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Letter to the editor

Response to the letter to the editor: "Is metabolic syndrome related to exercise autonomic modulation in obese adults? (Lopes et al., 2018)"

We would like to thank Lopes WA and collaborators (2018) for their letter and, especially, for their interest in our recently published study in Autonomic Neuroscience (Carvalho et al., 2012: 43–50). We hope that the following results and comments address the authors' concerns and thoughts and provide additional information in the field of autonomic modulation in obesity and related metabolic disorders.

The authors raised a very important point regarding sex-specific heart rate variability (HRV) response to submaximal exercise, hereby evaluated by the six-minute step test (6MST). Indeed, our new findings allow us to draw new conclusions and make inferences that could not be identified initially. We acknowledge that the combination of both sexes in a unique group may have contributed to a certain degree of uncertainty concerning sex-dependent effect in our published study. It is worth noting that we have balanced the men-women proportion across groups - women:men ratio 1:1 in normal-weight (NW) and 1.5:1 for both metabolically healthy (MHO) and unhealthy (MUHO) obese adults - in an attempt to prioritize sample statistical power. However, we would like to thank Lopes et al. for raising up this issue, which we are fully aware of. In a future larger study, we would certainly aim to analyze multiple age ranges in a sex-specific manner to address this gap in the literature.

After analyzing men and women separately, we could observe a consistency with our previous results regarding cardiovascular and metabolic responses to exercise (Table 1), that has been proven (once again) not to be affected by the presence of metabolic syndrome (MetS) but, instead, by obesity *per se* in both men and women. We can still observe a lower maximal oxygen uptake and more accentuated hemodynamic responses to exercise in both MHO and MUHO in comparison to the NW group.

Although the study by El Agaty et al. (2016) used an externally controlled, constant-paced step test, we agree that they had no control of the (heart rate, HR) intensity reached in the 3-minute step test. Contrary to their study, our results are uniform with regard to the intensity achieved in the 6MST. Men and women, regardless of obesity and metabolic profile, reached a near-maximal intensity ranging from 85 to 89% of the real peak HR that was directly measured by the cardiopulmonary exercise test (CPX). Only one subject (NW group) reached 59%HR during the 6MST and has been thus excluded from these exploratory investigations. Even though the cadence and intensity of the 6MST is determined by the patient himself, we could observe a very homogenous and regular pattern across groups and within each individual. Due to this high within-test homogeneity as well as to the similar level of physical fitness in the obese groups, we consider our sample size to be reasonably high to infer MetS real effect on autonomic impairment in obesity. This number of observations so far, however, prevents us from analyzing narrower range intervals of intensity separately or considering only very restricted exercise intensities that could provide us with further valuable information on exercise effort and recovery from different exercise intensities.

Although HRV in resting conditions has been widely investigated in the literature (Koenig and Thayer, 2016), there is still very scarce evidence on HRV during and after exercise owing to the difficulty of obtaining stationary or quasi-stationary HRV signals in these conditions. Due to the characteristic of the exercise test we chose (constant-load submaximal test sufficient to attain steady-state responses) (Fig. 1), we could perform the suggested sex-specific HRV analyses during and after exercise. The heart rate recovery (HRR) at 1 min after test cessation (Table 1), an important marker of increased risk of cardiovascular events and all-cause mortality in the general population (Qiu et al., 2017), was on average 30 to 38 bpm in men and 39 to 43 bpm in women for a passive exercise recovery and did not statistically differ between groups. Data on exercise recovery obtained from the last minutes (300 consecutive iRR) of a 6-min recovery period revealed further similarities and discrepancies of physiological responses in obese men and women with and without MetS (Table 2).

Table 1
Sex-specific cardiovascular, metabolic and ventilatory variables in the 6MST for each group.

	NW (n = 23)	MHO (n = 19)	MUHO (n = 23)
Men	n = 11	n = 7	n = 9
Performance (steps)	194 ± 26	147 ± 17[a]	159 ± 21[b]
VO_{2peak} ($mL\cdot kg^{-1}\cdot min^{-1}$)	23.5 ± 5.9	15.2 ± 2.3[a]	16.0 ± 2.1[b]
$VO_{2peakCPX}$ (%)	76 ± 12	83 ± 12	82 ± 12
HR_{peak} (bpm)	158 ± 20	150 ± 24	153 ± 15
$HR_{peakCPX}$ (%)	86 ± 11	85 ± 10	87 ± 8
$HR_{1st\ min}$ (bpm)	120 ± 25	118 ± 29	123 ± 15
HR Δ_{abs}	38 ± 18	32 ± 7	30 ± 9
HR $\Delta_{\%decrease}$	24 ± 11	22 ± 7	20 ± 6
SBP (mm Hg)	153 ± 15	167 ± 39[a]	178 ± 40[b]
DBP (mm Hg)	72 ± 12	78 ± 10[a]	85 ± 10[b]
Women	n = 12	n = 12	n = 14
Performance (steps)	179 ± 19	166 ± 19[a]	147 ± 22[b]
VO_{2peak} ($mL\cdot kg^{-1}\cdot min^{-1}$)	23.5 ± 5.9	15.1 ± 2.5[a]	15.9 ± 1.7[b]
$VO_{2peakCPX}$ (%)	76 ± 8	79 ± 10	85 ± 24
HR_{peak} (bpm)	162 ± 15	165 ± 12	158 ± 16
$HR_{peakCPX}$ (%)	88 ± 7	89 ± 6	88 ± 8
$HR_{1st\ min}$ (bpm)	119 ± 13	125 ± 11	117 ± 15
HR Δ_{abs}	43 ± 6	39 ± 13	41 ± 7
HR $\Delta_{\%decrease}$	26 ± 3	24 ± 7	26 ± 4
SBP (mm Hg)	142 ± 12	178 ± 36[a]	167 ± 22[b]
DBP (mm Hg)	67 ± 13	86 ± 16[a]	73 ± 11[b]

Kruskall-Wallis and Mann Whitney with Bonferroni adjustment for multiple comparisons for intergroup analysis: [a]MHO *vs* NW; [b]MUHO *vs* NW. HR, heart rate; VO_{2peak}, peak oxygen uptake relative to body weight; $\%VO_{2peak}$, percentage of relative VO_{2peak} at CPX, $\%HR_{peak}$, percentage of HR peak at CPX; V_E/VCO_2, minute ventilation-to-carbon dioxide output; SBP_{peak}, systolic blood pressure; DBP_{peak}, diastolic blood pressure.

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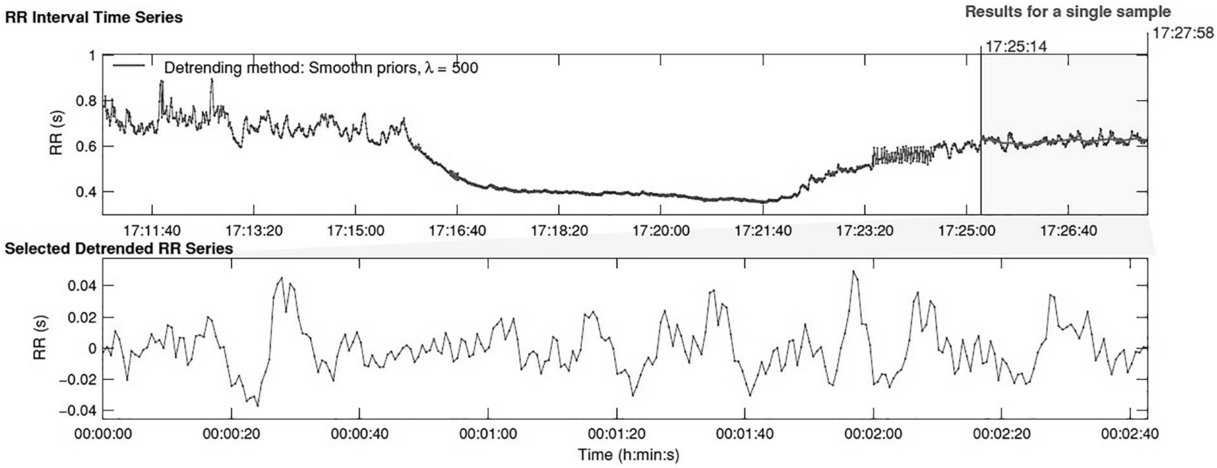

Fig. 1. Heart rate variability analysis during the recovery phase of the 6MST.

Our analyses included time-domain, geometric and non-linear HRV indices and excluded frequency-domain ones. The use of the frequency spectrum is considered to be inappropriate and hampers results interpretability in situations where the respiratory rate is high (such as during and after exercise) because the spectrum respiratory peak and the HRV high-frequency components are overlapped (Peçanha et al., 2017).

Our new findings suggest that, during exercise, obese men with MetS present a poorer overall HRV than those without MetS, as indicated by lower averaged SDNN, SD1 and SD2 values. On the other hand, the analyses of exercise recovery show that both obese groups presented lower overall variability (SDNN) and lower HRV complexity (ShanEn) than NW, but obese men with MetS presented with further overall variability impairment (TINN, SD1 and SD2) and delayed parasympathetic reactivation (RMSSD) when compared to non-obese individuals.

On the other hand, obese women with MetS also presented lower HRV linearity than both obese without MetS and NW during exercise. More interesting results were found during the recovery period. Both obese groups presented lower HRV complexity during the exercise recovery phase than NW young women. However, unhealthy obese women presented higher overall variability (SDNN, RRtri, TINN and SD2) than either normal-weight or obese women without any metabolic disorder, indicating a possible advantage of women's neuroadaptive response over men within the same condition or, one may argue, a delayed autonomic impairment across their lifespan (Ryan et al., 1994; Moodythaya and Avadhany, 2012). Indeed, Voss et al. (2015) have shown in a huge dataset of young and elderly healthy adults that the NN interval time series of women were less predictable and more complex than men. They have shown that, although the effect of sex on short-

Table 2
Sex-specific heart rate variability during and after submaximal exercise.

	NW		MHO		MUHO	
	Exercise	Recovery	Exercise	Recovery	Exercise	Recovery
Men						
MeanRRi (ms)	398.6 ± 51.7	616.7 ± 118.3	427.7 ± 38.0	616.2 ± 107.5	386.4 ± 28.1	578.9 ± 63.7
SDNN (ms)	2.9 ± 1.2	31.5 ± 19.5	3.5 ± 0.9	23.8 ± 17.3[a]	2.6 ± 0.6[c]	22.1 ± 12.8[b]
RMSSD (ms)	3.1 ± 0.9	15.8 ± 12.9	3.3 ± 1.2	11.8 ± 11.7	2.8 ± 0.2	7.4 ± 5.1[b]
RRtri	1.8 ± 0.3	7.2 ± 3.4	1.6 ± 0.2	5.9 ± 3.4	1.7 ± 0.3	5.7 ± 3.5
TINN (ms)	15.0 ± 5.9	145.5 ± 83.5	16.7 ± 5.2	105.0 ± 79.9	13.7 ± 8.8	97.5 ± 55.5[b]
SD1 (ms)	2.2 ± 0.7	11.2 ± 9.2	2.4 ± 0.8	8.4 ± 8.3	1.9 ± 0.2[c]	5.3 ± 3.6[b]
SD2 (ms)	3.5 ± 1.8	43.0 ± 26.2	4.3 ± 1.3	32.5 ± 23.1	3.1 ± 0.9[c]	30.7 ± 17.9[b]
DFAα1	0.8 ± 0.4	1.4 ± 0.2	0.9 ± 0.4	1.3 ± 0.3	0.7 ± 0.3	1.4 ± 0.1
DFAα2	0.8 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	1.1 ± 0.1	0.9 ± 0.2	1.0 ± 0.2
ShanEn	2.7 ± 0.2	3.4 ± 0.4	2.9 ± 0.4	3.6 ± 0.2[a]	2.8 ± 0.4	3.7 ± 0.3[b]
Women						
MeanRRi (ms)	384.2 ± 33.9	609.2 ± 61.7	375.8 ± 29.4	610.1 ± 59.1	391.9 ± 43.2	620.9 ± 76.7
SDNN (ms)	3.2 ± 1.5	19.9 ± 13.2	2.7 ± 0.7	20.6 ± 11.5	2.4 ± 0.8	24.9 ± 7.2[bc]
RMSSD (ms)	3.3 ± 1.2	12.7 ± 6.7	3.4 ± 0.9	8.4 ± 4.6[a]	2.9 ± 0.9	9.9 ± 5.0
RRtri	1.5 ± 0.2	4.9 ± 2.1	1.6 ± 0.2	4.9 ± 1.8	1.6 ± 0.3	6.5 ± 1.7[bc]
TINN (ms)	17.9 ± 8.1	91.3 ± 53.9	14.4 ± 7.3	84.1 ± 46.2	14.6 ± 6.9	110.0 ± 32.6[bc]
SD1 (ms)	2.3 ± 0.8	9.0 ± 4.8	2.4 ± 0.6	5.9 ± 3.3[a]	2.0 ± 0.6	7.0 ± 3.6
SD2 (ms)	3.8 ± 2.1	26.7 ± 18.2	2.9 ± 1.0	28.4 ± 15.9	2.7 ± 0.9	34.4 ± 10.3[bc]
DFAα1	0.7 ± 0.2	1.2 ± 0.3	0.5 ± 0.2	1.3 ± 0.2	0.6 ± 0.2	1.3 ± 0.3
DFAα2	0.9 ± 0.2	0.8 ± 0.3	0.8 ± 0.2	1.2 ± 0.1[a]	0.9 ± 0.1	1.2 ± 0.3[b]
ShanEn	2.8 ± 0.3	3.2 ± 0.3	2.8 ± 0.4	3.6 ± 0.4[a]	2.6 ± 0.2[bc]	3.7 ± 0.4[b]

Kruskall-Wallis and Mann Whitney with Bonferroni adjustment for multiple comparisons for intergroup analysis. Difference between [a]MHO *vs* NW; [b]MUHO *vs* NW; [c]MUHO *vs* MHO. MeanRRi, mean RR intervals; SDNN, standard deviation of all NN intervals; RMSSD, square root of the mean squared successive difference of RR intervals; NN50, number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals; RRtri, total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with bins of 7–8125 ms (1/128 s); TINN, baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals; SD1, instantaneous beat to beat variability; SD2, continuous beat to beat variability; DFA, detrended fluctuation analysis: short (α1) and long term (α2) fractal components; ShanEn, Shannon entropy.

term HRV was more important in younger ages and tended to disappear with aging, autonomic impairment was still more pronounced in men than in women.

Finally, it would certainly be of great interest to examine in future longitudinal-design studies whether metabolic improvement or early life onset of any metabolic disturbances, independently of lifestyle or weight loss changes, could affect long-term cardiac autonomic modulation in obese individuals. As HRV behaves differently in men and women with MetS (Stuckey et al., 2014), we also encourage further investigations to address the contribution of sex not only at rest but also in situations where physiological adaptations are challenged.

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