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Sex differences in the Buffalo Concussion Treadmill Test in adolescents with acute sport-related concussion

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ABSTRACT

Objectives: The Buffalo Concussion Treadmill Test (BCTT) is a safe and validated tool to assess exercise tolerance after sport-related concussion (SRC). Sex differences may affect the interpretation of this systematic exertion test in the concussed population, which is important for clinicians. The purpose of this study was to examine sex differences in BCTT performance in adolescents with acute SRC.
Design: Prospective cohort.
Methods: Male ($n = 103$, 15.3 ± 2 years) and female ($n = 87$, 15.1 ± 2 years) adolescents with SRC performed the BCTT within 10 days of injury. Heart rate (HR), HR threshold (HRt), Delta HR (difference between resting HR and HRt), symptom severity on Visual Analog Scale (VAS) and symptoms exacerbated on the BCTT were collected and compared.
Results: Males had lower resting HR (M: 70.9 ± 12 vs F: 75.7 ± 13 bpm, $p < 0.01$) and reached a lower HRt than females (M: 134.7 ± 23 vs F: 141.5 ± 25 bpm, $p = 0.05$). Sexes did not differ on Delta HR (M: 63.8 ± 26 vs F: 65.9 ± 24 bpm, $p = 0.57$), total treadmill time (M: 9.3 ± 5 vs F: 8.4 ± 4 min, $p = 0.20$), maximum VAS (M: 5.0 ± 2 vs F: 5.4 ± 2, $p = 0.18$) or incidence of a change in VAS (M: 91% vs F: 94%, $p = 0.43$) on the BCTT.
Conclusions: Although males may reach symptom exacerbation at a slightly lower mean HRt than females on the BCTT within 10 days of SRC, the BCTT provides comparable information and both sexes reach symptom exacerbation at similar Delta HR.

Practical implications

- There is no significant difference in Delta HR between male and female concussed adolescents during aerobic exercise testing.
- Male and female concussed adolescents report similar concussion-like symptoms; however, females more often report exercise intolerance due to increased symptom severity.
- Clinicians may use BCTT as a viable alternative or adjunct to other assessments that may decrease the variability of results between the sexes.

1. Introduction

Concussion, a subtype of mild traumatic brain injury (mTBI), results from sudden linear and/or rotational forces applied to the brain that trigger an acute and subacute pathophysiological cerebral metabolic response in the absence of gross structural changes to the brain.[1,2] The incidence of sport-related concussion (SRC) is high in contact sports. It is estimated there are 1.6–3.8 million sport-related traumatic brain injuries per year in the U.S., the majority being SRC.[3] This study focuses on adolescents because they constitute the bulk of SRC and appear to take longer to recover than children or adults.[4] In addition to symptoms reported at rest, adolescents who experience SRC often report symptom exacerbation with physical exercise, which is called *exercise intolerance*.[5] Exercise intolerance is suspected to be due to abnormalities in autonomic nervous system (ANS) function, cerebral blood flow (CBF) dysregulation, and/or altered cardiac function during exercise.[6,7] The Buffalo Concussion Treadmill Test (BCTT) systematically measures exercise intolerance in concussed patients[8] by determining the heart rate threshold (HRt) at which exercise-induced symptom exacerbation occurs.[9] The BCTT has been validated in several studies as a tool to assess exercise intolerance and is safe to perform in adolescents.[7,10,11]

Sex differences in height, weight, body mass, muscle mass, aerobic capacity, anaerobic capacity, genetics and hormones affect exercise performance.[12] Physiological differences between sexes have been measured during treadmill testing, including but not limited to peak oxygen consumption ($V.O_2$), exercise absolute carbon dioxide production ($V.CO_2$), maximal systolic blood pressure, and cardiac index (cardiac output normalized by body size).[13] Some studies report

Abbreviations: BCTT, Buffalo Concussion Treadmill Test.

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exertion testing is less sensitive and less specific in females for diagnosis and prognosis of cardiovascular dysfunction.[14] It has been suggested that physiological reasons explain males' better performance on aerobic tests, including different BMI, systemic blood flow, resting heart rate (HR), hormones, metabolism, and greater leg muscle mass.[15]

Some studies have identified sex differences in concussion incidence, symptom burden, and duration of recovery.[16] Females are more likely to report concussion-like symptoms on baseline testing[17] and post-injury.[16] Studies have also shown females are more likely to be concussed given equal game time exposure in sport (e.g. soccer) and are more likely to suffer persistent post-concussive symptoms (PPCS).[16] It has been suggested that neck strength and injury biomechanics may account for sex differences.[18] The recent discovery that females have axonal differences and greater probability of damage to microtubules than males when exposed to equivalent acceleration-deceleration forces suggests a brain anatomical explanation for the vulnerability of females.[19] While there have been many studies about sex differences in concussion, there is limited evidence about sex differences in exercise tolerance testing after concussion. Since exertion testing has become a common assessment tool in sports medicine, and an emerging tool for targeted HR exercise rehabilitation for athletes with SRC,[10,11] understanding sex differences in the results after SRC is important. To investigate these differences, we aim to compare symptom exacerbation and cardiovascular findings on the BCTT between male and female adolescents within 10 days of SRC. Given sex differences in exercise physiology and concussion vulnerability, we hypothesized that concussed adolescent males and females would differ in BCTT performance and physiological responses.

2. Methods

The University at SUNY Buffalo Institutional Review Board approved this prospective study. If eligible, consent of a parent and assent of the adolescent was obtained and participants performed the BCTT at the initial clinic visit after their physician's clinical evaluation.

Male and female adolescents (aged 13–18 years) presenting within 10 days of SRC were evaluated by an experienced sports medicine physician who diagnosed concussion based on history,[20] a concussion symptom questionnaire,[21] and a concussion-specific physical examination.[22] Exclusion criteria: (1) evidence of focal neurological deficit; (2) inability to exercise because of orthopedic or cervical spine injury; (3) increased cardiac risk according to American College of Sports Medicine criteria[23]; (4) history of moderate or severe TBI, defined as brain injury with a Glasgow Coma Scale score of 12 or less; (5) current medication treatment for ADHD, learning disorders, depression, anxiety, or other medications that can affect HR; and (6) symptom severity score of less than 5 on the initial visit Post Concussion Symptom Scale questionnaire.[24]

The BCTT has been validated in several studies and is safe to perform as soon as within 1-day of concussive head injury.[7,10,11] If a participant was eligible and gave assent and/or consent, the BCTT was completed on the same day as their initial visit. Before beginning the BCTT, participants rated their symptoms on a Visual Analog Scale (VAS, 0–10)[25] to determine initial symptom severity (Fig. 2) and resting HR was measured in a seated position after a 2-minute rest by Polar HR monitor (Model #FIT N2965, Kempele, Finland). The participant then walked on a level treadmill at 3.2 mph (3.6 mph in participants 5′10″ and above) at 0° incline. The incline was increased by 1° each minute for the first 15 min unless the participant was unable to continue due to symptoms or excessive fatigue.[11] The HR at exercise cessation was recorded as the HRt. The primary outcome measures were: presence of exercise intolerance on the BCTT (i.e., increase of 3 or more VAS points), HR, VAS, RPE[26] and exercise time. Secondary outcome was the qualitative symptoms experienced at symptom exacerbation.

Using data from healthy adolescents,[13] we assumed the mean maximal HR on the treadmill test to be 191 bpm in females and 194 bpm in males with a standard deviation of 7 bpm, following a normal distribution. Using a two-sided *t*-test we calculated a sample size of 170 participants (85 per sex) to be able to detect a significant difference in maximal HR between the sexes with 80% power and α of 0.05.

We assessed group-wise differences in continuous, normally distributed variables (age, height, weight, total symptom severity score on initial visit, days to initial visit, duration of BCTT, resting HR, HRt, Delta HR, maximum RPE, resting VAS, maximum VAS) using a two-sided *t*-test. Chi-square test was used to assess group-wise differences in categorical variables (previous concussions, physical examination signs, loss of consciousness, exercise intolerance, significant symptom exacerbation). Mean HR, VAS, and RPE were plotted against time with 95% confidence intervals (CI). HR values over time were plotted and a line-of-best fit was made for each sex. A *p*-value less than 0.05 determined statistical significance and all tests were 2-sided. Statistical analyses were performed using SAS 9.4.

3. Results

Out of 215 eligible participants, 20 participants elected to decline participation or did not have time to perform the BCTT on the first visit. Five participants were consented but were excluded because of incomplete HR data during the BCTT due to equipment failure. Hence, our final sample size consisted of 190 adolescents (103 males and 87 females). Demographics are presented in Table 1. Sexes did not differ in age or initial symptom severity; however, males were significantly taller ($p < 0.001$), heavier ($p < 0.001$), and had a greater number of previous concussions ($p = 0.003$) than females. Males also came to the clinic a mean of 1 day sooner than females ($p = 0.022$).

Results of the BCTT are presented in Table 2. Females had significantly higher resting HR ($p = 0.009$) and HRt ($p = 0.050$) than males, but there was no significant difference in Delta HR ($p = 0.569$). Males also reported greater perceived exertion at their maximum HR ($p = 0.025$) than females. Both sexes had similar incidence of a 1-point or greater VAS increase (91% in males and 94% in females, $p = 0.432$). A higher percentage of females met the stopping criterion of reaching exercise intolerance (3 or more points on the VAS) than males ($p = 0.019$), prompting earlier test cessation. Symptoms experienced on the BCTT are presented in Table 2. Specific symptoms were not recorded for 21 BCTTs; hence, only 169 participants were included in this subanalysis. Males and females did not differ in the type of symptoms

Table 1
Participant demographics.

	Males ($n = 103$)	Females ($n = 87$)	*p*-Value
Age (mean ± SD) in years	15.3 ± 1.5 years	15.1 ± 1.7 years	0.373
Height (mean ± SD) in meters	1.74 ± 0.09	1.62 ± 0.08	**<0.001**
Weight (mean ± SD) in kg	69.1 ± 14	60.0 ± 11	**<0.001**
Days since injury (mean ± SD)	4.7 ± 2.4	5.5 ± 2.2	**0.022**
Previous concussion (mean ± SD)	0.72 ± 0.9	0.38 ± 0.6	**0.003**
Initial symptom severity* (mean ± SD)	30.25 ± 18.5	34.42 ± 21.0	0.153
Loss of consciousness (%, n)	6.7% ($n = 7$)	5.7% ($n = 5$)	0.714

SD: standard deviation; *On post-concussion symptom scale, range 0–132. Significance was defined at the $p > 0.05$ level.

Table 2
Initial visit Buffalo Concussion Treadmill Test results and symptoms.

	Males (n = 103)	Females (n = 87)	*p*-Value
Resting HR	70.9 ± 12	75.7 ± 13	**0.009**
Maximum HR	134.7 ± 23	141.5 ± 25	**0.050**
Delta HR*	63.8 ± 26	65.9 ± 24	0.569
Resting RPE	6	6	> 0.999
Maximum RPE	14.0 ± 3	13.0 ± 3	**0.025**
Total Time (in minutes)	9.25 ± 4.6	8.41 ± 4.4	0.199
Resting VAS	2.89 ± 2.0	3.03 ± 1.9	0.613
Maximum VAS	4.96 ± 2.3	5.41 ± 2.2	0.175
Increase in VAS score*	91.3% ($n = 94$)	94.3% ($n = 82$)	0.432
Symptom exacerbation	76.7% ($n = 79$)	89.7% ($n = 78$)	**0.019**
Symptoms exacerbated			
Headache	67	63	0.683
Balance Problems / Dizziness	40	31	0.350
Nausea	5	7	0.444
Blurry vision or light sensitivity	8	5	0.298
Other**	7	3	0.246

HR: heart rate; Delta HR: Maximum HR – Resting HR; VAS: Visual Analog Scale (range 0–10); RPE: Borg's rating of perceived exertion (range 6–20); *: Defined as an increase of 1 or more points on the VAS from rest. **Three males reported fatigue, 2 males reported fogginess/inability to concentrate, 1 male reported increase in noise sensitivity and 1 male reported feeling irritable. Two females reported feeling fatigued and 1 female reported fogginess/inability to concentrate. Significance was defined at the $p > 0.05$ level.

reported, with headache and balance problems/dizziness being the most common for both sexes.

Mean HR values and RPE at each stage for both sexes are presented in Fig. 1. The rate of increase in HR (Fig. 1a) was significantly different between sexes, with females having a greater rate of mean HR rise than males (9.3 ± 5.5 bpm/min vs. 7.7 ± 3.1 bpm/min, respectively, ($p = 0.009$). No significant sex differences on RPE (Fig. 1b) were seen at any stage of the BCTT.

4. Discussion

Assessment of exercise tolerance is becoming an important method for the diagnosis and management of male and female athletes with SRC.[10,11] The BCTT is widely used because of its diagnostic and prognostic value, especially when performed early (within one week) after SRC.[9] Since there are differences among healthy males and females on tests of exercise performance,[12,13] it is important to know whether there are sex differences in concussed patients on a systematic test of their exercise tolerance. Contrary to our hypothesis, the data show that male and female adolescents have similar cardiovascular findings, RPE and symptomatology on the BCTT within one week of SRC. These findings have implications for prognosis and treatment since some studies show that females have a different response to concussion and a different recovery trajectory.[14]

Males and females in our study showed differences in height, weight, number of days since injury and previous concussion history. Differences in height and weight were expected because males are usually taller and heavier than females. Days since injury and previous concussion history were statistically different, however clinically the mean differences are minimal. Our data show that females had a higher resting HR and reached a higher HRt on the BCTT. We did not, however, find a significant sex difference in Delta HR. Although HRt appears to be inversely related to concussion severity, a lower HRt corresponds to longer recovery time, some studies have found Delta HR is more associated with duration of clinical recovery.[12] This is likely because Delta HR accounts for the individual's resting HR and there was a difference in resting HR in our study. In addition, our data show no sex differences in the type of symptoms reported on exertion. Headache exacerbation was the most common symptom reported, followed by dizziness/altered balance. Worsening of concussion-like symptoms on physical exertion is common after SRC and is considered to be a physiological biomarker of concussion. [10,11] Both sexes (91% of males and 94% of females) in our study reported an increase in VAS score during the BCTT. Females, however, more often experienced symptom exacerbation and subsequent exercise intolerance, prompting earlier BCTT cessation (90% vs. 77% of males, $p = 0.019$). The cause of symptom exacerbation is not yet fully understood but may involve abnormalities in dynamic CBF regulation, which is impaired after concussion.[27] Healthy females have greater CBF than males during exertion,[28] and they have high CBF during exertion after concussion which may be the cause for the difference in severity of symptom exacerbation.[7] Additional research is warranted to understand the pathophysiology of exercise-intolerance after concussion.

Our study has several limitations. There is wide variation in resting HR that is affected by modifiable factors such as mood, food intake, time of day, hours of sleep the night before, caffeine intake, fitness levels, body fat, etc. We did not control for these factors since testing was done as part of a regular clinic visit. Future researcher should assess the effects of these factors on the BCTT. In our sample, sexes were similar in age but males were heavier and taller than females. This could explain some of the differences in resting HR and HRt because higher blood pressure, which affects HR,[29] correlates with greater height in

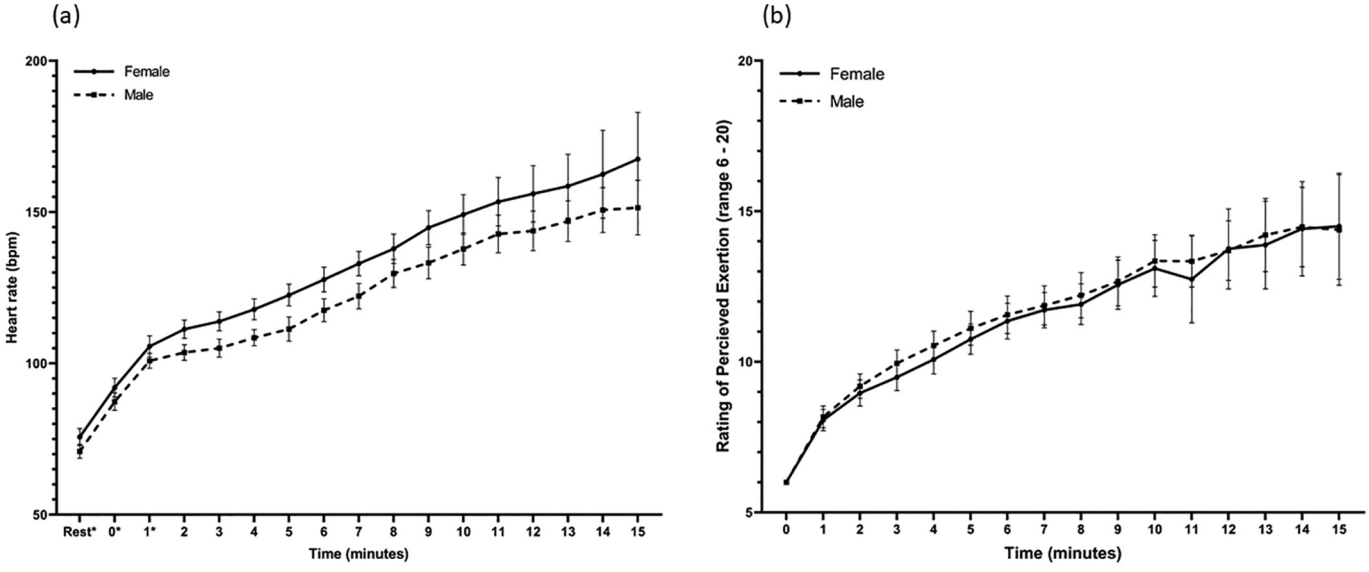

Fig. 1. Heart rate (a) and perceived exertion (b) during BCTT.

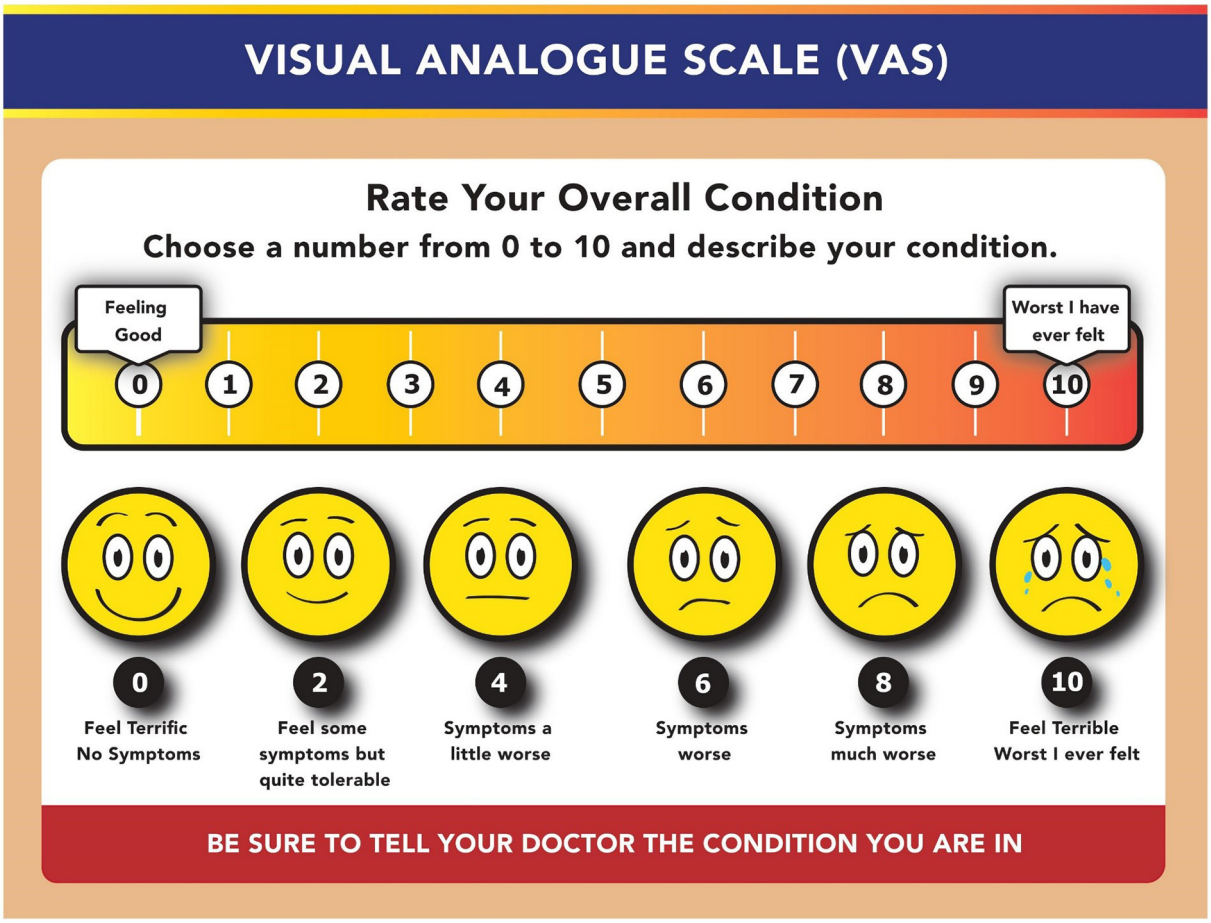

Fig. 2. Visual Analog Scale.

adolescents.[30] Female HR is also affected by menarche and the stage of the menstrual cycle, which we did not control for. However, there was no difference in variability for resting HR between the sexes (SD 12 in males and SD 13 in females), so we expect this to have minimal effect on our results. Lastly, our sample consisted of athletic adolescents evaluated acutely after injury, so our results may not be applicable to adults, younger children, the non-SRC population, or to a BCTT administered beyond the acute and sub-acute phases (more than 10 days). Future studies should include a more diverse population and control for some of the modifiable factors that can affect resting HR.

5. Conclusion

Male and female adolescents have similar responses to and performance on the BCTT within one week of SRC. Our study showed Delta HR, a validated prognostic indicator of delayed recovery, did not differ between the sexes. Despite the observation that females more often reported substantial symptom exacerbation prompting earlier termination of the treadmill test, males and females did not differ in the onset or type of symptoms reported during the BCTT. These data show that the BCTT provides valid data on concussion severity and prognosis equally well in males and females, which has implications for concussion diagnosis and treatment.

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Declaration of interest

The authors do not declare any conflicts of interest.

Confirmation of ethical compliance

The University at SUNY University at Buffalo Institutional Review Board approved this prospective study. If eligible, consent of a parent and assent of the adolescent was obtained and participants performed the Buffalo Concussion Treadmill Test at the initial clinic visit after their physician's clinical evaluation.

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