BMI) and Visit 1 hemodynamics (i.e., HR, SBP, and diastolic blood pressure (DBP)), CV-ANS function (i.e., HF-HRV, LF-HRV, and LF-SBP), respiration rate, BRS (i.e., BRSn-Avg, BRSn-Up, and BRSn-Dn), and MW outcomes (i.e., MW-HR, MW-SBP, and CMW) variables. The interaction effects from separate  $2 \times 2$  (group: control, concussion; visit: Visit 1, Visit 2) mixed ANOVAs were performed to determine if group-specific changes in hemodynamics (i.e., HR, SBP, and DBP), CV-ANS function (i.e., HF-HRV, LF-HRV, and LF-SBP), respiration rate, BRS (i.e., BRSn-Avg, BRSn-Up, and BRSn-Dn), and MW outcomes (i.e., MW-HR, MW-SBP, and CMW) variables occurred from Visit 1 to Visit 2. To explore the effect of RTP status on outcomes

**Table 1.** Demographic characteristics of participants

	Control ( <i>n</i> = 19)	Concussion ( <i>n</i> = 19)	95% CI for mean difference	Significance ( <i>P</i> value)
Age (years)	19.8 ± 1.3	19.8 ± 1.5	−0.97 to 0.97	1.00
Height (m)	1.71 ± 0.11	1.76 ± 0.14	−0.03 to 0.13	0.20
Weight (kg)	70.2 ± 14.4	75.3 ± 15.1	−4.39 to 13.7	0.30
BMI (kg/m <sup>2</sup> )	23.7 ± 2.2	24.4 ± 4.1	−1.61 to 2.73	0.61
Gender: M/F ( <i>n</i> )	10/9	11/8	—	1.00
Ethnicity: AA/Cauc/Hispanic ( <i>n</i> )	5/10/4	3/15/1	—	0.11
Past concussions ( <i>n</i> )	0.9 ± 1.9	0.5 ± 0.7	−0.22 to 1.07	0.19

NOTE: Data are presented as group mean ± SD. *P* values represent significant group main effects.

BMI, body mass index; M, male; F, female; AA, African American; Cauc, Caucasian; Hisp, Hispanic.

that were significant in the 2 × 2 analyses, separate 3 × 2 (group: control, RTP < 1 week, RTP ≥ 1 week; visit: Visits 1 and 2) mixed ANOVAs were also performed. Statistical analyses were carried out using IBM SPSS<sup>®</sup> Statistics 25 (IBM, Armonk, NY) and Jamovi software (version 1.2), and figures were created with GraphPad Prism<sup>®</sup> (version 8.4.1 for Windows, GraphPad Software, San Diego, CA). An *a priori* level of significance was set at *P* ≤ 0.05.

## Results

Nineteen intercollegiate athletes with a concussion and 19 control participants volunteered to participate in this prospective observational study. Demographic characteristics for the control and concussion groups are provided (Table 1). CV-ANS and hemodynamic information are also provided for each group by visit (Table 2). The demographic composition of participants in the control and concussion groups was similar and there were no statistical differences between groups. At Visit 1, hemodynamics, respiratory rate, and CV-ANS outcomes did not differ between groups, with the exception of MW-SBP, which was significantly lower in the concussion compared with the control group (*P* = 0.015, 95% CI of the mean difference: −0.76 to −0.09, Cohen's *d* = −0.87, Table 2). However, the group × visit interaction effect (*P* = 0.09, partial  $\eta^2$  = 0.08) did not reach significance. Separately, the group × visit interaction effect for LF-HRV was significant (*P* = 0.045, partial  $\eta^2$  = 0.11). However, the small effect size and marginal *P* value relative to the number of analyses performed suggests a likely trivial response in this variable. The MW-HR and MW-SBP plots are graphically

depicted to demonstrate the group mean and individual outcomes for each visit (Fig. 2).

The result of the BRS analyses showed significant main effects for group for all BRS indices (BRSn-Up: *P* = 0.001, *d* = −0.26, 95% CI of the mean difference: −1.32 to 0.162; BRSn-Dn: *P* < 0.001, *d* = −0.324, 95% CI of the mean difference: −1.56 to 0.01; BRSn-Avg: *P* < 0.001, *d* = −3.04, 95% CI of the mean difference: −0.68 to 0.06; Table 2). These results indicate large differences in BRS between those who have experienced a concussion compared with controls. None of the BRS group × visit interaction effects were significant (all *P*'s > 0.17), indicating no group-specific differences from Visit 1 to Visit 2. The main effects for visit were not significant for BRSn-Up (*P* = 0.12), BRSn-Dn (*P* = 0.053), or BRSn-Avg (*P* = 0.07). Since this effect was collapsed across group, the effect is not central to our research question.

The ratio between the MW-HR and MW-SBP, referred to as the cMW, was significantly elevated in the concussion group compared with the controls at Visit 1 (*P* < 0.001, 95% CI: 0.42–1.61, *d* = 1.12; Fig. 3). The group × visit interaction effect was significant (*P* < 0.001, partial  $\eta^2$  = 0.26) showing a marked decline in the concussion group from Visit 1 to Visit 2 (Fig. 3). The cMW demonstrated that more than 50% of the participants with concussion exceeded the control group distribution at V1; the cMW proportion of 3.0 appeared to be the threshold beyond which this differentiation occurred.

For the secondary analyses exploring the role of RTP status on cMW and BRSn-AVG, 13 participants with concussion were found to have symptoms for less than 1 week (i.e., RTP < 1 week) and six were symptomatic for more than 1 week

**Table 2.** Cardiovascular autonomic and hemodynamic profile of participants by visit and group

	Visit 1		P value (Group)	95% CI (mean difference)	Visit 2		P (Group × Visit interaction)
	Control	Concussion			Control	Concussion	
Heart rate (bpm)	63 ± 7	61 ± 10	0.30	−8.36 to 2.67	64 ± 9	64 ± 8	0.13
Systolic blood pressure (mmHg)	112 ± 20	118 ± 20	0.42	−7.95 to 18.80	114 ± 12	117 ± 17	0.56
Diastolic blood pressure (mmHg)	62 ± 5	66 ± 9	0.36	−2.70 to 7.23	66 ± 10	65 ± 11	0.47
Respiration rate (breaths per minute)	14.1 ± 0.6	14.0 ± 0.8	0.82	−0.62 to 0.50	13.9 ± 0.6	14.0 ± 0.5	0.64
Heart period power spectrum (ms <sup>2</sup> /Hz)							
High frequency (0.15–0.40 Hz)	3.33 ± 0.56	3.45 ± 0.47	0.49	−0.22 to 0.46	3.31 ± 0.55	3.25 ± 0.52	0.31
Low frequency (0.04–0.15 Hz)	3.54 ± 0.52	3.65 ± 0.38	0.44	−0.18 to 0.41	3.53 ± 0.42	3.46 ± 0.37	0.045
Mayer wave activity (~0.1 Hz)	4.38 ± 0.57	4.38 ± 0.63	1.00	−0.39 to 0.39	4.25 ± 0.65	4.16 ± 0.90	0.66
Systolic blood pressure power spectrum (mmHg <sup>2</sup> /Hz)							
Low frequency (0.04–0.15 Hz)	1.03 ± 0.41	0.98 ± 0.51	0.64	−0.38 to 0.24	1.02 ± 0.40	1.01 ± 0.40	0.71
Mayer wave activity (~0.1 Hz)	1.89 ± 0.39	1.46 ± 0.60	0.015	−0.76 to −0.09	1.88 ± 0.60	1.83 ± 0.58	0.092
Mayer wave activity proportion (cMW)	2.35 ± 0.46	3.36 ± 1.20	<0.001	0.42–1.61	2.31 ± 0.63	2.36 ± 0.91	<0.001
Baroreceptor sensitivity (ms/mmHg)							
BRSn-Avg	6.25 ± 2.56	2.91 ± 2.01	<0.001	−4.8 to −1.82	6.47 ± 2.37	4.05 ± 3.19	0.22
BRSn-Up	6.12 ± 2.66	2.97 ± 2.02	<0.001	−4.7 to −1.59	6.25 ± 2.33	4.00 ± 3.24	0.23
BRSn-Dn	6.46 ± 2.65	2.78 ± 2.10	<0.001	−5.26 to −2.10	6.69 ± 2.75	4.09 ± 3.20	0.17

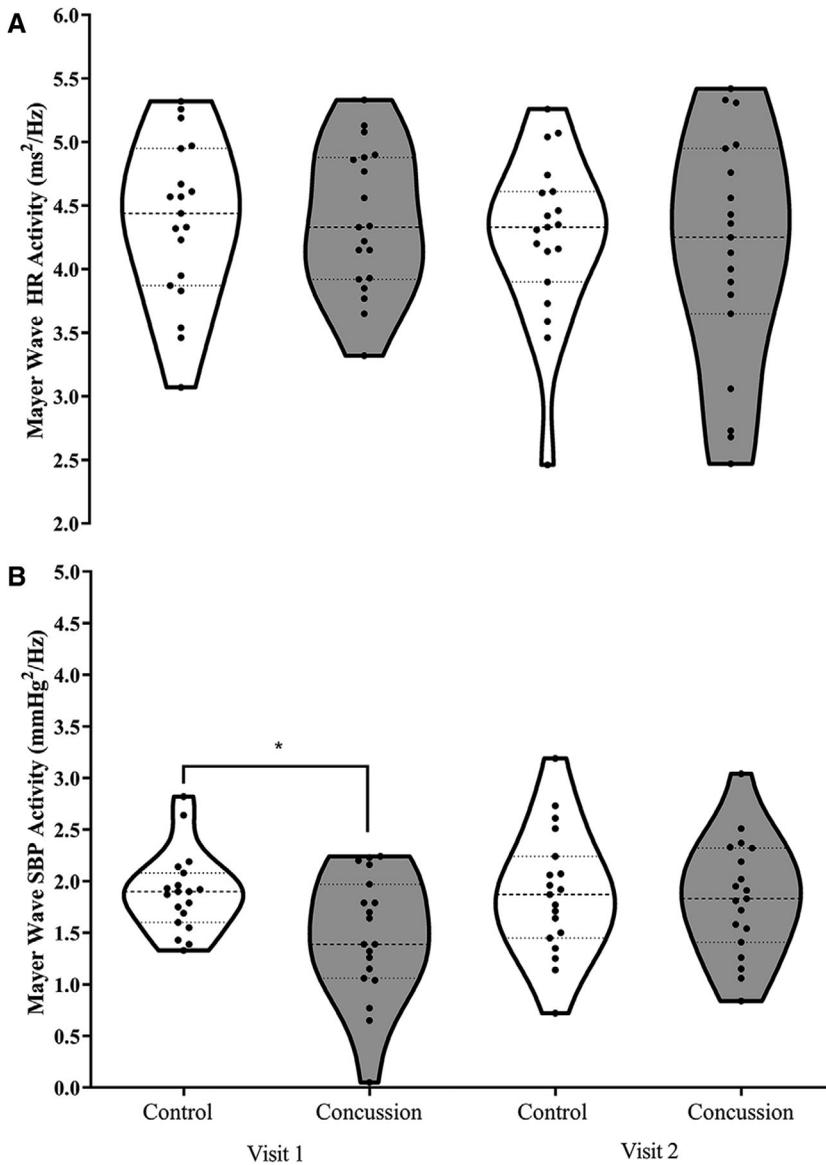
NOTE: Data are presented as the group mean ± SD. *P* values represent significant main effects for each visit. bpm, beats per minute; BRSn, normalized baroreceptor sensitivity; Hz, hertz; mmHg, millimeters of mercury.

(i.e., RTP ≥ 1 week). Between-subjects ANOVA at Visit 1 for cMW revealed that a significant difference existed between groups ( $P < 0.001$ ,  $\eta^2 = 0.33$ ). For this comparison, five out of six participants with RTP ≥ 1 week and five out of 13 participants with RTP < 1 week exceeded the 3.0 proportion. Tukey post-hoc tests indicated that the RTP ≥ 1 week group had a significantly greater cMW than the controls ( $P = 0.001$ , 95% CI: 0.64–2.63) and trended toward a significant difference between the RTP < 1-week group and control group ( $P = 0.064$ , 95% CI: −0.04 to 1.49) and between the RTP > 1 week and RTP < 1 week groups ( $P = 0.10$ , 95% CI: −0.14 to 1.95) (Fig. 4). The interaction effect for the group × visit analysis ( $P < 0.0001$ , partial  $\eta^2 = 0.36$ ) revealed the presence of a different group response in cMW from Visit 1 to Visit 2. Tukey post-hoc tests indicated that the RTP ≥ 1 week group had a significantly greater change in cMW than the control group from Visit 1 to Visit 2 ( $P < 0.001$ , 95% CI: −2.53 to −0.68), while the comparisons between +1 week and −1 week ( $P = 0.065$ , 95% CI: −1.89 to 0.05) and between −1 week and controls ( $P = 0.06$ , 95% CI: −1.39 to 0.03) did not reach significance. For the same analyses of BRSn-AVG, between-subjects ANOVA at Visit 1 revealed that a significant difference existed between groups ( $P < 0.0001$ ,  $\eta^2 = 0.36$ ). Tukey post-hoc tests indicated that the control group had a significantly higher BRSn-AVG than the RTP ≥ 1 week group ( $P = 0.006$ , 95% CI: 0.96–6.29) and the RTP < 1 week group ( $P = 0.001$ , 95% CI: 1.15–5.25)

(Fig. 5). The interaction effect for the group × visit analysis ( $P = 0.15$ ) did not achieve significance for the BRSn-AVG response from Visit 1 to Visit 2.

## Discussion

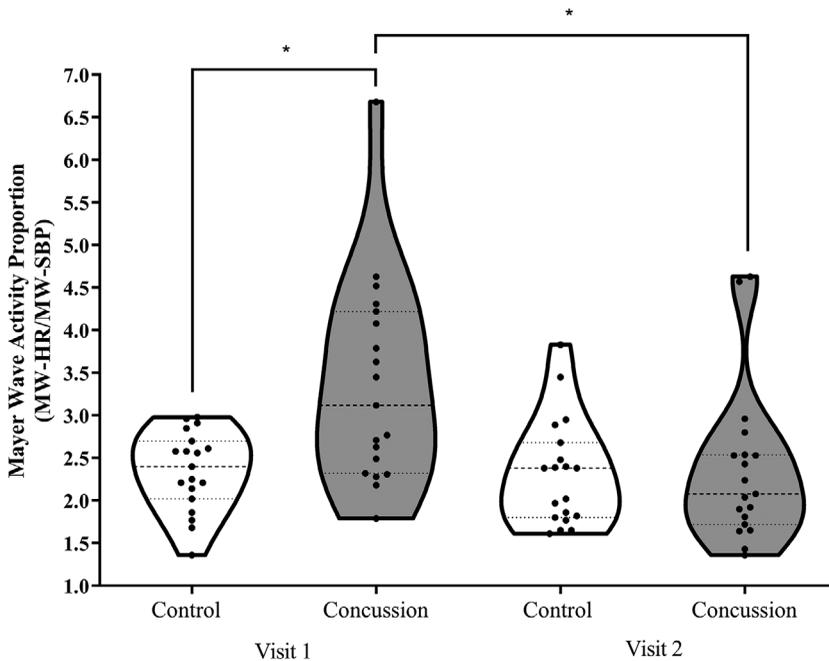
The current report has several novel insights as to how MW activity can inform about the presence of CV-ANS dysfunction after concussion injury while measurements were taken in the seated position during the first postinjury week. The changes in BRSn-AVG between groups at Visit 1 confirm our prior observations of reduced BRS after concussion<sup>15</sup> and underlie the impaired arterial baroreflex after concussion injury. The quantification of MW activity in the HR and SBP signals demonstrated that a concussion injury differentially impacted the CV-ANS outflow to the cardiac pacemaker and peripheral vasculature. The differential impact was highlighted by the computation of the cMW, which is the computed proportion between the respective MW activity in the HR and SBP signals. First, cMW was different between concussion and control groups within 48 h of injury (e.g., Visit 1) and demonstrated that more than 50% of the participants with concussion exceeded the control group distribution at Visit 1, with a proportion value of 3.0 appearing to be the point of delineation. If not for two control participants at Visit 2, the former statement would have been true for each visit as 36 out of 38 control group observations were less than 3.0. Second,



**Figure 2.** Truncated violin plots demonstrating the Mayer wave activity in the HR and SBP signals by group and visit. Each violin plot presents the group median (---) and interquartile range (.....). The truncation of each plot represents the minimum and maximum observation for each group. The dark circles within each plot represent each participant's data. \**P* < 0.001.

cMW identified a large percentage of those participants with concussion who experienced longer symptoms after injury, as demonstrated by the duration of time until entering the RTP protocol. In this scenario, ~38% of participants with RTP < 1 week and ~83% of participants with RTP ≥ 1 week exceeded the 3.0 proportion. There were no demographic or injury-related outcomes from the study that provided a basis for the differences between

those participants with concussion who had similar cMW, but different RTP durations. Third, given that the cMW is a proportion, the analyses revealed that the MW-HR activity was very consistent between groups and across visits, but the MW-SBP activity was below the control group observations in more than half of the participants with concussion at Visit 1; this threshold corresponded to an MW-SBP amplitude of ~1.4 mmHg<sup>2</sup>/Hz. Finally, with the

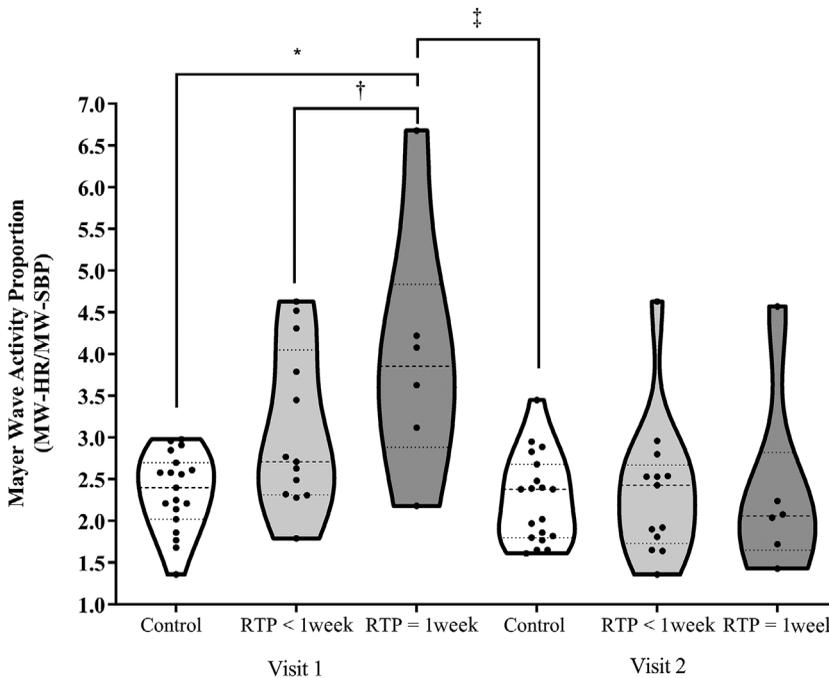


**Figure 3.** Truncated violin plots demonstrating the Mayer wave proportion by group and visit. Each violin plot presents the group median (---) and interquartile range (.....). The truncation of each plot represents the minimum and maximum observation for each group. The dark circles within each plot represent each participant's data. \* $P < 0.001$ .

exception for the BRS outcomes, the conventional metrics of CV-ANS function did not identify any group differences at the corresponding study visits. More specifically, the MW-SBP activity at  $\sim 0.1$  Hz identified a seemingly aberrant vasomotor pattern that the conventional LF-SBP metric, which encompasses the entire 0.04–0.15 Hz range, did not.

Under normal circumstances, the initiation of physiological work from a resting state or an orthostatic challenge leads to a well-orchestrated CV-ANS response to accommodate cardiac output and total peripheral resistance to meet the increasing demand or to buffer the SBP perturbation. These responses are completed through a several-step process and the magnitude of the response is partially determined by the initial blood pressure changes sensed by the loading/unloading of the arterial baroreceptors. Briefly, parasympathetic nervous system activity through the vagus nerve (cranial nerve X) is withdrawn from the sinoatrial node, permitting the heart rate (HR) to increase. In addition, resting state tonic inhibition of the RVLM is unencumbered and the disinhibited state per-

mits an increase of SNS outflow to the peripheral vasculature, sinoatrial node, and myocardium. The timing of these events is not entirely synchronized and the changes to HR precede the SBP response. It may be possible that the different MW activity in the HR and SBP signals among all participants, which is highlighted by the cMW, represents an intrinsic difference in the beat-to-beat regulation of the effector organs (i.e., heart and vasculature) under normal physiological situations. The concussive event disrupts this normal balance/rhythm, most notably to the peripheral vasculature in  $\sim 50\%$  of the concussed participants, leading to a larger cMW. Albeit not in the context of MW activity, a prior report demonstrated that the central autonomic centers and peripheral effector organs are subject to uncoupling after a traumatic brain injury such that HRV and BRS are inversely associated with the severity of neurological injury.<sup>41</sup> Researchers who study CV-ANS dysfunction after concussion posit that abnormal observations of HRV, BPV, or BRS after injury represent a lower magnitude uncoupling of what was previously demonstrated.<sup>9–11,14,16</sup>



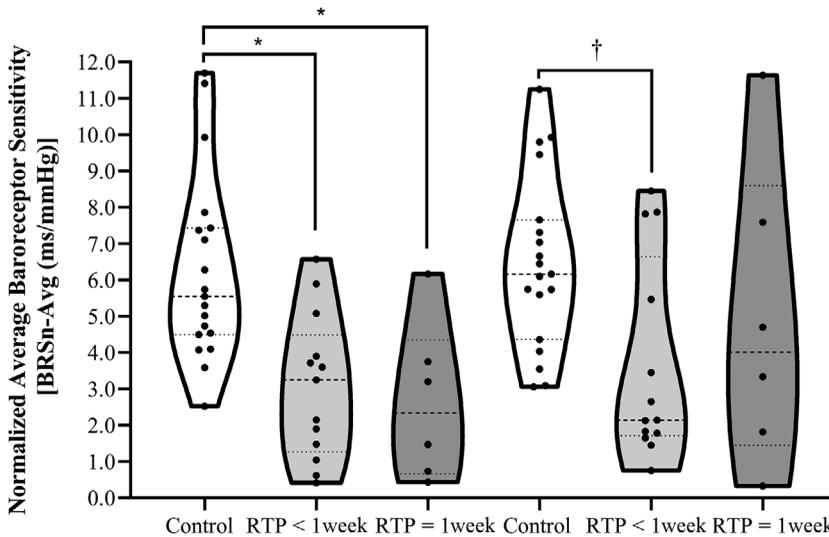
**Figure 4.** Truncated violin plots demonstrating the Mayer wave proportion by RTP group and visit. Each violin plot presents the group median (---) and interquartile range (.....). The truncation of each plot represents the minimum and maximum observation for each group. The dark circles within each plot represent each participant's data. \* $P = 0.001$ , † $P = 0.07$ , ‡ $P < 0.0001$ .

The computation of cMW appears to be the first parameter to objectively quantify this phenomenon such that specific individuals who may be subject to the greatest risk of having sustained a more severe neurological injury from the concussive event are identifiable.

MW oscillations in the ABP signal are strongly correlated with muscle sympathetic nerve activity (MSNA),<sup>25,26,42</sup> which is an invasive data collection procedure that uses a microelectrode inserted into a superficial, peripheral nerve.<sup>43,44</sup> The burst amplitude and activation patterns of MSNA have been rigorously studied and are an accepted measurement of sympathetic outflow from the central nervous system.<sup>25,26,42</sup> MW activity is ablated under controlled experimental conditions in neurologically intact persons receiving pharmacological blockade of sympathetic outflow.<sup>45,46</sup> In addition, demonstrations of blunted or paradoxical MW activity in the ABP signal of persons with spinal cord injury reinforce the impact of central nervous system trauma and blunted sympathetic outflow in real-life conditions.<sup>47-51</sup> Therefore, a finding that approximately 50% of our concussion cohort had

significantly blunted MW-SBP activity within 48 h of injury suggests that these persons experienced a diminution of efferent sympathetic outflow, despite having similar SBP and DBP measurements as the control group. The demonstration of reduced MW-SBP early after concussion, but not 1 week later, is a likely reflection of secondary, indirect consequences of the concussive insult manifesting as dysregulation of autonomic integration in the central nervous system and efferent outflow through the SNS, as opposed to being a direct effect of trauma. The absence of group differences for MW-HR activity was not entirely unexpected given that participants were in a seated and resting position, which are conditions predominated by parasympathetic drive to the sinoatrial node. Prior work in humans demonstrated that the use of atropine to induce a partial parasympathetic blockade of the heart decreased fluctuations across the HF and LF bands, which includes the MW frequency.<sup>30</sup>

Unfortunately, the novelty of using MW activity in the evaluation of persons with concussion injury limits the ability to reconcile the present observations with those that are already in the



**Figure 5.** Truncated violin plots demonstrating the BRSn-Avg by RTP group and visit. Each violin plot presents the group median (---) and interquartile range (.....). The truncation of each plot represents the minimum and maximum observation for each group. The dark circles within each plot represent each participant's data. \* $P < 0.001$ ; † $P < 0.05$ .

literature. There is inconsistency in the concussion and autonomic dysfunction (AD) literature due in large part to the use of different technology and data acquisition devices, time points for data collection, the use of different positions and provocations, and an absence of consensus about the most appropriate variables to report for the time and frequency domains and other emerging outcomes. These sentiments are more thoroughly described in a recent systematic review of AD and concussion.<sup>10</sup> Nonetheless, the current findings highlight that individuals who sustain a concussion may not all have the same CV-ANS reactions to injury. AD after a concussion does not appear to occur in all individuals following injury based on the similarity to control group observations at the 48-h time point. The presentation of AD is more likely to manifest in a similar pattern of unpredictability and inconsistency that is known to occur with the conventional clinical symptoms (e.g., affective, cognitive, somatic, vestibular-oculomotor, etc.). To account for this likelihood, the field will have to adopt new approaches and reach consensus on how to stratify concussed individuals by the presence or absence of AD, as opposed to only categorizing them as having a concussion. Further work is needed to help characterize how cMW or MW-SBP can inform about the presentation of AD and reduced BRS after concussion. In addition, the

use of self-reported symptoms and their respective magnitude, as well as other positive findings of dysfunction, should be incorporated into future studies to enable a better understanding of the functional impacts of AD on the postconcussive experience.

### Limitations and future directions

Some limitations of our study need to be considered. First, our cohort of concussed athletes was a small and fairly homogeneous sample of college-aged athletes, and the generalizability of the results to the general population is limited. This study, like others that evaluate CV-ANS after concussion, did not have preinjury data from which the postinjury outcomes could be compared with. A larger and more diverse cohort of recently concussed athletes from a broad range of sports is needed to reproduce our findings to enhance generalizability and long-term implications. The present study was performed while the participants were in the seated position. Therefore, these findings and threshold values are unlikely to be repeated if persons are evaluated in different postures (e.g., supine and standing) or while physiological and psychological provocations are performed.

### Conclusion

The current study demonstrates that MW activity at  $\sim 0.1$  Hz provides insight on AD that occurs

during the first week after sustaining a concussion that conventional metrics of CV-ANS function did not. The observed changes in MW activity after concussion were most notable in the ABP signal, suggesting that central efferent autonomic outflow to the peripheral vasculature was disrupted in some participants with concussion, but not others, without having an impact on SBP or DBP. With further exploration, this approach has the potential to serve as an autonomic biomarker to identify AD after concussion, especially in those with a longer symptomatic presentation.

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## Author contributions

M.F.L. was involved in conception and study design, acquisition of data, data/statistical analysis with interpretation, manuscript preparation, and final approval of the manuscript. A.N.H. and C.L.L. were involved in acquisition of data, manuscript preparation, and final approval of the manuscript. A.J.T. was involved in conception and study design, manuscript preparation, and final approval of the manuscript. J.P.W. was involved in data/statistical analysis with interpretation, manuscript preparation, and final approval of the manuscript.

## Competing interests

The authors declare no competing interests.

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