Cerebrovascular Reactivity Impairment after Sport-Induced Concussion

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[1]*Faculty of Kinesiology and Health Studies, University of Regina, Regina, Saskatchewan, CANADA;* [2]*Traumatic Stress Group, University of Regina, Regina, Saskatchewan, CANADA;* [3]*Department of Biomedical Physiology and Kinesiology, Simon Fraser University, Burnaby, British Columbia, CANADA;* [4]*Department of Pediatrics, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, CANADA; and* [5]*Department of Occupational Therapy, University of Alberta, Edmonton, Alberta, CANADA*

ABSTRACT

LEN, T. K., J. P. NEARY, G. J. G. ASMUNDSON, D. G. GOODMAN, B. BJORNSON, and Y. N. BHAMBHANI. Cerebrovascular Reactivity Impairment after Sport-Induced Concussion. *Med. Sci. Sports Exerc.*, Vol. 43, No. 12, pp. 2241–2248, 2011. **Purpose**: This study evaluated cerebrovascular reactivity (CVR) after a sport-induced concussion, also called mild traumatic brain injury (mTBI), by monitoring middle cerebral artery blood velocity (vMCA) with transcranial Doppler ultrasonography and simultaneous end-tidal carbon dioxide ($PETCO_2$) measurements. **Methods**: Thirty-one athletes (16–25 yr old) participated in this study. The participants were divided into two groups—healthy ($n = 21$) and mTBI ($n = 10$). Participants in the mTBI group suffered an mTBI within the last 7 d ($\bar{x} = 4.5 \pm 1.1$ d). Outcome measures included vMCA and $PETCO_2$ in response to breath holding (5 × 20 s, 40-s rest) and hyperventilation (5 × 20 s, 40-s rest). **Results**: Resting vMCA values between groups were not significantly different. Percentage change of vMCA was significantly different after the recovery period of the second hyperventilation ($P = 0.034$). mTBI subjects failed to return to resting levels after each breath hold. $PETCO_2$ changes mirrored the vMCA changes. **Conclusions**: These data suggest that normal CVR responses may be disrupted in the days immediately after occurrence of mTBI. Transcranial Doppler ultrasonography combined with expired gas measurements provides a useful method for assessing CVR impairment after mTBI. Further research, including serial monitoring after mTBI and analysis of CVR response to exercise, is warranted before any firm conclusions can be drawn. **Key Words:** MILD TRAUMATIC BRAIN INJURY, PATHOPHYSIOLOGY, CEREBROVASCULAR REACTIVITY, TRANSCRANIAL DOPPLER, CEREBRAL BLOOD VELOCITY, CONCUSSION

Incidence of sport-induced concussion or mild traumatic brain injury (mTBI), particularly in ice hockey, has increased considerably during the last decade (11). The majority of the research into mTBI has been directed toward the neuropsychological aspect of the injury, and not until recently has focus been placed on the pathophysiology of mTBI in the sport arena (24). Systemic physiological effects of mTBI include altered HR variability and decreased baroreflex sensitivity, cellular metabolism, and cerebral blood flow (13,18,20). Current treatment guidelines for mTBI focus on neuropsychological outcomes of pre- and postinjury testing and a gradual return-to-play protocol (28). Objective physiological measures are not reflected in these considerations. This lack of information leads to increased demand for research into pathophysiological effects of mTBI and their relationship to already established neuropsychological consequences.

Transcranial Doppler ultrasonography has been used in monitoring cerebral blood flow velocity (CBFV) in a variety of clinical conditions. The ability to noninvasively provide objective measures of the brain's response to outside stimuli has proved effective in previous research. The middle cerebral artery (MCA) is typically the vessel of choice for transcranial Doppler insonation. Velocity estimates using transcranial Doppler ultrasonography rely on the assumption that MCA diameter remains approximately constant, and much research has been completed operating under this assumption (3,31,35,44). Previous studies have reported that, in humans, the diameter of the MCA does not change significantly in response to changes in arterial carbon dioxide ($PaCO_2$) (16,36,43). Thus, it has been suggested that changes in mean MCA blood velocity (vMCA) are a relative indicator of changes in cerebral blood flow (12,31,43). Although human data are not available, it has been shown in rodents that changes to MCA diameter can be altered in response to changes in the local chemical environment of the vessel (15).

The most influential vascular modulator of CBFV is $PaCO_2$ (2), and the resultant reaction of changes in $PaCO_2$ is termed cerebrovascular reactivity (CVR). Numerous studies have analyzed CVR and cerebral autoregulation, and it should be recognized that the underlying mechanisms of

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each are distinct entities (7,19). Variations in $PaCO_2$ cause a vasodilatory response in the cerebral vasculature. Decreasing $PaCO_2$ or hypocapnia elicits a drop in vMCA and vice versa in response to hypercapnia or increased $PaCO_2$ (26,30,37). Others have illustrated that $PaCO_2$ and end-tidal carbon dioxide ($PETCO_2$) are well correlated, and therefore, the latter has been used as a surrogate for $PaCO_2$ (5,6).

CVR is impaired after a traumatic brain injury (9,17). Various methods and procedures are used to assess CVR in healthy and diseased subjects. CO_2 inhalation, acetazolamide, hyperventilation (HV), and breath holding (BH) are commonly used in analyzing CVR. BH and HV have been shown to be reliable and provide reproducible results in measuring CVR (27,37,39,42). Research into the duration that each of the methods should be performed is limited. Studies have shown that 20- to 30-s durations are acceptable and provide an optimal response to both BH and HV (8,25,26,37).

Multiple techniques can be used in examining the effects of mTBI on the functioning of the cerebrovascular system. This study proposed to observe and document vMCA changes in response to hypocapnia and hypercapnia in healthy and mTBI subjects as well as develop an experimental protocol, in light of the recent Concussion in Sport Group (CISG) guidelines (28), to further examine the pathophysiology of mTBI. We hypothesized that significantly different vMCA responses to hypercapnic and hypocapnic challenges would be elicited between healthy subjects and those having recently suffered mTBI. This information would provide a physiological benchmark in the recovery of an individual with mTBI or sport-induced concussion.

METHODS

Subjects. Thirty-one subjects (28 male, 3 female) were divided into two groups on the basis of previous history of mTBI. Twenty-one subjects were mTBI free in the previous 2 months before physiological assessment and were used as a control group. Ten of the subjects had suffered an mTBI within the previous 7 d. Average time since injury was 4.5 ± 1.1 d. All mTBIs were assessed by a certified athletic therapist using the Sport Concussion Assessment Tool guidelines and confirmed by a physician (28). Average age of all subjects was 21.4 ± 1.7 yr, height was 181.5 ± 8.7 cm, and weight was 83.7 ± 9.8 kg (see Table 1 for mTBI subjects' demographics). There was no previous history of cardiovascular disease or other metabolic conditions, nor were any subjects taking any medications. All healthy subjects were asymptomatic at rest as determined by the Sport Concussion Assessment Tool symptom checklist (28) and currently competing in their respective sport. All procedures were approved by the Research Ethics Board of the University of Regina. Informed written consent was obtained, and thorough explanations of the procedures and objectives of the study were given to each subject before participating.

Equipment. Transcranial Doppler ultrasonography was used to monitor cerebral blood velocity. A 1.6-MHz Doppler probe (Nicolet Companion III; VIASYS Healthcare, Burlington, Canada) was placed over the right temporal window and adjusted until an optimal signal of the MCA was found. Ultrasound gel was applied to enhance the quality of the signal, and search techniques previously described by others were used to ensure adequate signal-to-noise ratio (34). The probe was held in place by a thermally molded bracket attached to an adjustable headband strap (VIASYS Healthcare) preventing movement of the probe. The right MCA was initially selected for consistency of measurement and accessibility. If an optimal signal was not found on the right side, the left MCA was insonated (occurred in two healthy subjects). Others have shown no difference in vMCA from left to right sides in non–head-injured subjects (23). However, it must be noted that after more severe traumatic brain injury, regional changes may occur in the affected area of the brain (33,35). Cadence during BH and HV protocol was provided by an electronic metronome. An electronic cycle ergometer (ergoline 200p; ergoline, Bitz, Germany) was used during graded aerobic exercise. Breath-by-breath analysis of $PETCO_2$ was conducted using an automated expired gas analyzing system (SensorMedics Vmax 2200; VIASYS Healthcare).

Experimental protocol. A laboratory acclimation period of approximately 10 min occurred while subjects completed consent forms and medical histories. Once the transcranial Doppler probe was in place and the gas analysis system was set up and calibrated, each subject remained seated upright in a chair and was instructed to move minimally throughout the first part of the procedure. Baseline data were collected for 2 min. At the end of baseline collection, subjects were instructed to "take a normal breath and then hold it for 20 s." By using normal inspiration rather than a deep inspiration, a Valsalva effect was avoided, which may

TABLE 1. Demographics of mTBI subjects.

Subject	Days Since Injury	Age	Gender	Height (cm)	Weight (kg)	Sport
1	4	22	M	182	81	Hockey
2	7	16	M	176	65	Hockey
3	4	21	M	197	90	Hockey
4	5	19	F	160	68	Hockey
5	5	25	M	175	91	Hockey
6	3	21	F	163	63	Basketball
7	5	18	F	165	61	Hockey
8	4	23	M	185	83	Hockey
9	4	24	M	180	81	Hockey
10	4	21	M	194	91	Hockey
Mean ± SD	4.5 ± 1.1	21.0 ± 2.7	—	177.7 ± 12.5	77.4 ± 12.0	—

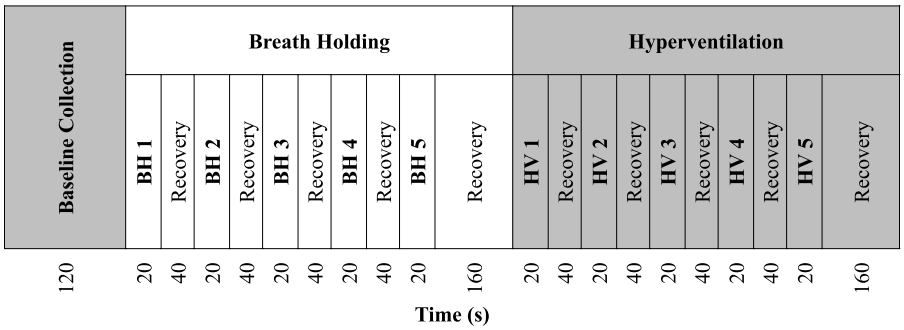

FIGURE 1—Chronological representation of the experimental testing protocol. The duration of each part of the challenge (s) is listed along the bottom of the chart.

cause an initial decrease in vMCA and lead to underestimation of reactivity (27). A countdown was given preparing each subject for BH. The 20-s hold was followed by 40 s of recovery or normal breathing. This was repeated five times. After 2 min of normal breathing, the subjects performed a 20-s HV at 36 breaths per minute using a metronome to maintain cadence. After 40 s of recovery, HV was repeated again for a total of five repetitions. Recovery data were then collected for an additional 2 min. Figure 1 provides a chronological outline of the testing protocol. All testing procedures followed the recommended return-to-play guidelines set forth by the second and third International Conferences on Concussion and Sport (28). If subjects became symptomatic or felt unable to continue, the test was to be immediately terminated. However, this situation did not arise throughout testing.

Outcome measurements. Data were sampled from the Doppler probe at 1 Hz and were analyzed offline. Mean resting values were computed by averaging the collected data during a 5-min span. Data were taken at the beginning and end of each BH. During HV, they were taken at 0, 5, 10, and 15 s from the beginning as well as at the end of each repetition. Percentage change in vMCA from resting values was calculated using the following formula:

$$\text{percentage change (\%vMCA)} = 100\left(\frac{\text{vMCA}_{\text{actual}} - \text{vMCA}_{\text{rest}}}{\text{vMCA}_{\text{rest}}}\right)$$

where $\text{vMCA}_{\text{actual}}$ is mean vMCA at each respective data point and $\text{vMCA}_{\text{rest}}$ is resting vMCA.

PETCO_2 values were collected at the same time points as the transcranial Doppler and were analyzed to assess the hyper- and hypocapnic response in all subjects.

Statistical analysis. Data were analyzed using statistical software (SPSS 15.0; Chicago, IL). Mean and SD were calculated for absolute vMCA values and %vMCA as well as PETCO_2. Because the participant groups were not equal in size, variance between groups was analyzed using the Levene test, and no violations of homogeneity were observed. A 2 (group) × 5 (repetition) repeated-measures ANOVA was used to compare responses to BH and HV between groups. Any significant *F*-ratios were subjected to *post hoc* analysis using independent *t*-tests. Resting values were compared using independent *t*-tests. All values are reported as mean ± SD. Statistically significant values have a *P* value of <0.05.

RESULTS

The coefficient of variation (CV) of vMCA and PETCO_2 was compared because of sample size differences between groups. In the healthy subjects, the CV of vMCA at rest (0.23) and during BH (0.20) and HV (0.21) was slightly higher than those of the mTBI group (0.16, 0.16, and 0.15, respectively). In terms of PETCO_2, the CV in the healthy group was also slightly higher than the mTBI group at rest (0.11 vs 0.05) and during BH (0.13 vs 0.08) and HV (0.19 vs 0.11). However, as mentioned above, the Levene test was not violated.

TABLE 2. Comparison of absolute and percentage vMCA change (mean ± SD) after each 20-s breath hold and HV.

		Absolute vMCA Change ($\text{cm}\cdot\text{s}^{-1}$)			Percentage vMCA Change (%)		
Repetition		Healthy	mTBI	*P*	Healthy	mTBI	*P*
BH	1	5.1 ± 6.5*	10.5 ± 9.9	0.961	13.7 ± 9.7**	14.7 ± 18.7*	0.957
	2	4.6 ± 7.2	4.6 ± 6.7	0.728	9.8 ± 12.8*	9.7 ± 16.1	0.848
	3	4.0 ± 7.8	1.0 ± 4.4	0.358	7.6 ± 13.5*	−0.5 ± 18.7	0.119
	4	6.9 ± 8.5*	6.0 ± 4.7	0.318	9.5 ± 12.9*	5.8 ± 16.8	0.544
	5	3.7 ± 5.6	7.8 ± 5.3	0.886	10.2 ± 18.6*	6.3 ± 19.0*	0.468
HV	1	−19.9 ± 11.8**	−22.5 ± 7.0*	0.265	−28.2 ± 17.1**	−36.7 ± 8.4**	0.182
	2	−19.5 ± 7.1**	−14.2 ± 5.0*	0.461	−35.2 ± 11.2**	−38.8 ± 9.1*	0.294
	3	−16.1 ± 5.2**	−9.2 ± 6.0	0.610	−36.2 ± 12.1**	−40.5 ± 9.3**	0.273
	4	−14.9 ± 6.6**	−8.3 ± 4.2	0.534	−39.2 ± 7.2**	−42.5 ± 11.3*	0.364
	5	−14.4 ± 6.0**	−9.5 ± 2.2*	0.467	−40.4 ± 7.9**	−42.1 ± 12.2*	0.662

Values are expressed as mean ± SD.
P indicates statistical value between groups for each trial. Significant changes from resting values within groups are indicated with symbols.
* $P < 0.05$.
** $P < 0.001$.

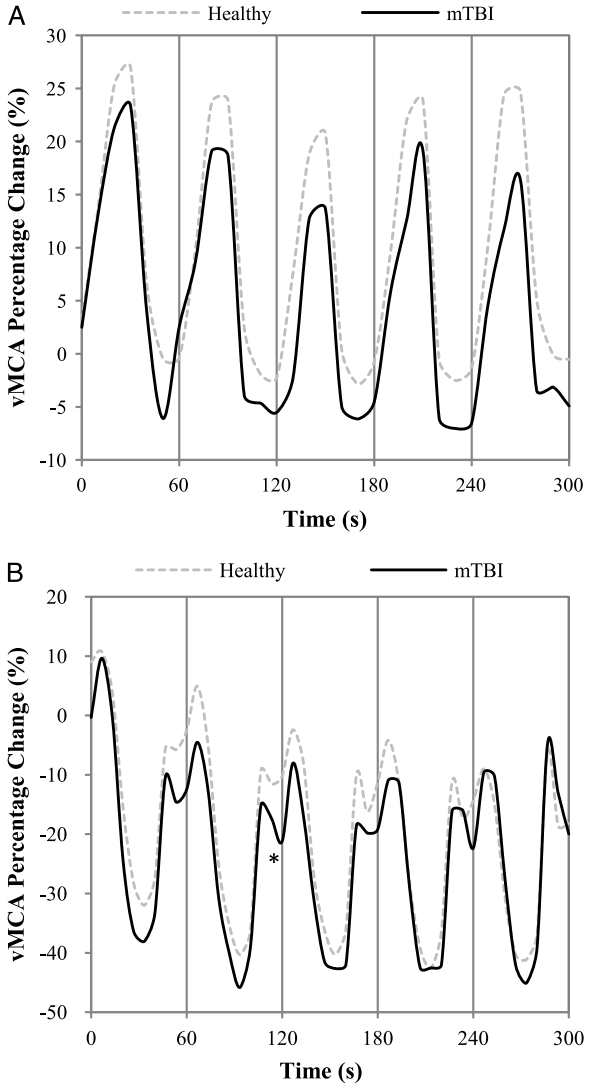

FIGURE 2—A, %vMCA response to five consecutive trials of 20-s breath holds in healthy (n = 21) and mTBI (n = 10) subjects. B, %vMCA response to five consecutive trials of 20-s HV in healthy (n = 21) and mTBI (n = 10) subjects. *Solid vertical lines* indicate beginning of each repetition. *Significant difference between groups, $P < 0.05$.

Resting values. Resting vMCA values in the healthy and mTBI groups were 52.5 ± 12.1 and 55.0 ± 8.8 $cm \cdot s^{-1}$, respectively, and did not differ statistically. Resting $PETCO_2$ was 35.8 ± 3.9 mm Hg in the healthy group and 34.0 ± 1.8 mm Hg in the mTBI group and did not differ significantly at rest.

BH (hypercapnia). Subjects in the mTBI group failed to return to resting vMCA levels (within 4.5%) after trials 3, 4, and 5. Healthy subjects returned to within 2.5% of resting values after each repetition. The groups did not differ significantly. A transient overshoot as rebreathing occurred was exhibited in both groups. Peak vMCA occurred approximately 5 s after the end of each BH. All repetitions of BH elicited a significant increase in %vMCA ($P < 0.05$).

%vMCA change after 20 s of BH ranged from 7.6% ± 13.5% to 13.7% ± 9.7% ($\bar{x}$ = 10.2% ± 13.5%) in the healthy subjects. The mTBI subjects' %vMCA change in each trial ranged from −0.5% ± 18.7% to 14.7% ± 18.7% ($\bar{x}$ = 7.2% ± 17.8%). There were no significant differences between groups after each BH repetition. %vMCA changes throughout the hypercapnic trial are summarized in Table 2 and Figure 2A.

As illustrated in Figure 3A, mean $PETCO_2$ after each BH was 40.6 ± 5.0 mm Hg with individual repetitions ranging from 39.6 ± 6.1 to 41.0 ± 4.9 mm Hg. $PETCO_2$ after each BH in the healthy subjects ranged from 41.0 ± 4.9 to 41.6 ± 5.1 mm Hg ($\bar{x}$ = 41.2 ± 4.9 mm Hg), whereas in the mTBI subjects, it ranged from 33.6 ± 6.2 to 40.5 ± 1.3 mm Hg ($\bar{x}$ = 37.9 ± 4.2 mm Hg). There were no significant differences between groups after each repetition. However,

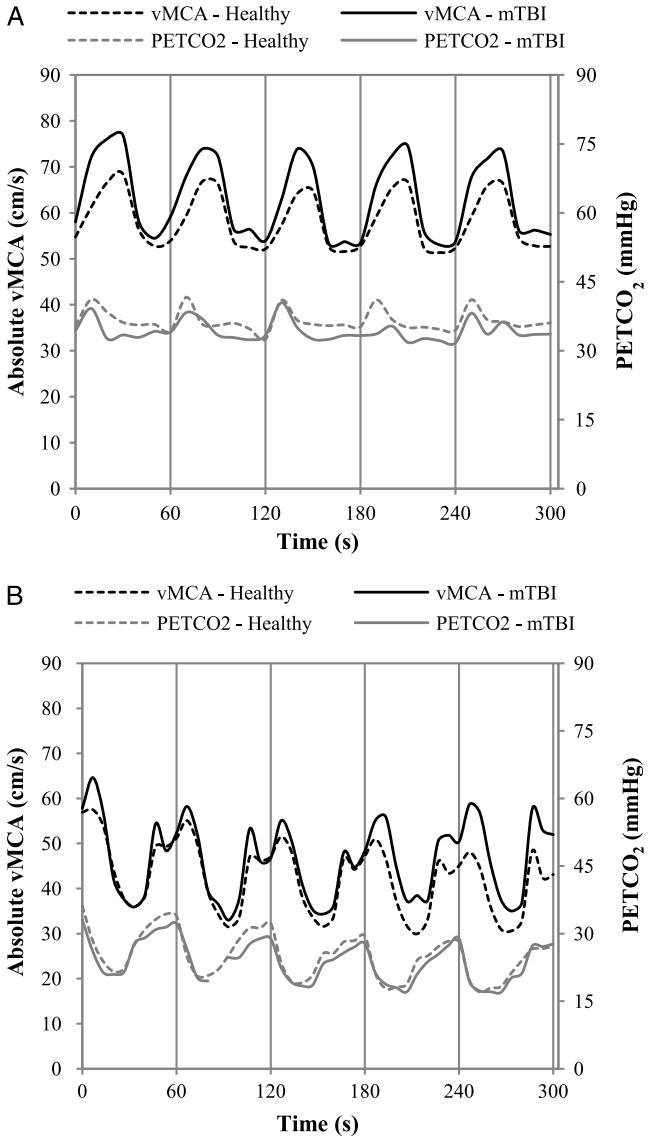

FIGURE 3—A, Absolute vMCA and $PETCO_2$ response to five consecutive trials of 20-s breath holds in healthy (n = 21) and mTBI (n = 10) subjects. B, Absolute vMCA and $PETCO_2$ response to five consecutive trials of 20-s HV in healthy (n = 21) and mTBI (n = 10) subjects. *Solid vertical lines* indicate beginning of each repetition.

there was a significant interaction effect of repetition and group after each BH trial ($\lambda = 0.386$, $F_{4,20} = 7.969$, $P = 0.001$).

HV (hypocapnia). During the HV trial, all subjects were able to keep pace with the established breathing rate using the metronome. Healthy subjects demonstrated significant %vMCA decreases ($P < 0.001$) during each 20-s HV ranging from −28.2% ± 17.1% to −40.4% ± 7.9% ($\bar{x}$ = −35.8% ± 12.2%). mTBI subjects also showed a significant decrease after each repetition. Decreases in the mTBI group ranged from −36.3% ± 11.2% to −42.5% ± 11.3% ($\bar{x}$ = −40.2% ± 10.3%). %vMCA differed statistically between groups after the recovery period of the second repetition (−10.2% ± 11.4% vs −21.2% ± 6.4%, $P = 0.016$). %vMCA changes throughout the hypocapnic trials are summarized in Table 2 and Figure 2B.

Mean $PETCO_2$ throughout the sample after each HV was 20.2 ± 4.1 mm Hg. After each HV in healthy subjects, $PETCO_2$ ranged from 18.2 ± 3.6 to 22.3 ± 4.2 mm Hg ($\bar{x}$ = 20.5 ± 4.3 mm Hg). In mTBI subjects, $PETCO_2$ after each repetition ranged from 16.9 ± 2.0 to 21.5 ± 1.6 mm Hg ($\bar{x}$ = 18.5 ± 2.7 mm Hg). $PETCO_2$ throughout the HV challenge was not different between groups. Figure 3A illustrates the changes in $PETCO_2$ throughout the hypercapnic challenge.

Similar to the hypercapnic trial, the lowest vMCA values throughout each repetition of HV occurred approximately 5 s after returning to normal breathing. Some of the subjects experienced light-headedness that resolved quickly with commencement of normal breathing. This is a normal reaction in some people, and precautions were taken to avoid injury if syncope occurred (i.e., chair with armrests, personnel). No syncope events occurred during testing for any subjects.

DISCUSSION

This study examined the effects of mTBI on the cerebrovascular responses to hypercapnia and hypocapnia and is similar in nature to previous research presented by Tegeler et al. (41) in which cerebrovascular abnormalities in athletes were observed after mTBI even after neurocognitive function was restored. Using transcranial Doppler ultrasonography, our study incorporated a valid, reliable testing protocol to observe and document differences between healthy and mTBI-injured athletes while still following the current recommended return-to-play guidelines (28). With the surging interest into mTBI in sport, this study provides additional information and further insight into cerebrovascular pathophysiology after mTBI. The primary finding in our study was that under resting conditions, vMCA was not different between groups, but when challenged with a physiological stress (i.e., BH, HV), the mTBI group demonstrated impairment in CVR after mTBI.

A previous study suggested that the degree of uncoupling between the autonomic and cardiovascular systems was dependent upon severity of the initial trauma (18). Furthermore, athletes suffering mTBI typically become neuropsychologically asymptomatic within 2–14 d (22). In a study by Gall et al. (14), self-reported signs and symptoms of junior hockey players suffering an mTBI, without missing any playing time, returned to baseline values in approximately 2 d. These hockey players showed no significant differences in resting HR but elicited abnormal HR variability in response to submaximal exercise. It was proposed that the severity of neurological damage occurring with mTBI was insufficient to induce any significantly different cardiovascular responses at rest.

Conceptually, the concussed athletes in our current study elicited a similar cerebrovascular response pattern to hyper- and hypocapnia as the cardiovascular abnormalities in the study by Gall et al. (14). Resting vMCA values showed no significant difference between groups and fell within normal values established previously (4,34). However, once physiological stress (i.e., BH/HV) was introduced, significant differences between groups were observed at various times throughout the duration of testing. There were indications of cerebrovascular abnormality throughout the testing protocol of this study. For example and although not statistically significant, a trend was observed where the mTBI subjects' CBFV failed to return to resting levels after successive hypercapnic challenges, whereas healthy subjects reached baseline levels. Second, there were significant differences between groups after the hypocapnic trials.

As shown in Figure 2A, the mTBI subjects failed to return to resting vMCA values after the 40-s recovery time between BH trials. The healthy subjects returned to near-baseline values (within 2.5%) within 30 s after the cessation of holding their breath, although this was not significantly different between groups. Similar to this, there was a significant difference between groups after recovery during one of the HV trials. These observations are interesting to note and may be an indicator of delayed physiological responses after mTBI.

Because athletes are typically in better physiological condition than normal or diseased populations, recovery time after exercise is believed to be shorter than what is required in other untrained populations. This, in theory, should allow high-level athletes to better tolerate physiological stressors such as BH and HV. As proposed by Gall et al. (14), a single physiological stressor such as BH or HV would not provide enough physiological stress to induce any abnormal responses. In previously published research, vMCA values have been shown to return to resting values 20 to 40 s after BH in normal, healthy subjects (32,37). Thus, recovery time provided in this study should be adequate in allowing return to resting levels. Normalization of vMCA has been shown to be a slower process after HV than after BH (32,37). Our results are similar in that healthy subjects returned to near-baseline levels after BH but remained decreased after each HV.

Resting $PETCO_2$ levels were similar to levels found in recent research (29,44). Hypercapnic $PETCO_2$ levels in the mTBI subjects did not reach the lower limit of mild hypercapnia (≥5 mm Hg above resting levels) suggested previously (38). Hypercapnic $PETCO_2$ levels in our study were, on average, 41.2 ± 4.9 mm Hg in the healthy group and

37.9 ± 4.2 mm Hg in the mTBI group. This may be due to an underestimation of $PaCO_2$ when using $PETCO_2$ measurements, which may have influenced the analysis of CVR. Although a high correlation between $PaCO_2$ and $PETCO_2$ has been observed, $PaCO_2$ is often over- or underestimated when determined from expired gas measurements alone (5,40). Barton and Wang (5) found that $PETCO_2$ significantly underestimated $PaCO_2$ levels by up to 9 mm Hg during hypercapnia but was similar to $PaCO_2$ levels during hypocapnia. In a recent study, $PETCO_2$ increases of 5.4 ± 6.1 mm Hg after BH and decreases of 7.2 ± 4.1 mm Hg after HV were shown (10). In our study, the average increase of $PETCO_2$ after BH in the healthy group was 6.8 ± 4.5 mm Hg, which exceeds increases previously published. To note, our healthy subjects also illustrated a mean decrease of 12.1 ± 3.8 mm Hg after HV.

A second consideration to keep in mind regarding the outcome of our study is related to the average number of days after injury. Most studies show that the majority of athletes are asymptomatic and ready to return to play after 7–10 d (14). The physiological changes between the onset of injury and full recovery are not well documented, and this study provides some preliminary information. We showed that by day 4.5 ± 1.1 (range = 3–7 d) after injury, abnormal physiological changes still exist. Moreover, we were still able to establish a valid, easily administered protocol for monitoring the physiological consequences of sport-induced mTBI that was consistent with the guidelines proposed by the CISG (28). This is important from a physiological and administrative perspective as it suggests that the guidelines proposed by the CISG provide a safe approach for return to play.

Although the results of this study are interesting and provide further insight into the pathophysiology of mTBI, there are many methodological considerations that should be addressed. First, percentage changes were primarily used in discussing the differences between groups. As described in previous research (1,8,21,31), the use of percentage change was implemented for two reasons: 1) using percentage change allows for the reduction of individual variability that is not related to the methodology of the study, and 2) using these values allows for comparison with previous and future studies (31).

Although the use of the BH method for inducing hypercapnia was easily administered, it proved to be effective in changing $PaCO_2$ levels. However, we recognized that it differs from more commonly used steady-state methods. Longer time courses (90–300 s) of hypercapnia are typically used to allow vMCA to reach steady state in response to changes in $PaCO_2$ (3). In this study, two limitations of a repeated BH method were evident. BHs lasting only 20 s fail to achieve steady-state status, and continuous $PETCO_2$ data are absent throughout the maneuver because of the use of expired gas analysis. However, the methods implemented in this study provide short-term transient changes and address the notion of Gall et al. (14) that mTBI-induced abnormalities may not be present at rest and are only exacerbated in response to sufficient physiological stress. By performing repeated BH as well as HVs, the subjects in the study were exposed to aggressive testing protocols that more closely simulate intermittent activity associated with many types of sporting activities, which has implications with regards to current return-to-play decision guidelines. Although steady-state vMCA may not have been established in response to BH and HV, our observed changes in vMCA were noted using a repeated method and should be considered in future research.

As stated in the "Methods" section, only the right MCA was monitored in this study (with the exception of two subjects whose left MCA was monitored). In more severe traumatic brain injury, it is well known that significant differences in CBFV and CVR may exist between the ipsilateral and contralateral sides of the brain affected by injury (33,35). In these types of injuries, Glasgow Coma Scale scores are commonly ≤8, whereas in mTBI, scores are defined as being between 13 and 15. However, as stated earlier, a large number of people suffering mTBI will be self-reportedly asymptomatic within 2 d (14). mTBI has been commonly called physiologic without anatomical disruption of the brain, and when considering the lack of neurological signs associated with mTBI, it may be plausible that regional differences do not exist as in more severe TBI. The results of this study should not be discounted because of the lack of bilateral monitoring, but future mTBI research should monitor CBFV bilaterally to account for any differences that may be present.

CONCLUSIONS

In summary, CVR may be altered after mTBI. As supported previously by Gall et al. (13,14), the fact that responses are unchanged at rest but are abnormal once subjected to physiological stress seems to indicate that impairment in CVR is present after mTBI. This provides further support that a physiologically challenging protocol, like the one devised here, is needed to confirm whether athletes are fully recovered physiologically before returning to play. Further research into the pathophysiology of mTBI and its relationship to systemic physiological function is warranted before firm conclusions can be drawn about whether a protocol such as this is a feasible tool in managing mTBI. Future controlled studies using multimodal integrative physiological techniques (i.e., transcranial Doppler, near-infrared spectroscopy, blood pressure) on consecutive days immediately after the injury are needed to increase our understanding of the mechanism(s) of recovery from mTBI. This will provide an in-depth look into the cerebrovascular pathophysiology of mTBI as well as the relationship between mTBI and the CVR mechanism.

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The authors report no conflict of interest.

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