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Diet associated with exercise improves baroreflex control of sympathetic nerve activity in metabolic syndrome and sleep apnea patients

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Abstract

Purpose We tested the hypothesis that (i) diet associated with exercise would improve arterial baroreflex (ABR) control in metabolic syndrome (MetS) patients with and without obstructive sleep apnea (OSA) and (ii) the effects of this intervention would be more pronounced in patients with OSA.

Methods Forty-six MetS patients without (noOSA) and with OSA (apnea-hypopnea index, AHI > 15 events/h) were allocated to no treatment (control, C) or hypocaloric diet (− 500 kcal/day) associated with exercise (40 min, bicycle exercise, 3 times/week) for 4 months (treatment, T), resulting in four groups: noOSA-C ($n = 10$), OSA-C ($n = 12$), noOSA-T ($n = 13$), and OSA-T ($n = 11$). Muscle sympathetic nerve activity (MSNA), beat-to-beat BP, and spontaneous arterial baroreflex function of MSNA (ABR_{MSNA}, gain and time delay) were assessed at study entry and end.

Results No significant changes occurred in C groups. In contrast, treatment in both patients with and without OSA led to a significant decrease in weight ($P < 0.05$) and the number of MetS factors ($P = 0.03$). AHI declined only in the OSA-T group (31 ± 5 to 17 ± 4 events/h, $P < 0.05$). Systolic BP decreased in both treatment groups, and diastolic BP decreased significantly only in the noOSA-T group. Treatment decreased MSNA in both groups. Compared with baseline, ABR_{MSNA} gain increased in both OSA-T (13 ± 1 vs. 24 ± 2 a.u./mmHg, $P = 0.01$) and noOSA-T (27 ± 3 vs. 37 ± 3 a.u./mmHg, $P = 0.03$) groups. The time delay of ABR_{MSNA} was reduced only in the OSA-T group (4.1 ± 0.2 s vs. 2.8 ± 0.3 s, $P = 0.04$).

Conclusions Diet associated with exercise improves baroreflex control of sympathetic nerve activity and MetS components in patients with MetS regardless of OSA.

Keywords Metabolic syndrome · Obstructive sleep apnea · Sympathetic nervous system · Baroreflex control · Exercise · Diet

Introduction

Metabolic syndrome (MetS) is characterized by a cluster of cardiovascular risk factors, including central obesity, glucose intolerance, dyslipidemia, and elevated blood pressure (BP) levels [1]. Several lines of evidence support the concept that MetS is associated with sympathetic hyperactivation [2–4]. In addition, recent findings suggest that the sympatho-excitation in MetS is related to alterations in arterial baroreflex (ABR) control [3, 5].

Because obesity is a risk factor for obstructive sleep apnea (OSA), MetS and OSA frequently coexist in clinical practice [6]. In fact, observational studies show that approximately 60% of patients with MetS suffer from OSA [6], which is

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characterized by recurrent upper airway obstructions during sleep, intermittent hypoxemia, and sleep fragmentation [7, 8]. Recent evidence consistently suggests that OSA concurrent with MetS contributes to worse autonomic and vascular dysfunction [5, 9, 10]. OSA exacerbates muscle sympathetic nerve activity (MSNA) [2, 3, 5] and impairs ABR in MetS patients [2, 3, 5]. The clinical implications for these findings rely on the fact that both ABR dysfunction and increased MSNA are associated with a poor prognosis in patients with cardiovascular diseases [11, 12].

Currently, the therapy using continuous positive airway pressure (CPAP) is the standard treatment of OSA with beneficial effect on BP, insulin resistance, and serum triglyceride levels in patients with obesity [13]. In addition, changing one's lifestyle is strongly recommended for patients with MetS [1]. Previous studies have demonstrated that exercise and a hypocaloric diet provoke a remarkable reduction in body weight [14–16]. Moreover, this non-pharmacological strategy reduces sympathetic nerve activity [15, 16] and improves the ABR of heart rate [15] in MetS patients. However, the treatment of OSA with CPAP seems not to promote weight loss [17] or reverse MetS [18]. Unknown is whether diet associated with exercise improves the ABR of sympathetic nerve activity in MetS patients with OSA. In the present study, we investigated the effects of a hypocaloric diet combined with exercise on time delay and sensitivity of ABR of MSNA and heart rate (HR), MSNA, and systolic BP (SBP) in MetS patients with and without OSA. We made the following hypothesis: (i) diet and exercise will improve ABR of MSNA and HR in MetS patients independent of the presence or absence of OSA and (ii) the effects of this intervention would be more pronounced in patients with OSA.

Methods

The study was approved by the ethics committee, and the signed informed consent was obtained during the screening visit. Subsequently, the patients were submitted to measurement of office BP, blood tests, clinical evaluation, and to determine if they fulfilled the criteria to take part in the study. In a sitting position, three office BP recordings were obtained with a mercury sphygmomanometer at 5-min intervals, and the average of these measurements was used to determine office BP. Following 12 h of overnight fasting, blood samples were collected to determine HDL-c, triglycerides, and plasma glucose concentrations. After clinical evaluation, all participants underwent a nocturnal polysomnography to detect the absence or presence of OSA (apnea-hypopnea index, AHI > 15 events/h). Then, the subjects with and without OSA (OSA and noOSA, respectively) were allocated to either a hypocaloric diet associated with exercise (treatment) or control (C) in a 1:1 ratio. Polysomnography, cardiopulmonary exercise testing, microneurography, beat-to-beat BP, and spontaneous ABR and cardiac and peripheral spectral analysis were assessed at baseline and at study end (after 4 months).

Subjects

MetS patients were recruited from the Exercise Cardiology Ambulatory Unit of the Heart Institute (InCor), University of São Paulo Medical School, and some of the patients in the present study participated in other research protocols that have already been published by our group [5, 19]. Patients were diagnosed with MetS by Adult Treatment Panel III (ATP-III) Report criteria [1], and according to international guidelines, only patients that did not have any indication for medical treatment were enrolled in the present study. Initially, 95 patients with MetS were recruited. We excluded patients taking any medications, smokers, those with a history of excessive alcohol consumption, and individuals participating in a regular exercise-training program. From the remaining 59 patients, 22% were excluded, because of the need for drug intervention, pregnancy, or starting smoking during the protocol. Thus, 46 patients with MetS represent the study population; they were assigned to four groups: (1) noOSA-C ($n = 10$); (2) OSA-C ($n = 12$); (3) noOSA-T ($n = 13$); and (4) OSA-T ($n = 11$).

Polysomnography

As previously described [7, 20], the sleep pattern was recorded during a nocturnal polysomnography. According to international guidelines, apnea was defined as complete cessation of airflow for at least 10 s, whereas hypopnea was defined as a reduction (> 50%) in respiratory signals for at least 10 s associated with oxygen desaturation of > 3% or an arousal. The AHI was calculated by sum of episodes of apnea and hypopnea per hour of sleep. OSA was defined by an AHI of at least 15 events per hour of sleep and all patients with OSA had predominantly (> 50%) obstructive events [5, 19].

Cardiopulmonary exercise testing

All patients underwent cardiopulmonary exercise testing as previously described [21] on a braked cycle ergometer, using a ramp protocol with work rate increments (e.g., 10, 15, or 20 W) every minute at 60 rpm to exhaustion. Peak values of oxygen (VO_2) uptake were averaged from the last 30-s interval and were considered as the maximal exercise capacity (peak VO_2). Ventilatory anaerobic threshold and respiratory compensation point were assessed as previously described [21].

Miscellaneous measurements

As previously described [5, 19], multiunit nerve postganglionic MSNA was recorded using the microneurography technique, HR was measured through ECG lead II, arterial pressure was quantified non-invasively on a beat-to-beat basis by a finger photoplethysmography device (Finapres 2300, Ohmeda), and respiratory activity was measured with a piezoelectric belt placed around the upper abdomen.

Experimental protocol

On the experimental day, all patients abstained from caffeine or other types of stimulants for 12 h and any type of physical activity for 24 h. The protocol experiment was performed between 8:00 and 10:00 AM, with the patients in a supine position in a quiet room which was kept comfortably warm (22 to 24 °C). After obtaining an adequate sympathetic nerve recording and stabilization of the autonomic and cardiovascular variables, baseline recordings of MSNA, HR, arterial pressure, and respiratory activity were taken for 10 min.

Autonomic control

Cardiac and peripheral autonomic control was measured as previously described and in accordance with international standards [22]. Briefly, the variability of R-R interval (RRi), systolic arterial pressure (SAP), and respiratory rate was analyzed by autoregressive spectral algorithm. The spectral densities detected in low-frequency band (LF 0.04 to 0.15 Hz) reflecting sympathetic modulation predominance and in high-frequency band (HF 0.15 to 0.40 Hz), since synchronized with spontaneous breathing, are markers of cardiac vagal modulation. Furthermore, the LF-to-HF ratio of RRi was calculated for estimation of the cardiac sympathovagal balance (LF_{RRi}/HF_{RRi}) [5, 21–23].

Arterial baroreflex control

Arterial baroreflex control of MSNA and HR was quantified using the transfer function analysis by means to bivariate autoregressive identification procedure [5, 23]. This procedure quantifies several parameters [e.g., gain, coherence (K^2), and phase shift (Φ)] of transfer function between input (SAP) and output (MSNA or HR) signals. The gain measures the intensity of the response of arterial baroreflex control of MSNA and HR, being expressed in a.u./mmHg and ms/mmHg, respectively [5, 23]. The time delay of baroreflex control, an index that quantifies the latency of the response this reflex arc, was quantified by means of ratio to phase shift and angular velocity in LF range, being expressed in seconds [5, 23].

Intervention

OSA and noOSA patients allocated into the treatment group underwent supervised exercise program (60 min of exercise training, 3 times/week) during 4 months. As previously described [15, 16, 19, 21], each exercise session consisted of 8% of stretching, 67% of cycling on an ergometer bicycle, 17% of local strengthening exercises, and 8% cool down with stretching exercises. The patients began their training program at the HR corresponding to the anaerobic threshold and the aerobic exercise intensity was progressively increased up to the HR corresponding to the respiratory compensation point.

Simultaneous to the exercise-training program, patients consumed a hypocaloric diet. As previously described [19], the basal energy demands were estimated using the FAO/WHO/UNU equation multiplied by a factor of 1.3 [19]. In the present study, energy intake was reduced 500 kcal/day during the 4 months of intervention. The hypocaloric diet consisted of an eating plan divided into five meals. The food composition was divided into 55–75% carbohydrates, 15–30% fat, and 10–15% protein [19]. Adherence to the nutritional program was controlled during monthly visits, in which the patients were weighed and encouraged to record their daily consumption to evaluate adherence to the hypocaloric dietary program.

Statistical analysis

The data are presented as mean ± standard error. A chi-square (χ^2) test was used to assess categorical data differences. For each continuous or discrete variable, the Lèvene and Kolmogorov-Smirnov tests were used to assess the homogeneity and normality of distribution, respectively. All parametric data were compared using a two-way ANOVA. When a significant difference was found, Scheffé's post hoc comparison test was used. Wilcoxon or Mann-Whitney tests were used when appropriate. A value of $P < 0.05$ was considered statistically significant.

Results

Physical characteristics and MetS criteria pre- and post-treatment are shown in Table 1. The treatment significantly decreased body weight, BMI, waist circumference, and office SBP and significantly increased peak of oxygen uptake regardless of the presence of OSA, but had no effect on glucose, triglyceride, and HDL-cholesterol levels (Table 1). However, office DBP significantly decreased after intervention only in the noOSA group (Table 1). No significant changes were found in the control groups over the 4-month duration of the study. Interestingly, we observed that after 4 months of diet associated with exercise, approximately 42% of the noOSA

Table 1 Physical characteristics and metabolic syndrome criteria at baseline and after 4 months

	noOSA				OSA			
	C		T		C		T	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Physical characteristics								
Sex (male/female)	3/7		7/6		8/4		7/4	
Age (years)	44 ± 2		45 ± 2		48 ± 3		52 ± 2	
Body weight (kg)	88 ± 3	88 ± 3	89 ± 3	83 ± 3* †	90 ± 4	90 ± 4	87 ± 3	80 ± 2* †
BMI (kg/m^2)	32 ± 1	32 ± 1	32 ± 1	30 ± 1* †	32 ± 1	32 ± 1	32 ± 1	29 ± 1* †
VO_2 peak (mL/kg/min)	22 ± 1	21 ± 1	26 ± 2	30 ± 1* †	24 ± 2	24 ± 1	24 ± 2	29 ± 2* †
Metabolic syndrome criteria								
Waist circumference (cm)	105 ± 2	105 ± 1	105 ± 2	100 ± 2* †	108 ± 2	106 ± 2	106 ± 2	98 ± 2* †
Glucose (mg/dL)	101 ± 3	98 ± 4	99 ± 2	98 ± 2	100 ± 3	103 ± 3	110 ± 4	101 ± 4
HDL-c (mg/dL)	39 ± 2	41 ± 3	43 ± 3	45 ± 3	40 ± 3	42 ± 4	41 ± 2	42 ± 2
Triglycerides (mg/dL)	220 ± 44	234 ± 42	179 ± 17	156 ± 17	190 ± 31	180 ± 30	177 ± 27	158 ± 21
Office SBP (mmHg)	131 ± 4	130 ± 4	132 ± 3	118 ± 3* †	130 ± 5	130 ± 4	138 ± 7	121 ± 4*
Office DBP (mmHg)	87 ± 3	89 ± 2	89 ± 3	79 ± 3* †	89 ± 3	88 ± 4	92 ± 4	87 ± 3

Values are mean ± SE. *noOSA*, metabolic syndrome without obstructive sleep apnea patients; *OSA*, metabolic syndrome with obstructive sleep apnea patients; *C*, control group; *T*, treatment group (hypocaloric diet associated with exercise training); *Pre*, pre-intervention; *Post*, post-intervention; *BMI*, body mass index; *VO_2 peak*, peak oxygen uptake; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure. *$P < 0.05$ vs. pre; † $P < 0.05$ vs. C

($P = 0.03$) and 36% of the OSA (P = 0.03) patients no longer had a diagnosis of MetS. The individual representative values of the number of factors for diagnosis of MetS in patients with and without OSA pre- and post-control or treatment are shown in Fig. 1.

The effects of treatment on sleep pattern characteristics are presented in Table 2. In the noOSA group, no significant changes in the nocturnal polysomnography parameters were observed after intervention. In contrast, the treatment caused a significant reduction in the arousal index, AHI, and SaO_2 <

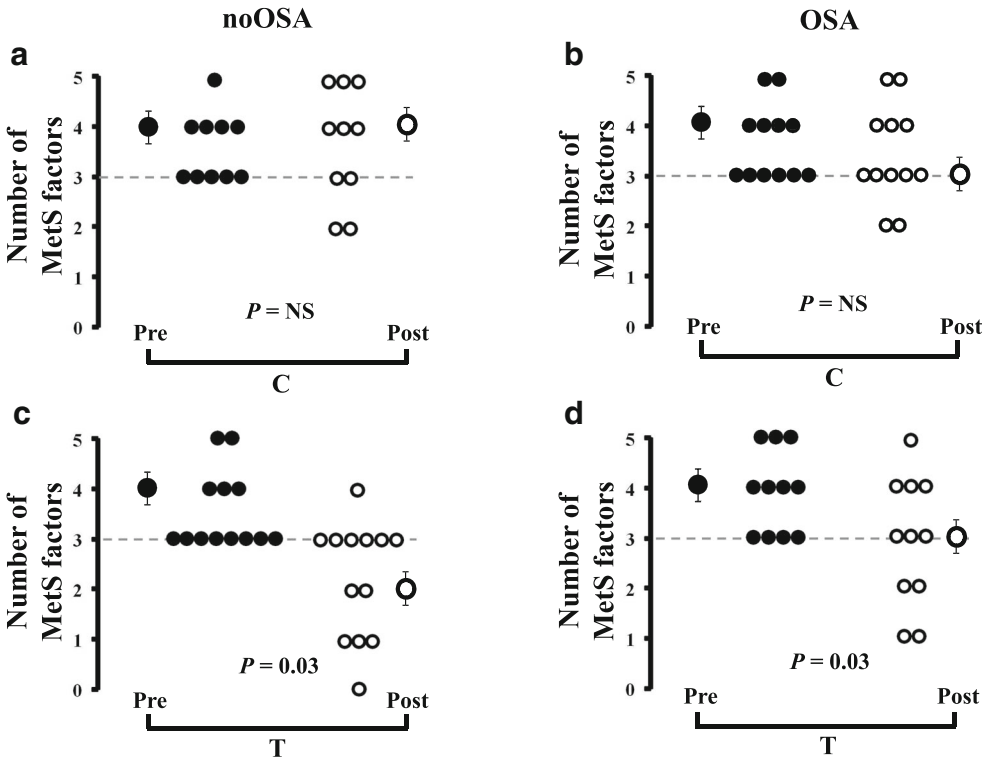

Fig. 1 Individual representative values of the number of factors for diagnosis of metabolic syndrome (MetS) in patients with (OSA) and without obstructive sleep apnea (noOSA) in the pre- and post-intervention periods. Note that hypocaloric diet associated with exercise training (T) significantly decreased the number of factors for diagnosis of MetS in both noOSA (**c**) and OSA (**d**) groups. No significant changes were observed in patients in the control (C) groups (**a**, **b**)

Table 2 Sleep pattern characteristics

	noOSA				OSA			
	C		T		C		T	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Total sleep time (min)	407 ± 20	398 ± 18	381 ± 10	371 ± 23	389 ± 24	405 ± 36	398 ± 20	417 ± 14
Sleep efficiency (%)	89 ± 3	84 ± 4	87 ± 2	84 ± 5	82 ± 5	83 ± 7	87 ± 2	89 ± 2
Stage 1 (%)	5 ± 2	6 ± 1	4 ± 1	5 ± 1	6 ± 2	9 ± 3	7 ± 2	6 ± 2
Stage 2 (%)	59 ± 2	60 ± 3	59 ± 3	63 ± 3	61 ± 4	57 ± 6	61 ± 2	57 ± 5
Stage 3 (%)	10 ± 2	12 ± 4	9 ± 2	9 ± 2	12 ± 3	12 ± 5	7 ± 1	12 ± 4
REM (%)	20 ± 2	18 ± 2	21 ± 2	18 ± 2	17 ± 1	18 ± 2	20 ± 2	20 ± 2
Arousal index (events/h)	8 ± 2	11 ± 2	14 ± 2	14 ± 3	19 ± 4	35 ± 9	21 ± 3	16 ± 5* †
AHI (events/h)	8 ± 1	10 ± 3	9 ± 1	9 ± 1	37 ± 7	48 ± 12	31 ± 5	17 ± 4* †
Minimum SaO_2 (%)	89 ± 1	87 ± 1	86 ± 1	87 ± 1	80 ± 2	79 ± 3	79 ± 2	83 ± 2* †
SaO_2 < 90% (%)	1 ± 1	2 ± 1	1 ± 1	2 ± 1	11 ± 1	10 ± 1	10 ± 1	2 ± 1* †

Values are mean ± SE. *noOSA*, metabolic syndrome without obstructive sleep apnea patients; *OSA*, metabolic syndrome with obstructive sleep apnea patients; *C*, control group; *T*, treatment group (hypocaloric diet associated with exercise training); *Pre*, pre-intervention; *Post*, post-intervention; *REM*, rapid eyes movement; *AHI*, apnea-hypopnea index; SaO_2, saturation of oxygen; $SaO_2 < 90\%$, time of saturation of oxygen below 90%. *$P < 0.05$ vs. pre; †$P < 0.05$ vs. C post

90% and a significant increase in minimum SaO_2 in the OSA group. However, this group still had moderate OSA (on average) after 4 months of treatment (Table 2). In the noOSA-C and OSA-C groups, no changes in sleep patterns were observed.

The treatment significantly reduced MSNA in noOSA-T and OSA-T patients (Fig. 2a, b). After 4 months, the levels of MSNA in the OSA-T group were significantly lower compared with those in the OSA-C group (Fig. 2b).

The patients who underwent treatment had reduced cardiac sympathetic modulation (LF_{RRi}), sympathovagal balance (LF_{RRi}/HF_{RRi}) and increased cardiac parasympathetic modulation (HF_{RRi}) in patients with MetS with and without OSA (Table 3). However, treatment reduced the SAP variability (variance) and vascular sympathetic modulation (LF_{SAP}) only in the OSA-T patients (Table 3). No changes in cardiac and peripheral autonomic control were observed in the noOSA-C and OSA-C groups (Table 3).

Treatment significantly increased the gain in ABR_{MSNA} (Fig. 3a, c) and ABR_{RRi} (Table 3) in noOSA and OSA patients. This intervention significantly decreased the time delay (response) of ABR_{MSNA} (Fig. 3d) and ABR_{RRi} (Table 3) in OSA patients, but caused no significant changes in noOSA patients (Fig. 3b and Table 3, respectively). No significant changes in the gain and time delay of ABR_{MSNA} and ABR_{RRi} were observed in noOSA-C and OSA-C groups.

Discussion

The novel findings from the present study are that diet associated with exercise (i) reduced the number of components of MetS regardless of OSA presence; (ii) improved sleep pattern in MetS patients with OSA; (iii) increased the gain of ABR_{MSNA} and ABR_{RRi} in MetS patients with and without OSA; and (iv) decreased the time delay of ABR_{MSNA} and ABR_{RRi} in OSA groups, but caused no changes in noOSA groups after 4 months of treatment.

The treatment proposed in the present study resulted in several beneficial effects in both patients with and without OSA, including not only weight loss but also a decrease in the number of components of MetS. Of note, the waist circumference and office SBP declined regardless of the presence of OSA, but office DBP significantly decreased after treatment only in the noOSA group. The effects of treatment on diastolic BP were less pronounced in the OSA group than those in the noOSA group. The precise reasons for this heterogeneous response are not clear, but we speculated that residual OSA after treatment might mitigate the impact of treatment on vascular resistance.

To our knowledge, few studies have evaluated the effect of this treatment in patients with MetS considering the impact of OSA. We found that the amelioration in the sleep pattern observed in the present study by improvements in arousal index, AHI, and minimum oxygen saturation was not accompanied by sleep efficiency or significant sleep architecture improvements. This apparent inconsistency may be related to the relative small sample size comprised in this study. This is an interesting issue to be clarified in future studies that address a larger population.

The evaluation of the effect of diet or exercise alone in OSA severity is out of the scope of this study. However, it has been described that the magnitude of the effect of the

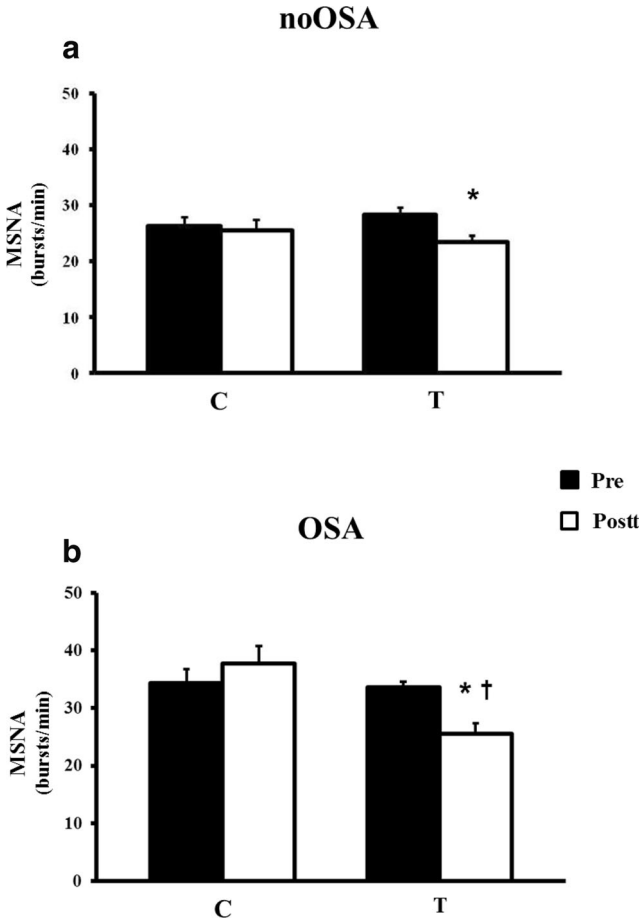

Fig. 2 Resting muscle sympathetic nerve activity (MSNA) in patients with metabolic syndrome without obstructive sleep apnea (noOSA, **a**) and in patients with obstructive sleep apnea (OSA, **b**) in the hypocaloric diet associated with exercise training (T) and control (C) groups, pre- and post-intervention. Note that T reduced MSNA in noOSA (**a**) and in OSA (**b**) groups. In addition, in patients with OSA after intervention, MSNA levels were lower (**b**) in the T group compared with those in the C group. Asterisk symbol indicates difference vs. pre, $P < 0.05$. Dagger symbol indicates difference vs. C after 4 months (post), $P < 0.05$

intervention on the OSA severity depends of the percentage of weight loss reached at the end of treatment [24]. Thus, our study confirms that diet associated with exercise is mandatory in the treatment of patients with MetS. In fact, we have systematically observed this treatment improves the AHI in patients with MetS [19].

The mechanisms involved in the amelioration of OSA are out of the scope of the present study. However, someone could suggest that this treatment increased neck muscle or decreased fluid accumulation in the neck. The result of such changes is the attenuation of upper airway narrowing and collapsibility [25].

Another important new finding in our study is the significant improvement in ABR function after treatment. Besides being an important modulator of sympathetic outflow, ABR has important clinical implications once that the reduced ABR is directly associated with worse prognosis in patients with cardiovascular disease [26]. In the present study, we found that treatment increased ABR of both MSNA and HR in both MetS patients with and without OSA. Despite the uncertainty regarding the mechanisms underlying the amelioration of arterial baroreflex control, there are some potential candidates to explain such autonomic reflex change. The ability of the ABR to translate spontaneous oscillations in BP depends on deformation of the carotid sinus and aortic arch in response to acute changes in intravascular pressure [27]. Exercise training associated or not with diet causes a variety of vascular effects including improvement in arterial compliance and endothelial function [28]. Thus, changes in compliance and endothelial function caused by exercise and diet may play a pivotal role in the amelioration of ABR.

Interestingly, the effects of this non-pharmacological treatment on arterial baroreflex control were more pronounced in patients with MetS with OSA than those in patients without OSA. The reduction in the time delay of ABR_{MSNA} and ABR_{RRi} was observed in OSA patients, but not in noOSA patients. The change in the time delay of ABR_{MSNA} and ABR_{RRi} may be associated with the reduction in the arterial pressure variability (variance) and vascular sympathetic modulation (LF_{SAP}). Alternatively, the reduction in the time delay of ABR_{RRi} may be due to the increase in cardiac parasympathetic modulation, because treatment significantly increased cardiac vagal modulation. The lack of change in the time delay of ABR_{MSNA} and ABR_{RRi}, arterial pressure variability (variance), and vascular sympathetic modulation (LF_{SAP}) in the noOSA group might be expected, because these physiological parameters are not altered in these patients. In a recent study, we found no difference in the time delay of ABR_{MSNA} and ABR_{RRi}, arterial pressure variability (variance), and vascular sympathetic modulation (LF_{SAP}) between MetS patients without OSA and healthy controls [5].

The reduction in MSNA has clinical implications. Accumulated evidence shows that an increased sympathetic nerve activity is associated with a poor prognosis [12]. Of course, the improvement in arterial baroreflex sensitivity is a potential mechanism to explain the reduction in sympathetic activity. However, we cannot disregard that the reduction in MSNA may also be related to improvement in chemoreflex control [29]. In a recent study, we reported that peripheral and central chemoreflex control of MSNA is substantially increased in patients with MetS and OSA [29] and that treatment decreases this autonomic dysfunction [19].

This study has some strengths and limitations. The strengths are that all the patients underwent polysomnography, considered the "gold standard" for diagnosing OSA. Second, the spontaneous breathing during experimental protocol reinforces the findings on physiological effects of diet and exercise in ABR. We know that respiratory activity contributes

Table 3 Cardiac and peripheral autonomic control

	noOSA				OSA			
	C		T		C		T	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
R-R interval								
Variance (ms^2)	2532 ± 596	1512 ± 171	1523 ± 338	2712 ± 372	1712 ± 212	2180 ± 375	1077 ± 206	2353 ± 381
VLF abs. (ms^2)	939 ± 189	759 ± 147	609 ± 145	1259 ± 248	1031 ± 233	1333 ± 294	549 ± 141	1184 ± 197
LF abs. (ms^2)	896 ± 302	470 ± 137	676 ± 166	795 ± 160	507 ± 75	612 ± 88	403 ± 188	625 ± 94
LF n.u. (%)	63 ± 5	67 ± 3	65 ± 4	53 ± 6* †	74 ± 3	75 ± 5	76 ± 3	57 ± 5* †
HF abs. (ms^2)	697 ± 305	283 ± 60	324 ± 85	642 ± 128	174 ± 33	236 ± 25	124 ± 28	545 ± 180* †
HF n.u. (%)	38 ± 4	32 ± 3	35 ± 4	46 ± 6* †	26 ± 3	25 ± 5	24 ± 3	40 ± 5* †
LF/HF	2.1 ± 0.5	2.7 ± 0.5	2.5 ± 0.4	1.7 ± 0.4* †	3.4 ± 0.6	2.9 ± 0.3	3.9 ± 0.7	1.8 ± 0.4* †
Gain of ABR (ms/mmHg)	15 ± 1	10 ± 1	14 ± 1	19 ± 1* †	7 ± 1	6 ± 1	7 ± 1	11 ± 1* †
Time delay of ABR (s)	1.6 ± 0.2	1.8 ± 0.2	1.7 ± 0.2	1.5 ± 0.1	2.9 ± 0.4	3.3 ± 0.4	2.9 ± 0.3	1.5 ± 0.2* †
Systolic arterial pressure								
Variance ($mmHg^2$)	32 ± 7	32 ± 6	23 ± 4	19 ± 3	29 ± 3	49 ± 9	38 ± 5	22 ± 3* †
LF abs. ($mmHg^2$)	5 ± 1	5 ± 1	6 ± 1	4 ± 1	8 ± 2	10 ± 1	7 ± 1	3 ± 1* †
HF abs. ($mmHg^2$)	3 ± 1	3 ± 1	2 ± 1	2 ± 1	2 ± 1	3 ± 1	4 ± 1	1 ± 1*

Values are mean ± SE. *noOSA*, metabolic syndrome without obstructive sleep apnea patients; *OSA*, metabolic syndrome with obstructive sleep apnea patients; *C*, control group; *T*, treatment group (hypocaloric diet associated with exercise training); *Pre*, pre-intervention; *Post*, post-intervention; *VLF*, very low frequency; *LF*, low frequency; *HF*, high frequency; *abs.*, absolute unit; *n.u.*, normalized unit; *LF/HF*, sympathovagal balance; *ABR*, arterial baroreflex control. *$P < 0.05$ vs. pre; †$P < 0.05$ vs. C pos

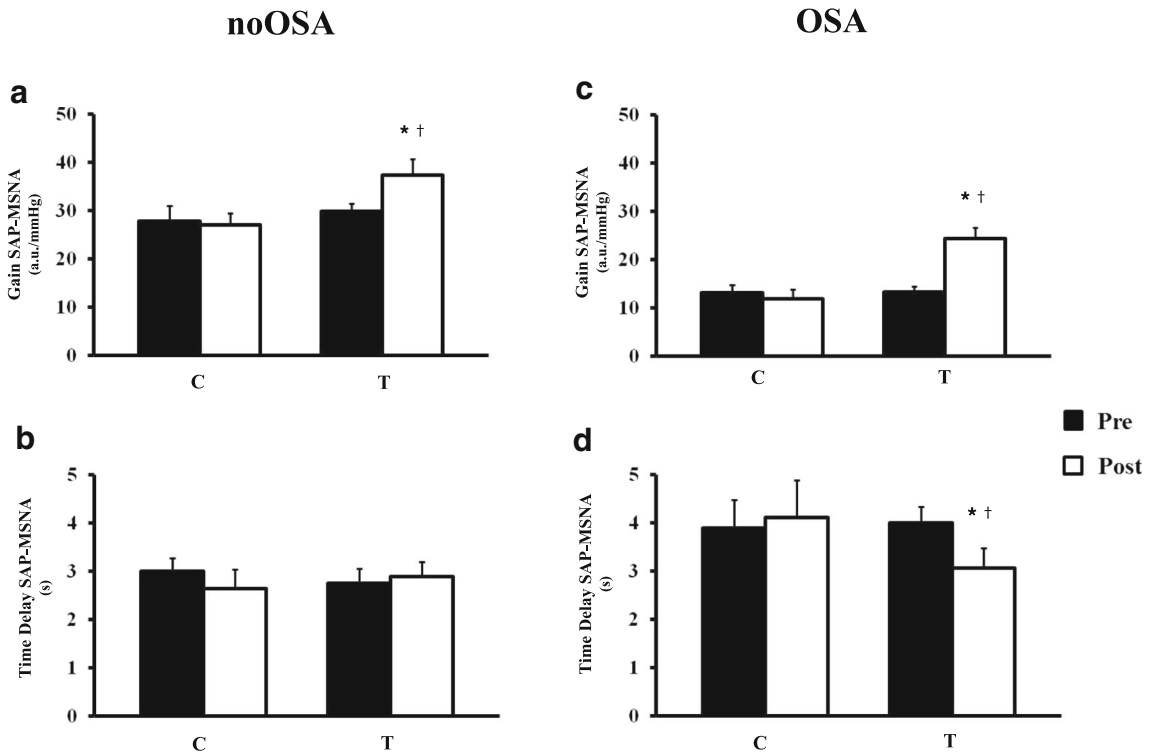

Fig. 3 Sensitivity of arterial baroreflex control (ABR) of muscle sympathetic nerve activity (gain SAP-MSNA) and latency of ABR of MSNA (time delay SAP-MSNA) in patients with metabolic syndrome without obstructive sleep apnea (noOSA, **a**, **b**, respectively) and in patients with OSA (OSA, **c**, **d**, respectively) in the hypocaloric diet associated with exercise training (T) and control (C) groups, pre- and post-intervention. Note that T increased gain SAP-MSNA (**a**) and OSA groups (**c**). In addition, after intervention, gain SAP-MSNA levels in both T groups were higher in comparison with those in the C groups. Besides, only in the OSA group, the time delay SAP-MSNA decreased after T (**d**) and their levels were lower than those in the C group. Asterisk symbol indicates difference vs. pre, $P < 0.05$. Dagger symbol indicates difference vs. C group after 4 months (post), $P < 0.05$

importantly to short-term modulation of autonomic nervous system. For example, controlled deep breathing at 0.10 Hz promotes ABR overestimation under resting conditions [30]. On the other hand, isocapnic hyperventilation at 0.32 Hz reduces the ABR gain when compared with normal quiet breathing in the same frequency band [31]. As spontaneous breathing was synchronized in HF band during data analysis, the control of this possible bias strengthens our findings. Lastly, the absence of medications reinforces our findings about the real effect of this non-pharmacological treatment. The following limitations should be acknowledged: although there was no significant difference in sex distribution between groups, the number of women in the OSA group was lower than that in the noOSA group. It is unlikely this difference influenced our interpretation, because a recent study [32] demonstrated that MSNA is similar between men and women with MetS [32]. The treatment lasted for 4 months. Thus, the effects of a longer period of intervention on the baroreflex control of MSNA and HR are unknown.

In conclusion, diet associated with exercise improves ABR_{MSNA} function and sympathetic modulation and MetS components in patients with MetS, regardless of OSA. It has been documented that weight loss intervention combined with CPAP therapy had an additional beneficial effect on BP, insulin resistance, and serum triglyceride levels in patients with obesity and OSA [13]. Because patients with MetS had residual OSA events after diet and exercise, it is possible that the association of diet, exercise, and CPAP may exert an incremental effect on MetS and decrease the cardiovascular risk in patients with MetS and OSA. Further studies are needed to confirm this hypothesis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical standards The study has been performed in accordance with the ethical standards laid down by the 1964 Declaration of Helsinki. The study was approved by the Scientific Commission of the Heart Institute (InCor), University of São Paulo Medical School and by the Human Subject Protection Committee of the Clinical Hospital Medical School of the University of São Paulo (no. 1038/07). Informed consent was obtained from all subjects prior to inclusion.

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Comment

Positive effects of diet and exercise have been shown to be beneficial in patients with metabolic syndrome (MetS) in numerous publications, but the authors succeeded to show positive changes in patients with MetS and sleep apnea by analysing baroreflex control and sympathetic activity in a well-designed study with supervised exercise and diet program.

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