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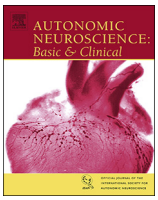

Sex differences in cardiac vagal reactivation from the end of isometric handgrip exercise and at the onset of muscle metaboreflex isolation

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ABSTRACT

A parasympathetic reactivation is an underlying mechanism mediating the rapid fall in heart rate (HR) at the onset of post-exercise ischemia (PEI) in humans. Herein, we tested the hypothesis that, compared to men, women present a slower HR recovery at the cessation of isometric handgrip exercise (i.e., onset of PEI) due to an attenuated cardiac vagal reactivation. Forty-seven (23 women) young and healthy volunteers were recruited. Subjects performed 90s of isometric handgrip exercise at 40% of maximal voluntary contraction followed by 3-min of PEI. The onset of PEI was analyzed over the first 30s in 10s windows. Cardiac vagal reactivation was indexed using the HR fall and by HR variability metrics (e.g., RMSSD and SDNN) immediately after the cessation of the exercise. HR was significantly increased from rest during exercise in men and women and increases were similar between sexes. However, following the cessation of exercise, the HR recovery was significantly slower in women compared to men regardless of the time point (women vs. men: Δ-14 ± 8 vs. Δ-18 ± 6 beats.min^{-1} at 10s; Δ-20 ± 9 vs. Δ-25 ± 8 beats.min^{-1} at 20s; Δ-22 ± 10 vs. Δ-27 ± 9 beats.min^{-1} at 30s; $P = .027$). RMSSD and SDNN increased at the cessation of exercise in greater magnitude in men compared to women. These findings demonstrate that women had a slower HR recovery at the cessation of isometric handgrip exercise and onset of PEI compared to men, suggesting a sex-related difference in cardiac vagal reactivation in healthy young humans.

1. Introduction

Post-exercise ischemia (PEI) following isometric handgrip exercise is a well-established technique to isolate muscle metaboreflex activation in humans (Alam and Smirk, 1937). While arterial blood pressure (BP) and sympathetic nerve activity remain elevated during PEI, the exercise-induced increase in heart rate (HR) is typically reported to return to resting values (Fisher et al., 2015). The rapid fall in HR at the end of exercise over the first 30 s of PEI is a confounding and complex response during the transition between exercise and PEI (Fisher et al., 2010). The potential explanation for this observation is a cardiac parasympathetic reactivation, probably due to the loss of central command and muscle mechanoreceptors inputs and/or baroreflex mechanisms, as proposed by others (Fisher et al., 2010; Iellamo et al., 1999; O'Leary, 1985). To gain more insight into the mechanisms underlying the rapid fall in HR at the onset of PEI, Fisher et al. (2010) evaluated the autonomic control of HR during the first minute of PEI by employing a pharmacological approach in healthy men. They found that HR rapidly returned towards baseline under both control and sympathetic blockade condition, while the HR fall was slower and less complete under parasympathetic blockade. Thus, this previous study provided strong evidence that rapid fall in HR in the first's seconds at the onset PEI is primarily mediated by cardiac vagal reactivation, which overcomes cardiac sympathetic activation induced by metaboreflex isolation. Although Fisher et al. (2010) elucidated the autonomic mechanisms whereby HR is regulated by the muscle metaboreflex, the possible sex differences on this rapid cardiac vagal reactivation immediately upon the cessation of the exercise are unknown. This becomes important because alterations in autonomic function contribute to the risk of sudden death, likely related to abnormal HR profiles (Jouven et al., 2005). For example, delayed HR recovery from exercise (attributed to altered parasympathetic reactivation) has been reported as a powerful independent predictor of mortality in healthy adults (Cole et al., 1999; Imai et al., 1994).

The existence of sex differences in cardiac vagal reactivation at the cessation of isometric handgrip exercise is highly plausible given that

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several previous studies have shown marked sex differences in autonomic function (Hart et al., 2011; Hart et al., 2009; Prodel et al., 2018a; Prodel et al., 2018b; Samora et al., 2019; Samora et al., 2018; Teixeira et al., 2018c). We recently demonstrated that muscle metaboreflex interacts with arterial-cardiac baroreflex to the neural control of cardiovascular and hemodynamic adjustments to exercise in a sex-dependent manner (Samora et al., 2018). In this previous study, we demonstrated that spontaneous cardiac baroreflex sensitivity and indexes of HR variability (HRV) related to parasympathetic activity (e.g., RMSSD and HF component) are enhanced during 3-min of PEI in men but not (or less increased) in women. Nevertheless, whether these previous findings about sex differences are already manifested immediately upon the cessation of the exercise, which is known to be primarily mediated by cardiac vagal reactivation, remains to be determined. Thus, the purpose of the present study was to test the hypothesis that women present a slower HR recovery than men at the cessation of isometric handgrip exercise and onset of PEI due to an attenuated cardiac vagal reactivation.

2. Material and methods

2.1. Participants

Participants refrained from caffeine/alcohol and physical exercise for at least 12 h prior to testing. All participants were healthy, normotensive, non-smoker and physically active. None had used any controlled medications and had no history or symptoms of cardiopulmonary, metabolic or neurological diseases. All study procedures were approved by the University of Brasília research ethics committee (CAAE 76504017.1.0000.0030) in accordance with the Declaration of Helsinki. All participants read and signed a specific informed consent form before enrolment. Forty-seven participants were enrolled in the present study. Part of this sample has already being tested and used in a previous study from our laboratory that tested a different hypothesis (Samora et al., 2018). All participants were tested at the same time of day in the same quiet, temperature-controlled room (22–24 °C). All women were non-users of oral contraceptive pills for at least six consecutive months and were studied during the early follicular phase of their menstrual cycle (i.e. first five days after menstruation onset). The first visit was for familiarization with all the study equipment and procedures. Weight and height were determined via standard methods, and body mass index (BMI) calculated.

2.2. Cardiovascular measurements

Participants performed three maximal efforts each separated by at least 1-min, and the higher value was considered the maximal voluntary contraction (MVC). Participants were in a seated position and resting baseline hemodynamic measures were recorded for the 10-min. HR, systolic, diastolic and mean BP were continuously measured on a beat-to-beat basis by photoplethysmography using a Finometer device (Human NIBP Controller, AD instruments, NSW, Australia), placed at the middle finger of the non-dominant hand, with the hand positioned at heart level. Brachial arterial BP was also measured with an automated digital sphygmomanometer (Dixtal, DX2022, Brazil) for absolute measures of BP to confirm finger measurement accuracy. Respiratory movements were monitored using a pneumatic belt placed around the subjects' abdomen (MLT 1132 Piezo Respiratory Belt Transducer – ADInstruments) to ensure that the subjects did not perform Valsalva maneuver during the protocol. The BP waveform was sampled at 1000 Hz and stored for offline analysis (Powerlab, AD Instruments, Bella Vista, New South Wales, Australia with LabChart 8 software, ADInstruments).

2.3. Post-exercise ischemia protocol

Participants performed 90-s of isometric handgrip exercise at 40% of MVC followed by 3-min of PEI to isolate skeletal muscle metaboreflex. The exercise intensity was controlled and maintained by visual feedback of the researcher's computer screen. PEI was achieved by the rapid inflation of a cuff positioned around the exercising arm to supra systolic pressure (240-250 mmHg) 5 s before the end of the exercise. The cuff was released following completion of PEI.

2.4. Data and statistical analysis

Five minutes of data segments were used for the calculation of average cardiovascular variables at rest. The exercise response was analyzed using 10s windows average during the last 30s of exercise while the onset of PEI was analyzed during the first 30s immediately upon cessation of exercise. A beat-to-beat RR interval data was used to calculate the HRV in a software developed in Matlab with a graphical interface (SinusCor 1.0.0, Brazil) which was previously validated against standard software (Bartels et al., 2017). HRV was evaluated in time domain methods providing information on ultra-short variability of the signal as root mean square of successive RR interval differences (RMSSD), the standard deviation of the normal RR intervals (SDNN) and percentage of successive RR intervals that differ by more than 50 ms (pNN50) (Esco and Flatt, 2014; Hamilton et al., 2004; Nussinovitch et al., 2011). All these measurements of ultra-short-term variation estimate high-frequency variations in HR that is primarily mediated by parasympathetic nerve activity and are highly correlated (Task, 1996). The normality distribution of the data was verified by *the Shapiro-Wilk* test. Subjects' characteristics were compared using independent sample *t-test*. Two-way analysis of variance (ANOVA) for repeated measures followed by Students t-test with Bonferroni correction was used to investigate significant main effects and interactions. Statistical significance was set at $P < .05$ and values are presented as mean ± S.D. All statistical analyses were conducted using IBM SPSS® Statistics *software* (version 20) and figures were plotted using Prism, version 8.0 (GraphPad Software Inc., San Diego, United States) for *Windows*.

3. Results

The subject's characteristics are presented in Table 1. Women and men were matched for BMI, however, men had higher weight, height, and MVC than women (all $P < .05$).

The hemodynamics responses at rest and during isometric handgrip exercise are presented in Table 2.

Resting systolic and mean BP was lower in women compared to men. As expected, systolic, diastolic and mean BP increased during isometric exercise with men achieving a higher value than women. HR significantly increased and RR interval decreased during isometric handgrip exercise in a similar magnitude in men and women. HRV indices similarly decreased during exercise in men and women.

Fig. 1 displays the recovery of HR and mean BP at the cessation of

Table 1
Subjects characteristics.

	Men (n = 24)	Women (n = 23)	P value
Age (years)	21 ± 2	23 ± 3	0.04
Height (m)	1.78 ± 0.06	1.63 ± 0.07	< 0.001
Weight (kg)	78 ± 10	62 ± 10	< 0.001
BMI (kg/m^2)	24.6 ± 2.8	23.1 ± 2.6	0.06
MVC (N)	615 ± 140	401 ± 73	< 0.001

Value represents means ± S.D. BMI, body mass index; MVC, maximum voluntary contraction.
P value is derived from an independent sample t-test.

Table 2
Hemodynamic variables and heart rate variability at rest and during isometric handgrip exercise.

	Men	Women	*P* value		
			Sex	Time	Interaction
Systolic BP, mmHg					
Rest	115 ± 8	100 ± 5*	< 0.001	< 0.001	0.001
Exercise	164 ± 21†	131 ± 16*,†			
Δ	50 ± 20	32 ± 14*	0.001		
Diastolic BP, mmHg					
Rest	59 ± 8	57 ± 5	0.015	< 0.001	0.037
Exercise	88 ± 13†	79 ± 9*,†			
Δ	28 ± 11	22 ± 9*	0.038		
Mean BP, mmHg					
Rest	77 ± 7	71 ± 5*	< 0.001	< 0.001	0.014
Exercise	113 ± 14†	98 ± 10*,†			
Δ	36 ± 13	27 ± 10*	0.013		
Heart rate, beats.min^{-1}					
Rest	71 ± 9	74 ± 9	0.893	< 0.001	0.148
Exercise	96 ± 13	93 ± 13			
Δ	24 ± 12	19 ± 12	0.156		
RR interval, ms					
Rest	856 ± 127	827 ± 101	0.840	< 0.001	0.121
Exercise	639 ± 96	658 ± 86			
Δ	−217 ± 108	−169 ± 103	0.121		
Heart rate variability					
RMSSD, ms					
Rest	50.49 ± 22.93	47.82 ± 18.82	0.846	< 0.001	0.450
Exercise	25.91 ± 17.52	26.71 ± 10.84			
Δ	−24.58 ± 13.93	−21.11 ± 17.17	0.448		
SDNN, ms					
Rest	67.38 ± 25.74	59.93 ± 18.48	0.473	< 0.001	0.200
Exercise	31.75 ± 19.52	31.84 ± 14.50			
Δ	−35.62 ± 20.62	−28.09 ± 19.03	0.200		
pNN50, %					
Rest	27.04 ± 15.59	25.91 ± 13.47	0.840	< 0.001	0.783
Exercise	7.79 ± 12.69	7.55 ± 7.49			
Δ	−19.25 ± 10.12	−18.36 ± 11.92	0.784		

Value represents means ± S.D. BP, blood pressure; RMSSD, root mean square of successive RR interval differences; SDNN, standard deviation of the normal RR intervals; pNN50, percentage of successive RR intervals that differ by more than 50 ms.

* $P < .05$ vs men.

† $p < .05$ vs rest within group.

exercise. The HR recovery was slower in women (10s: Δ-14 ± 8 beats.min^{-1}; 20s: Δ-20 ± 9 beats.min^{-1}; and 30s: Δ-22 ± 10 beats.min^{-1}) compared to men (10s: Δ-18 ± 6 beats.min^{-1}; 20s: Δ-25 ± 8 beats.min^{-1}; and 30s: Δ-27 ± 9 beats.min^{-1}) regardless of time point ($P = .027$ Fig. 1A). Notably, the fall in mean BP was similar between men (10s: Δ-7 ± 7 mmHg; 20s: Δ-16 ± 9 mmHg; and 30s: Δ-13 ± 9 mmHg) and women (10s: Δ-5 ± 5 mmHg; 20s: Δ-14 ± 7 mmHg; and 30s: Δ-13 ± 6 mmHg; $P = .386$) at the cessation of exercise (Fig. 1B).

Fig. 2 shows the recovery of RR interval and the cardiac vagal

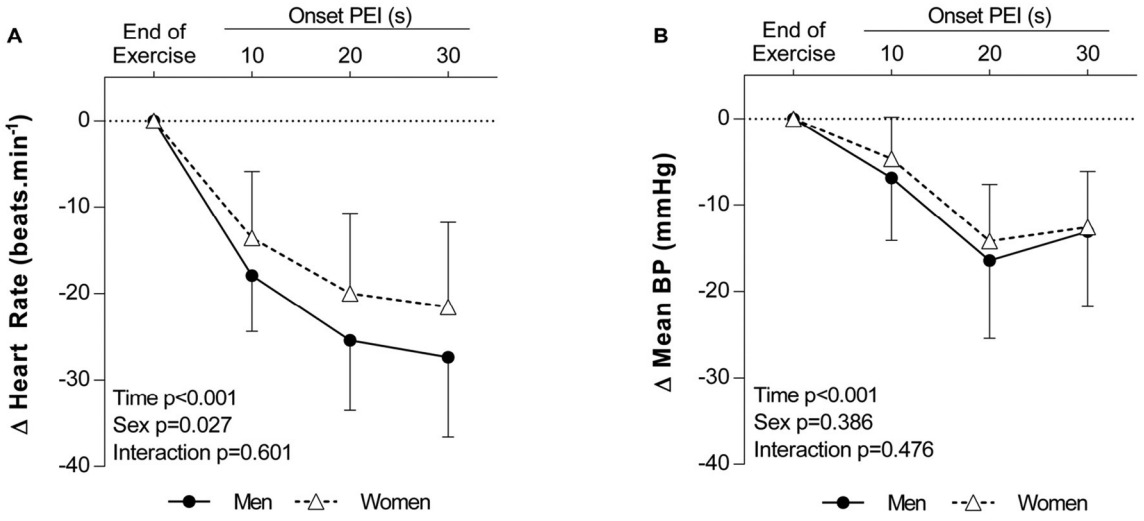

Fig. 1. Change in heart rate (A) and mean blood pressure (B) at the cessation of isometric handgrip exercise and onset of muscle metaboreflex activation. BP, blood pressure; PEI, post-exercise ischemia.

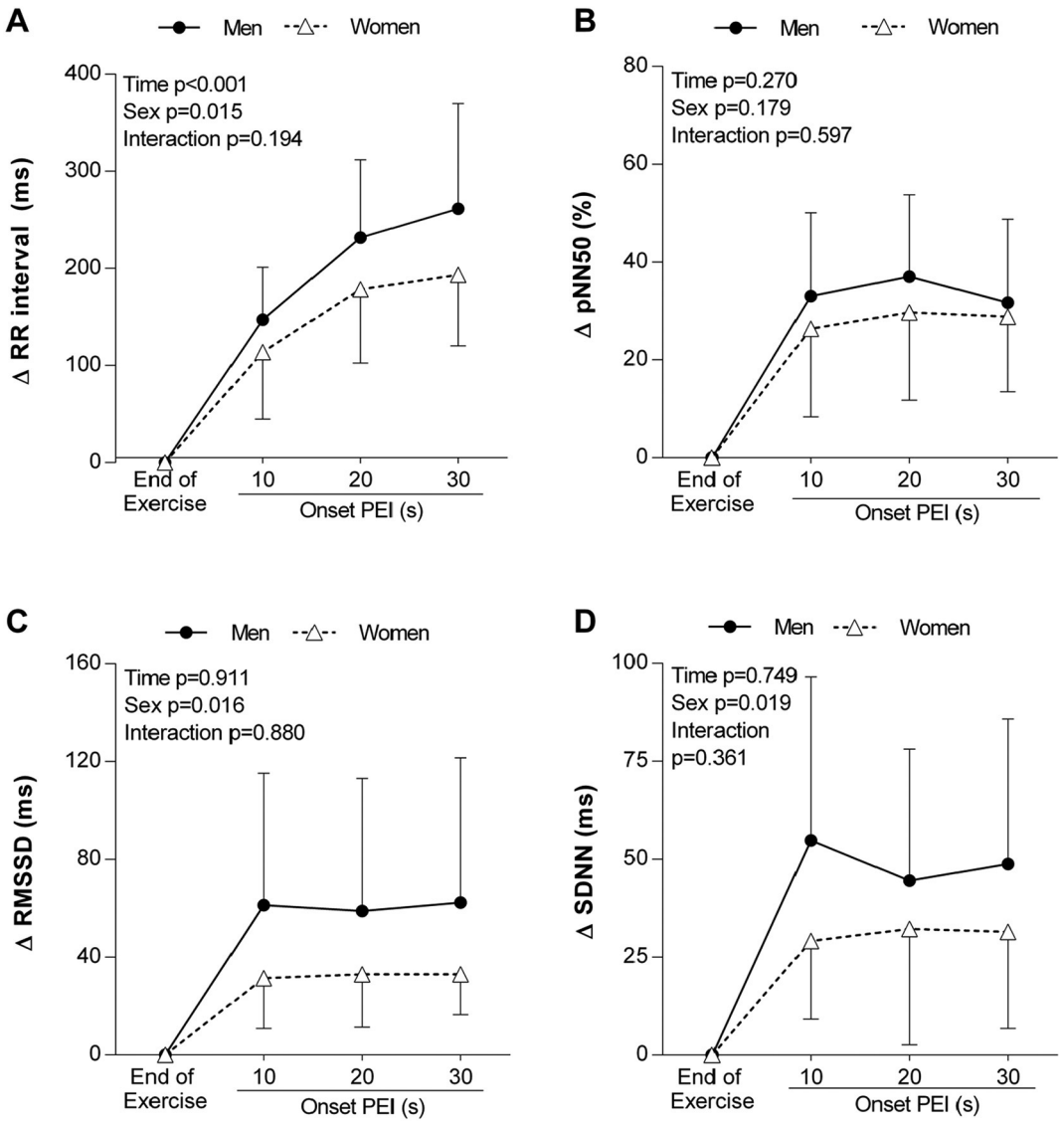

Fig. 2. Change in RR interval (A) and heart rate variability indexes (B to D) at the cessation of isometric exercise and the onset of muscle metaboreflex activation. PEI, post-exercise ischemia; pNN50, percentage of successive RR intervals that differ by more than 50 ms; RMSSD, root mean square of successive RR interval differences; SDNN, standard deviation of the normal RR intervals.

reactivation represented by pNN50, RMSSD and SDNN at the cessation of exercise. The RR interval rise was slower in women (10s: Δ114 ± 69 ms; 20s: Δ179 ± 76 ms; and 30s: Δ194 ± 73 ms) compared to men (10s: Δ 147 ± 54 ms; 20s: Δ232 ± 80 ms; and 30s: Δ261 ± 108 ms) regardless of time point (P = .015; Fig. 2A). The increase in RMSSD (Fig. 2C) and SDNN (Fig. 2D) was lower in women compared to men at the cessation of exercise (P = .016 and P = .019, respectively).

4. Discussion

Previous studies have elucidated, via pharmacological approaches, that a parasympathetic mechanism plays a predominant role in mediating the rapid fall in HR at the onset of muscle metaboreflex isolation (i.e., PEI) in humans. Herein, we posit that this HR recovery at the cessation of isometric handgrip exercise might be dependent on whether the subject is male or female, given a plethora of previous studies in the literature indicating sex differences in autonomic function (Hart et al., 2011; Hart et al., 2009; Prodel et al., 2018a; Prodel et al., 2018b; Samora et al., 2019; Samora et al., 2018). The main finding of the present study is that women demonstrated a slower recovery in HR at the cessation of isometric handgrip exercise compared to men, while the fall in mean BP was similar between sexes. In addition, increases in both RMSSD and SDNN at the cessation of exercise were lower in women compared to men. Overall, these findings suggest for the first time a sex-related difference in cardiac vagal reactivation immediately upon the cessation of isometric exercise and onset of PEI.

HR increases during exercise in an intensity-dependent manner and it is partially mediated by a withdrawal of parasympathetic tone primarily due to activation of central command (Mitchell et al., 1989) and skeletal muscle mechanoreceptors (Gladwell et al., 2005; Teixeira et al., 2018b). On the other hand, the muscle metaboreflex contributes to an increase in BP via augmented peripheral vasoconstriction instead of playing a substantial role in cardiac regulation (Rowell and O'Leary, 1985; Teixeira et al., 2018a; Teixeira et al., 2020). Isolated activation of the muscle metaboreflex via PEI support this observation in which there is a maintenance of the exercise-induced increases in sympathetic nerve activity, vascular resistance and BP, while HR returns towards baseline (Alam and Smirk, 1937; Teixeira et al., 2019; Teixeira et al., 2020). Elegantly, Fisher and collaborators (Fisher et al., 2010) used a challenging pharmacological approach eliminating cardiac parasympathetic or sympathetic tone to examine the autonomic control of HR during

metaboreflex activation in humans. It was suggested that the muscle metaboreflex provides sympathetic drive to the heart in humans, but that is generally masked during PEI by an increase in cardiac parasympathetic tone, probably explained by the loss of neural inputs from central command and muscle mechanoreceptors upon the cessation of the exercise and/or baroreflex mechanism (Iellamo et al., 1999; O'Leary, 1985). In this regard, indexes from HR variability in which estimate parasympathetic nerve activity (i.e. RMSSD and HF component) also are augmented during PEI (Fisher et al., 2010; Teixeira et al., 2018a). These data suggest that even though there is an increase in cardiac sympathetic nervous activity mediated by isolated muscle metaboreflex activation via PEI, the tachycardia is masked by augmented cardiac parasympathetic tone due to vagal reactivation. Importantly, for the first time, Fisher et al. (2010) demonstrated that the rapid HR fall in the first 30 s of PEI is primarily dependent on cardiac vagal reactivation, which overcomes the sympathetic outflow to the heart. However, to date, it is unknown whether there are sex differences in this cardiac vagal reactivation at the onset of PEI following isometric exercise.

In the present study, there are no sex differences in HR response to exercise (Table 2). However, HR recovery upon the cessation of the isometric exercise was slower in women compared to men regardless of the time point (Fig. 1A). Since the fall in mean BP was similar between sexes at the cessation of exercise (Fig. 1B), our data clearly suggest an attenuated cardiac vagal reactivation rather than a counteraction of the arterial baroreflex per se mediating the HR responses. This attenuated cardiac vagal reactivation in women was also confirmed by the lower HRV indexes (i.e. RMSSD and SDNN; Fig. 2) compared to men at the cessation of exercise. Furthermore, we previously demonstrated an increase in cardiac baroreflex sensitivity in men but not in women during PEI followed by isometric exercise (Samora et al., 2018). The arterial baroreflex determined by spontaneous cardiac baroreflex sensitivity reflects the gain at the operating point of the full cardiac baroreflex and the sensitivity at this locus is heavily dependent on cardiac parasympathetic activity (Fisher et al., 2009; Teixeira et al., 2018a). Therefore, the lack of increase in cardiac baroreflex sensitivity in women during PEI supports the contention that women have an attenuated cardiac vagal reactivation and this is clearly observed immediately upon cessation of exercise (i.e., during the transition between exercise and PEI) in the present investigation.

Notably, HR recovery has clinical applications and previous studies have suggested that delayed HR recovery is an independent predictor of mortality (Cole et al., 1999; Imai et al., 1994; Jouven et al., 2005). Nevertheless, it is still controversial whether sex affects HR recovery after dynamic exercise (Antelmi et al., 2008; Arena et al., 2010; Nunes et al., 2014). For example, de Mendonca et al. (2017) demonstrated that there is no sex difference in HR at the 1st minute of recovery after cycling exercise. Interestingly, after performing multiple regression analyses, these authors found an interaction between sex and maximal oxygen uptake that can potentially predict HR at the 2nd minute of recovery. Despite the aforementioned discrepancies, a sex-depended effect on HR recovery has been posited. Although our present data partially support these previous findings, we would like to highlight a few aspects. It may be that these conflicting findings are partially attributable to differences in autonomic dynamics during recovery from exercise. In general, HR deceleration following a standard exercise test (i.e., treadmill and cycle ergometer) reflects a combination of vagal reactivation and sympathetic withdrawal (Imai et al., 1994; Pierpont and Voth, 2004). However, in our approach, the sympathetic outflow is steadily elevated via metaboreflex activation (i.e., PEI) (Fisher et al., 2013; Teixeira et al., 2019). Further, we have analyzed only the first 30-s of PEI based on previous studies indicating a major role of cardiac vagal reactivation in mediating the rapid fall in HR (Fisher et al., 2013; Fisher et al., 2010). As such, our data demonstrated, for the first time, sex differences in cardiac vagal reactivation after cessation of isometric exercise during the onset of PEI. Importantly, our data support that autonomic control of circulation at rest and during exercise is affected by sex (Hart et al., 2011; Hart et al., 2009; Prodel et al., 2018a; Prodel et al., 2018b; Samora et al., 2019; Samora et al., 2018). Nevertheless, we believe that further research is warranted to explore the sex differences in HR recovery after whole-body exercise and the potential role of PEI as a laboratory technique to further our understanding on the relationship between autonomic tone and clinical outcomes.

The present study was not without limitations. First, we studied only young, healthy and physically active participants, which does not allow extrapolation of our results to other populations such as older, sedentary, and/or diseased individuals. Second, we did not screen and report race/ethnicity in this study, although the majority of the participants are Latin-Americans and Caucasians. Thus, our findings cannot be extrapolated to all racial/ethnic groups, as significant racial differences have been observed in cardiovascular parameters (Drew et al., 2020; Young et al., 2020). Third, we have employed ultra-short-term HRV measures and hence one could argue that this could be a limitation. However, previous studies have demonstrated excellent validity/reliability indices between ultra-short-term HRV measures (i.e., 10-s windows) and wider window measures (e.g., 5-min) in healthy subjects (Dekker et al., 1997; Hamilton et al., 2004; Nussinovitch et al., 2011), athletes (Esco and Flatt, 2014), elderly population (de Bruyne et al., 1999) and patients during and after myocardial infarction (Karp et al., 2009).

In summary, our study demonstrates that women have a slower HR recovery at the cessation of isometric handgrip exercise and onset of PEI compared to men, suggesting a sex-related difference in cardiac vagal reactivation in healthy young humans.

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Declaration of competing interest

None of the authors declares a conflict of interest.

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