Effects of Exercise Training on Left Ventricular Diastolic Function Markers in Patients with Obstructive Sleep Apnea: A Randomized Study

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Abstract

Background: Exercise training (ET) is an adjunctive treatment for obstructive sleep apnea (OSA) and its consequences. However, the effects of exercise on heart remodeling are unknown in the population with OSA.

Objective: We investigated the effect of ET on markers of diastolic function, sleep parameters, and functional capacity in patients with OSA.

Methods: Sedentary patients with OSA (apnea-hypopnea index, AHI ≥15 events/hr) were randomly assigned to untrained (n=18) and trained (n=20) strategies. Polysomnography, cardiopulmonary exercise test, and echocardiography were evaluated at the beginning and end of the study. ET consisted of 3 weekly sessions of aerobic exercise, resistance exercises, and flexibility training (72 sessions, completed in 11.65±0.86 months). A two-way analysis of variance (ANOVA) was used, followed by Tukey's post-hoc test. The level of statistical significance was set at p<0.05 for all analyses.

Result: Thirty-eight patients were included (AHI:45±29 events/hr, age:52±7 y, body mass index: 30±4 kg/m^2). They had similar baseline parameters. ET caused a significant change in OSA severity (AHI:4.5±18 versus -5.7±13 events/hr; arousal index:1.5±8 versus -6.1±13 events/hr, in untrained and trained groups respectively, p<0.05). The trained patients had an increase in functional capacity after intervention. ET improved isovolumetric relaxation time (IVRT, untrained=6.5±17.3 versus trained=-5.1±17.1 msec, p<0.05). There was a significant correlation between changes in IVRT and arousal index in the trained group (r =-0.54, p<0.05). No difference occurred in the other diastolic function parameters evaluated.

Conclusion: ET promotes modest but significant improvement in AHI, functional capacity, and cardiac IVRT, a validated parameter of diastolic function.

Keywords: Sleep Apnea; Obstructive; Heart Ventricles; Exercise.

Introduction

Obstructive sleep apnea (OSA) is characterized by episodes of total or partial upper airway obstructions during sleep. These respiratory events result in oxygen (O$_2$) desaturation, arousals, sleep fragmentation, and negative intrathoracic pressure that potentially impair the cardiovascular system.[1,2] The negative intrathoracic pressure in particular leads to increased thorax and consequently an increase in preload. These responses may result in dilation of the right ventricle[3] and left ventricular (LV) septal deviation,[4] which contribute to cardiac diastolic dysfunction. Hypoxia also causes increased inflammatory cytokines, decreased

bioavailability of nitric oxide, and oxidative stress, all of which contribute to arterial stiffness,[5,6] which in turn increases LV afterload in OSA patients. In the long term, these responses can cause LV remodeling,[7] contributing to diastolic dysfunction in patients with OSA.[8]

It has been reported that diastolic dysfunction markers can be improved with exercise training (ET).[9] ET improves diastolic function in healthy volunteers[10] and patients with heart failure.[11] Active elderly people have better diastolic function (reduced peak A wave, increased E wave) compared with their sedentary peers.[12] Experimental evidence showed that elderly rats with diastolic dysfunction had decreased isovolumetric relaxation time (IVRT), increased E/A ratio,[9] increased E wave, and decreased E wave deceleration time[13] after 10 and 12 weeks of aerobic training, respectively. Also, Baynard et al.[14] found decreased IVRT in obese patients with metabolic syndrome who underwent 10 consecutive days of aerobic training.

ET promotes many benefits in patients with OSA. The benefits include decreased apnea-hypopnea index (AHI) and muscle sympathetic nerve activity,[15,16] and reduced body weight and blood pressure (BP).[15] This information suggests that ET may be a useful nonpharmacological method for improving LV diastolic function markers related to OSA severity. However, no information is available about the effects of ET on LV diastolic function markers in patients with OSA without other major comorbidities. The aim of this study was to investigate the effect of ET on diastolic function markers, sleep parameters, and functional capacity in patients with recently-diagnosed OSA. We hypothesized that ET would improve parameters of diastolic function associated with improvement in OSA severity.

Materials and Methods

Subjects

We invited male and female individuals aged 40 to 65 y to undergo a standard nocturnal polysomnography at the Sleep Laboratory at the Heart Institute (InCor), School of Medicine, University of São Paulo. These volunteers were part of a large study investigating the effects of ET on cerebral function in patients with OSA. In the present study, in order to evaluate the effect of ET on diastolic function markers in OSA patients without other major diseases, we opted to exclude major confounders such as patients with body mass index (BMI) >40 kg/m², smoking or alcohol abuse (2 or more drinks/d), cardiopulmonary

disease, chronic renal disease, diabetes mellitus, history of psychiatric disorders, shift workers, hypertension (resting BP >140/90 mmHg on more than one occasion), use of medicines that affect sleep or the vascular system, and any OSA treatment. Of note, some study subjects took part in our previous research dealing with the effects of exercise training on muscle metaboreflex control[16] and cardiac autonomic modulation.[17] The sample size calculation for the present study was based on mean and standard deviation scores reported in a previous study.[18] With 18 participants in this cross-sectional study design, we anticipated a priori that our sample size would be sufficient to detect a 10% difference in diastolic function markers between groups, assuming a power of 0.80 and significance level of 0.05 (2-sided). The Institutional Committee on Human Research (InCor-HCFMUSP) approved the study (0833/10), and all subjects provided written informed consent. Patients were randomly assigned to either the untrained or exercise-trained group on a one to one basis. Full nocturnal polysomnography, maximal exercise capacity, and echocardiographic measurements were performed at baseline and the end of the study.

Sleep study

All participants underwent overnight polysomnography (Embla N7000, Medcare Flaga, Reykjavik, Iceland) at the Sleep Laboratory of the Heart Institute (InCor), University of São Paulo Medical School. Polysomnography was performed using standardized techniques, with a standard staging system for sleep stages used as previously described.[16] Obstructive hypopneas were defined as a reduction of at least 30% of the airflow amplitude captured by the nasal cannula, lasting at least 10 s, associated with oxyhemoglobin desaturation greater than 3% and/ or arousal. The sum of apnea and hypopneas per hours of sleep determined AHI. Considering the consistent evidence suggesting that mild OSA is not associated with increased cardiovascular risk,[19] we used a more conservative AHI cut-off of ≥15 events/hr of sleep.

Echocardiogram

Echocardiographic measurements were performed with commercially available ultrasound equipment (Vivid E9, GE Vingmed, Horton, Norway) using a 4 MHz multifrequency transducer, with patients in the left lateral decubitus position. Echocardiographic examination was performed as follows: 1) a comprehensive 2-dimensional echocardiogram, to exclude presence of structural heart

disease; 2) measurements of LV diameters and wall thickness, with resultant ejection fraction (Teichholz) and LV mass[20] and mass index; 3) two-dimensional guided conventional and tissue Doppler echocardiography to evaluate diastolic function and estimate LV filling pressures. For mitral valve inflow tracings, the volume sample was positioned between the free edges of mitral valve leaflets, parallel to the flow obtained from color flow mapping. Three consecutive beats were selected for offline measurements at the end of expiration. Peak E (early) wave, A (late) wave, E wave deceleration time, and isovolumic relaxation time (IVRT) were measured, and the E/A ratio was calculated. IVRT (msec) was measured as the time between closing of the aortic valve and the earliest detection of mitral flow. Tissue Doppler tracings were obtained from the apical 4-chamber view with the sample volume positioned in the basal septal and lateral mitral annulus to assess early septal diastolic myocardial velocity (e') wave and late septal diastolic myocardial velocity (a') wave. The E/e' ratio was calculated for lateral and septal velocities and the average of these measurements was used for analysis. All measurements were performed according to American Society of Echocardiography and the European Association of Cardiovascular Imaging.[20] Echocardiography was performed by a physician blinded to the group to which each participant was assigned. Intraobserver and interobserver variability of IVRT was measured in 10 individuals by 2 independent observers.

Cardiopulmonary exercise test

Maximal exercise capacity was determined with a maximal progressive cardiopulmonary exercise test (SensorMedics - Vmax Analyzer Assembly, Encore 29S) on an electromagnetically braked cycle ergometer (Via Sprint 150P, Ergoline, Bitz, Germany), with work-rate constant increments (5 to 20 W/min) at 60 to 70 rpm until exhaustion as previously described.[21] Peak oxygen uptake (peak VO$_2$) was defined as the maximum VO$_2$ attained at the end of the exercise period in which the subject could no longer maintain the cycle ergometer velocity at 60 rpm.

Exercise training protocol

Supervised ET consisted of 3 weekly sessions lasting 50 mins in the first month and 60 mins from the second month onwards. Each session was distributed as follows: 5 mins of stretching; 40 mins (30 mins in the first month) of aerobic exercise (cycle ergometer), with intensity varying between the anaerobic threshold and the point of respiratory compensation (detected from the cardiorespiratory capacity test), which was measured by heart rate; 10 mins of resistance exercises; 5 mins of relaxation. The subjects in the untrained group were asked to control their non-participation in systematic physical activity programs during the control period.

Statistical analysis

Data are expressed as mean ± standard deviation (SD). The Kolmogorov–Smirnov test was used to assess the normality of the data distribution for each variable studied and Levene's test was used to assess the homogeneity of variance for each variable studied. The categorical variable was expressed as absolute frequency. A χ^2 test was used to compare differences according to sex. Unpaired Student's t tests were used to determine differences between groups (baseline and delta changes). Two-way analysis of variance with repeated measures was used to compare within and between group differences before and after intervention. In case of significance, Tukey's post-hoc test was used. Pearson correlation analysis was used to examine the association between changes in echocardiographic parameters and changes in arousal index. $P<0.05$ was considered statistically significant. Statistical analysis were performed using STATISTICA 12 (StatSoft Inc., Tulsa, OK, United States) software. Interobserver and intraobserver variability were calculated as the difference between the 2 observations divided by the means of the observations and are expressed as percentages.

Results

We initially selected 98 potentially eligible patients who were referred for the following examinations: conventional nocturnal polysomnography, echocardiography, and cardiopulmonary testing. Of these, 46 had no diagnosis of OSA, 2 had asymptomatic LV systolic dysfunction (LV ejection fraction<50%), and 6 had hypertension. Thus, 44 patients diagnosed with OSA were included in the study and were randomly assigned to the untrained group (n = 22) or the exercise-trained group (n = 22) through the recruitment sequence at the ratio of 1:1, in which one subject was selected for the untrained group and the next subject was selected for the exercise-trained group. One additional patient in the untrained group

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started continuous positive airway pressure treatment and 3 did not complete the protocol evaluations, including echocardiography; thus 18 patients in this group remained in the study. In the trained group, 2 patients did not complete the ET. Thus, 20 patients remained in this group. Descriptive statistics are presented in Table 1. There was no difference in physical, baseline cardiovascular, functional capacity, sleep, or echocardiographic measurements between untrained and trained groups with OSA. For more details of baseline echocardiographic measurements, see Supplemental Content Table S1.

Post-intervention measures

In the present study, 100% (72 sessions) of the post-intervention measurements were obtained by 11.65±0.86 months. The untrained group was paired with the exercise-trained group. Table 2 presents the physical, hemodynamic, and functional capacity post intervention measurements in both untrained and trained groups. There were no significant differences in physical characteristics after the intervention period. Regarding the hemodynamic parameters, there were also no significant differences in systolic BP, diastolic BP, or heart rate measurements in either

Table 1 – Baseline physical, cardiovascular, functional capacity, sleep, and echocardiographic parameters.

Parameters	Untrained (n=18)	Trained (n=20)	p Values
Physical			
Sex, M/F	12/6	8/12	0.18
Age, y	50±6	53±7	0.20
BMI, kg/m²	29±4	30±4	0.62
Cardiovascular			
SBP, mm Hg	121±11	119±12	0.53
DBP, mm Hg	78±8	78±6	0.82
HR, beats/min	65±10	68±8	0.37
Functional capacity			
Peak VO₂, ml/kg/min	26±6	23±6	0.11
Sleep			
Total sleep time, min	388±47	360±60	0.11
AHI, events/hr	43±26	47±31	0.71
Arousal index, events/hr	31±16	33±17	0.79
O₂ desaturation, events	33±26	41±31	0.34
Echocardiographic			
E wave, cm/sec	74±14	72±13	0.69
A wave, cm/sec	66±17	68±14	0.73
E/A ratio	1±0.3	1±0.2	0.30
IVRT, msec	89±12	90±15	0.93
DT, msec	209±55	205±34	0.76
Septal e', cm/sec	9±2	9±2	0.94
Septal a', cm/sec	9±2	10±2	0.20
Septal E/e'	9±2	8±2	0.55
Lateral e', cm/sec	11±3	10±2	0.26
Lateral a', cm/sec	10±2	10±3	0.47
Lateral E/e'	7±2	7±2	1.00
E/e' average	8±2	8±2	0.88

Values are presented as means ± SD. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; Peak VO₂: peak oxygen uptake; AHI: apnea-hypopnea index; O₂: oxygen; IVRT: isovolumetric relaxation time; DT: E wave deceleration time. A χ² test was used to compare differences according to sex. Differences between groups were analyzed using Unpaired Student's t tests.

Table 2 – Physical characteristics, cardiovascular parameters, functional capacity, and sleep parameters before and after the intervention period.

Parameters	Pre	Post	Change (Δ)
Physical			
BMI, kg/m²			
Untrained	29±4	30±4	0.2±0.9
Trained	30±4	30±3	(-)0.1±1.2
Cardiovascular			
SBP, mm Hg			
Untrained	121±11	123±15	2.2±13.2
Trained	119±12	114±10	(-)5.4±15.7
DBP, mm Hg			
Untrained	78±8	78±8	(-)0.6±10.8
Trained	78±6	77±6	(-)0.3±9.1
FC, beats/min			
Untrained	65±10	66±10	0.9±12.7
Trained	68±8	66±7	(-)2.3±5.5
Functional capacity			
Peak VO$_2$, ml/kg/min			
Untrained	26±6	25±7	(-)1.1±1.9
Trained	23±6	26±7*†	3.9±2.9††
Sleep Parameters			
Total sleep time, min			
Untrained	388±47	392±51	3.9±44
Trained	360±60	371±56	11±66
AHI, events/hr			
Untrained	43±26	48±29	4.5±19
Trained	47±31	41±25	(-)5.7±13††
Arousal Index, events/hr			
Untrained	31±16	33±19	1.5±8
Trained	33±17	26±14*	(-)6.1±13††
O$_2$ desaturation, events			
Untrained	32±26	44±30*	11±20
Trained	41±31	37±23†	(-)4.3±13††

*Values are expressed as means ± SD. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; Peak VO$_2$: peak oxygen consumption; AHI: apnea-hypopnea index. Pre and post-intervention data were analyzed using two-way ANOVA with repeated measurements followed by Tukey's post-hoc test. Change (Δ) data were analyzed using Unpaired Student t test. *$p<0.05$ within groups; † $p<0.05$ between groups after intervention period; ††$p<0.05$ between groups in mean difference in change.*

group. There was a significant increase in peak VO$_2$ in the trained group (p=0.0001). The comparison between groups showed that the changes in peak VO$_2$ were greater in the trained group than those observed in the untrained group (p=0.0001).

Concerning the sleep parameters, AHI slightly increased in the untrained group and decreased in the trained group. There was a significant increase in O$_2$ desaturation in the untrained group (p=0.03), whereas no change was found in the trained group. Arousal index slightly increased in the untrained group and significantly decreased in the trained group (p<0.05). The comparisons between groups showed that the absolute arousal index value was significantly improved in the trained group in the post-intervention period. The comparisons between groups showed that

there were significant differences between the groups in delta changes in AHI (p=0.03), O_2 desaturation (p=0.001), and arousal index (p=0.02).

The echocardiographic measurements (Table 3) were unchanged in untrained and trained groups (see Supplemental Content - Table S2 for more details about echocardiographic measurements before and after the intervention). IVRT slightly increased in the untrained group and decreased in the trained group. The comparison between groups showed that absolute IVRT was significantly lower (p=0.01) in the trained group in the post-intervention period (Figure 1A) with a significant difference between groups in changes after intervention (Figure 1B). Further analysis showed a significant association between the changes in IVRT and changes in arousal index in the trained group (r = -0.54, p<0.05).

Interobserver variability was 2±6% and intraobserver variability was 1±6% for IVRT.

Discussion

The main novel findings of the current randomized study are the following: 1) ET improves IVRT and ameliorates sleep severity and functional capacity; 2) changes in IVRT are associated with amelioration of sleep severity.

IVRT represents the interval between closure of the aortic valve and opening of the mitral valve[22] and is influenced by intraventricular mitral and aortic pressure gradients. Danica et al[23] reported that in the early stages of diastolic dysfunction, IVRT increases in patients with OSA compared to patients without OSA. Prolonged IVRT has also been used by several authors as an indicator of impaired LV diastolic function in patients with OSA compared to controls.[24-27] A previous study[28] showed that patients with AHI ≥ 40 events/hr had significantly longer IVRT than those with AHI < 40 events/hr (106 ± 19 msec vs. 93 ± 17 msec, respectively; p = 0.005).

Table 3 – Echocardiographic parameters before and after the intervention period.			
Parameters	**Pre**	**Post**	**Mean difference in change (Δ)**
Echocardiographic			
E wave, cm/sec			
Untrained	74±14	75±15	1.1±12.1
Trained	72±13	74±14	1.4±10.6
A wave, cm/sec			
Untrained	66±17	68±17	2.2±8.5
Trained	68±14	69±12	1.0±9.0
E/A ratio			
Untrained	1±0.3	1±0.3	0±0.3
Trained	1±0.2	1±0.3	0±0.2
IVRT, msec			
Untrained	89±12	96±10	6.5±17
Trained	90±15	85±11†	(-)5.1±17††
DT, msec			
Untrained	209±55	211±41	1.7±48.0
Trained	205±34	210±46	5.6±39.9
Septal e', cm/sec			
Untrained	9±2	9±3	(-)0.1±2.3
Trained	9±2	9±2	(-)0.1±1.9

Septal a', cm/sec			
Untrained	9±2	10±2	1.0±2.8
Trained	10±2	10±2	(-)0.3±2.1
Septal E/e'			
Untrained	9±2	9±3	0.5±2.4
Trained	8±2	9±3	0.5±2.1
Lateral e', cm/sec			
Untrained	11±3	11±3	0.2±2.3
Trained	10±2	11±2	0.6±2.0
Lateral a', cm/sec			
Untrained	10±2	10±2	0.9±2.6
Trained	10±3	10±3	(-)0.1±2.1
Lateral E/e'			
Untrained	7±2	7±2	0±1.5
Trained	7±2	7±1	0±2.2
E/e' average			
Untrained	8±2	8±2	0.2±1.5
Trained	8±2	8±2	0.1±1.3

Values are expressed as means ± SD. IVRT: isovolumetric relaxation time; DT: E wave deceleration time; †p<0.05 between groups after intervention period. Pre and post-intervention data were analyzed using two-way ANOVA with repeated measurements followed by Tukey's post-hoc test. Change (Δ) data were analyzed using Unpaired Student's t tests. ††p<0.05 between groups in mean difference in change.
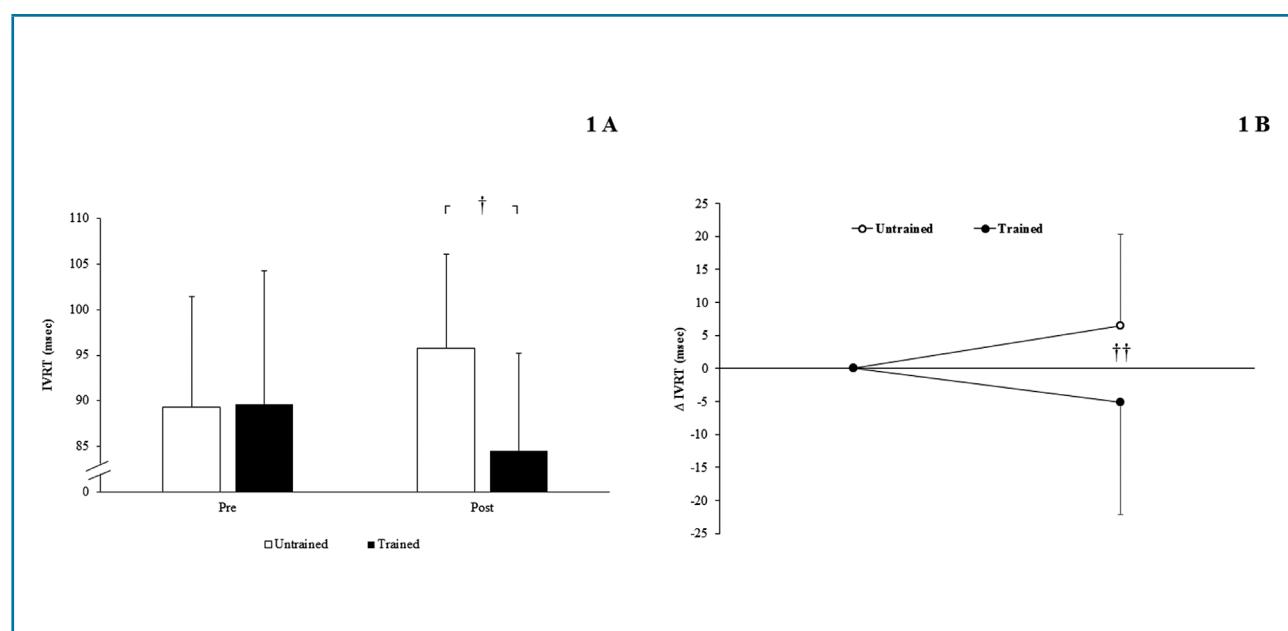

Figure 1 – 1A, B. Absolute values (A) and delta (Δ) changes (B) in isovolumetric relaxation time in untrained and trained groups. Values are presented as means ± SD. †P<0.05 = between groups in the post intervention period; ††P<0.05 = between groups in mean difference in change. Data were analyzed using two-way ANOVA with repeated measurements followed by Tukey's post-hoc test.
IVRT: isovolumetric relaxation time

IVRT was longer in metabolic syndrome patients[14] compared with non-metabolic syndrome patients and a 10-day training program resulted in a 17.5% decrease in IVRT. Another interventional study using 12 weeks of effective nasal continuous positive airway pressure induced significant reductions in IVRT (p<0.05) in patients with OSA.[18] In the present study, IVRT slightly increased in the untrained group and decreased in the trained group. The comparison between groups showed that absolute IVRT was significantly lower in the trained group in the post-intervention period with significant differences between groups after intervention. Our results concerning the effects of ET on IVRT are in line with the results of these previous studies. Of note, there is a possibility that IVRT will change first because it is an energy-dependent phase and is the first to change in patients with grade I dysfunction.

In the present study, overall training effects were found for changes in sleep severity. The comparisons between groups showed that changes in AHI, O_2 desaturation, and arousal index were greater in the trained patients than in the untrained patients. Amelioration of sleep pattern after ET has also been reported in heart failure[21] and metabolic syndrome patients.[15] ET reduces the accumulation of fluid in the neck region in patients with OSA.[29,30] The accumulation of rostral fluid in the neck region in patients with OSA causes collapse of the upper airways by reducing air space.[31] Reduction of fluid in the neck contributes to the decrease in AHI and improves sleep quality in patients with OSA.[30,31]

It has been reported that after each arousal, there is an increase in pulmonary capillary wedge pressure, which can lead to a concomitant reduction in LV compliance in patients with OSA.[32] Arousals and O_2 desaturation events in patients with OSA result in increased sympathetic nerve activity, vascular resistance, afterload, and arterial stiffness.[5-7] These factors can contribute to diastolic dysfunction in patients with OSA. On the other hand, in our present study, amelioration in arousal index was significantly associated with changes in IVRT (r = -0.54, p<0.05). Individuals with greater decreases in arousal index also had greater decreases in IVRT. Other possible mechanisms of ET involved in the amelioration of IVRT are beyond the scope of this study. However, we see some potential explanations for such changes. ET improves endothelial function[33,34] and coronary microvascular perfusion, increasing cardiac blood flow.[9] Likewise, arterial stiffness, measured by brachial-ankle pulse wave velocity and cardio-ankle vascular index decreases in exercise-trained subjects.[35] ET decreases muscle sympathetic activity and increases forearm vascular conductance in patients with OSA.[15] All of these factors can contribute to improving ventricular relaxation and reducing IVRT. Our study also shows that ET provoked a significant increase in peak VO_2 in patients with OSA. This response has several implications. Physical capacity is a marker of prognosis. The survival rate is higher in people with greater physical capacity regardless of comorbidities.[36] The increase in peak VO_2 provides evidence of the effectiveness of our exercise paradigm.

The reported prevalence of diastolic dysfunction among OSA patients varies from 23% to 56%,[18,28,32,37] depending on the sample size and the method of diastolic dysfunction assessment. However, in numerous studies, LV diastolic dysfunction was observed in OSA patients,[37] together with arterial hypertension,[24,38] LV hypertrophy,[27,39] or older age.[32] Notwithstanding, the influence of these comorbidities in our study is unknown. In the present study, using tissue Doppler echocardiography, diastolic dysfunction was only observed in 2 patients.

In the present study, the groups were similar in several baseline variables that can influence baseline diastolic function parameters, including BMI, level of physical activity (functional capacity), age, gender, and systolic function. In addition, other variables that may influence diastolic function, such as diabetes and cardiovascular disease were not included in this study.

Our study has potential limitations. The present study was planned to carry out 6 months of supervised ET performed 3 times a week, totaling 72 training sessions. However, in contrast with what was planned, the exercise-trained individuals were actually able to participate in the training with a frequency ranging from 1 to 3 times a week, which is something that happens in real life. Thus, we decided to extend the duration of the ET protocol to complete the 72 sessions (11.65±0.86 months). Notwithstanding, in the present study, 72 exercise sessions, regardless of frequency, caused significant improvements in functional capacity and sleep and ameliorated IVRT. These results suggest that LV dysfunction in moderate to severe OSA should be confirmed by large data, excluding confounding factors. On the other hand, as OSA leads to a worsening of prognosis over time, the

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prevention of decline in the parameters of diastolic function seems to be beneficial in these patients.

Conclusion

Supervised ET ameliorates sleep severity, improves functional capacity, and could prevent progression of diastolic abnormalities in the cardiac IVRT parameter, at least in the early stages before major structural changes may have developed. These results confer an important role for this nonpharmacological strategy in the treatment of moderate to severe OSA.

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Author contributions

Conception and design of the research e Statistical analysis and writing of the manuscript: Durante BG, Ueno-Pardi LM; Acquisition of data: Durante BG, Silva RF, Goya TT, Jordão CP, Lima MF; Analysis and interpretation of the data: Durante BG, Lima MF, Rodrigues ACT, Rodrigues AG; Critical revision of the manuscript for intellectual content: Durante BG, Rodrigues ACT, Drager LF, Lorenzi Filho G, Alves MJNN, Negrão CE, Ueno-Pardi LM.

Potential Conflict of Interest

No potential conflicts of interest relevant to this article were reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Research Committee at the Heart Institute (SDC 3536/10/125) and by the Human Subject Protection Committee at the Clinical Hospital of the School of Medicine of the University of São Paulo (0833/10). All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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*Supplemental Materials

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