HHS Public Access

Author manuscript

Respir Physiol Neurobiol. Author manuscript; available in PMC 2021 July 01.

Published in final edited form as:

Respir Physiol Neurobiol. 2021 January ; 283: 103557. doi:10.1016/j.resp.2020.103557.

Impact of obstructive sleep apnea on cardiopulmonary performance, endothelial dysfunction, and pulmonary hypertension during exercise

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Abstract

Rationale: OSA has been associated with reduced exercise capacity. Endothelial dysfunction and exercise-induced pulmonary hypertension (ePH) may be mediators of this impairment. We hypothesized that OSA severity would be associated with impaired exercise performance, endothelial dysfunction, and ePH.

Methods: Subjects with untreated OSA were recruited. Subjects underwent endothelial function, and cardiopulmonary exercise testing with an echocardiogram immediately before and following exercise.

Results: 22 subjects were recruited with mean age 56 ± 8 years, 74 % male, BMI 29 ± 3 kg/m^2, and AHI 22 ± 12 events/hr. Peak $\dot{V}O_2$ did not differ from normal (99.7 ± 17.3 % predicted; p = 0.93). There was no significant association between OSA severity (as AHI, ODI) and exercise capacity, endothelial function, or pulmonary artery pressure. However, ODI, marker of RV diastolic dysfunction, and BMI together explained 59.3 % of the variability of exercise performance ($p < 0.001$) via our exploratory analyses.

Conclusions: Exercise capacity was not impaired in this OSA cohort. Further work is needed to elucidate mechanisms linking sleep apnea, obesity, endothelial dysfunction and exercise impairment.

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Disclosures

All authors have nothing to disclose. Resmed provided a philanthropic donation to UC San Diego. Dr. Malhotra reports income from Merck and Livanova related to medical education.

Keywords

Obstructive sleep apnea; Cardiopulmonary exercise test; Endothelial function; Pulmonary hypertension; Lung

1. Introduction

Obstructive sleep apnea (OSA) is a common disorder with well recognized and important cardiovascular sequelae including systemic hypertension, heart attack, and stroke (Benjafield et al., 2019). OSA treatment studies focusing on secondary prevention of cardiovascular disease have been largely negative, (Drager et al., 2017; McEvoy et al., 2016) leading some to argue for a focus on earlier recognition and a better understanding of populations at risk for adverse health consequences from OSA.

Recent data (Beitler et al., 2014) have suggested that OSA patients have impaired exercise tolerance during cardiopulmonary exercise testing (CPET), which might reflect early cardiovascular disease or a relatively deconditioned state. Since exercise performance is a powerful predictor of mortality amongst healthy persons, (Myers et al., 2002) variability in extent of exercise impairment amongst individuals with OSA could provide insight into factors that might increase a person's risk of adverse health consequences. Such findings would be of particular interest in OSA patients without established cardiovascular disease. In addition, weight loss is notoriously difficult to accomplish in OSA, perhaps because diet and exercise goals are difficult to accomplish.

Systemic endothelial dysfunction may be an important cause or consequence of exercise impairment. As a cause, endothelial dysfunction might be a marker of subclinical coronary disease or myocardial impairment and it is associated with increased cardiac events (Suwaidi et al., 2000). In addition, endothelial dysfunction might lead to pulmonary hypertension (PH), which is often mild in OSA patients at rest, but may be substantial during exercise (Arias et al., 2006; Sajkov et al., 1999; Tolle et al., 2008).

Recent advancement in technology has allowed a more comprehensive assessment of multiple aspects of endothelial dysfunction. Several non-invasive techniques have been developed to assess endothelial function instead of the gold standard technique that requires intracoronary or intra-brachial infusions of vasoactive agents. One of them is peripheral arterial tonometry (PAT) that evaluates the response to reactive hyperemia such as EndoPAT. The advantages of this technique are that it is non-invasive, simple, and reproducible with less observer dependent compared to ultrasound-based techniques (Hamburg et al., 2008; Tousoulis et al., 2005). In addition, new echocardiographic techniques, such as tissue velocity (TVI) and strain imaging, have recently emerged as interesting techniques that may detect early signs of right ventricular involvement in the course of PH. Furthermore, exercise echocardiography is a non-invasive screening method that may be able to detect PH at an early stage and has been shown to be useful for risk stratifications of therapy for PH patients (Grunig et al., 2013). Combining exercise and strain imaging of echocardiography may further improve the sensitivity of PH detection among patients with OSA.

Our study sought to examine the relationship between exercise performance and OSA severity, with a focus on systemic endothelial dysfunction and pulmonary hypertension as potential mechanisms. We hypothesized that OSA subjects have impaired exercise capacity due to impaired endothelial dysfunction that may manifest as pulmonary hypertension or right ventricular dysfunction during exercise. We also tested whether a relationship existed between AHI and peak $\dot{V}O_2$ after adjusting for differences in baseline covariates.

2. Materials and methods

2.1. Subjects

Subjects ages 18–65 years with BMI < 35 kg/m^2 with OSA were recruited from University of California, San Diego (UCSD) Sleep and Cardiology clinics. Subjects had previously undergone sleep testing for OSA including polysomnogram or home sleep testing and none was currently being treated for OSA. All subjects underwent level 3 home sleep testing to confirm and evaluate the severity of OSA (apnea-hypopnea index ≥ 5 events/h). Exclusion criteria included current and recent CPAP use (in the past 3 months), history of prior routine CPAP use (more than 3-month daily use of CPAP), ischemic heart disease, heart failure, valvular heart disease, pulmonary disease, uncontrolled or insulin-dependent diabetes, other major systemic illness (other than controlled hypertension), smoking, >3 oz/day alcohol use, illicit drug use, or any conditions that precluded performance of CPET. The UCSD Institutional Review Board approved the protocol, and written informed consent was obtained from all subjects.

2.2. Protocol

Subjects underwent a level III home sleep test (Apnealink Air, ResMed Inc, San Diego, CA) to quantify OSA severity. Studies were scored by a registered polysomnographic technologist (RPSGT) blinded to the study outcomes according to American Academy of Sleep Medicine guidelines (Chicago criteria) (Flemons et al., 1999). The Apnea Hypopnea Index (AHI) is the number of apnea and hypopnea events per hour of sleep, and it is used to grade the severity of sleep apnea: AHI < 5 is normal; 5 ≤ AHI < 15 is mild; 15 ≤ AHI < 30 is moderate; 30 ≤ AHI is severe. The Oxygen Desaturation Index (ODI) is the number of 4% mean oxygen desaturation event per hour of sleep. ODI is used to assess the severity of nocturnal hypoxemia, and it has shown different correlation with cardiovascular complications from AHI (Hayashi et al., 2003; Yk et al., 2002). Epworth Sleepiness Scale (ESS) and the Pittsburgh Sleep Quality Index (PSQI) were used to evaluate sleep quality and sleep related symptoms.

Endothelial function was measured using EndoPAT (EndoPAT2000; Itamar, Caesarea, Israel). EndoPAT measures digital pulse amplitude with probes placed on the tip of each index finger as described previously (Hamburg et al., 2008). Briefly, the EndoPAT system is based on peripheral arterial tonometry (PAT) of the index finger as the reaction to hyperemia induced by occlusion of the brachial artery for 5 min. EndoPAT was performed after at least 15 min rest in the supine position in a quiet, dim-lighted, air-conditioned room immediately before the cardiopulmonary exercise test (CPET). After occlusion of the brachial artery is relieved, the surge of blood flow causes an endothelium-dependent, flow-mediated dilatation

and an increase in the PAT signal. The ratio between post- and pre-occluded measurement of the PAT signal, calculated by the specialized software, (Munir et al., 2008) is defined as reactive hyperemia index (RHI) or EndoScore with a RHI ≤ 1.67 defining endothelial dysfunction. Arterial stiffness, defined as augmentation index (AI), is also calculated by pulse waveform analysis of the PAT signal during EndoPAT test. AI is considered as an independent risk factor for cardiovascular disease but not necessarily correlated with endothelial function. Lower AI values correlate with better arterial elasticity. Because AI is inversely related to heart rate, (Lantelme et al., 2002) AI values are standardized by mathematically adjusting to a standard heart rate of 75 beats per minute (AI@75).

Baseline physical activity was measured using the International Physical Activity Questionnaire (IPAQ), which is a validated self-report survey evaluating physical activity over the preceding 7 days (Craig et al., 2003). Results are reported as estimated metabolic equivalents of task (METs) x minutes per week.

After EndoPAT testing, subjects underwent a standard and doppler echocardiographic examination at rest. Baseline transthoracic echocardiography was performed by an experienced echocardiographer. Four chamber, long axis, short axis, and subxiphoid views were obtained. Tricuspid regurgitant velocity and left ventricular outflow velocity-time integral were obtained first, such that both parameters could be obtained within 1 min of stopping exercise. Immediately following echocardiogram, subjects performed a maximum, symptom-limited CPET using a modified Naughton protocol on a treadmill under supervision of a trained pulmonologist or cardiologist. Subjects breathed through with a respiratory circuit equipped with two-way non-rebreathing valve (Hans Rudolph 2700 Respiratory Valve, Hans Rudolph Shawnee KS). Mixed expired respiratory gas exchange measurements were obtained with a metabolic cart (ParvoMedics TrueOne 2400 system; Parvo Medics Inc., Sandy, UT). After a 2-min resting period to collect baseline gas-exchange measurements, subjects began exercising on the treadmill at 1 mile per hour (MPH) at 0% grade and the speed was increased at 0.5 MPH intervals until at comfortable walking speed for a 3-minute warm-up period. The ramp protocol was then started by increasing 3% grade every 2 min until a maximum grade of 21 %. All subjects were encouraged to exercise until volitional fatigue. During testing, heart rate, ECG, and pulse oximetry were recorded continuously. Blood pressure, breathlessness and leg fatigue as assessed by Borg CR10 scale were recorded at 2-min intervals. Peak $\dot{V}O_2$ as calculated as the average of the 4 highest consecutive 15 s values of oxygen uptake and ventilatory threshold was defined by the V-slope method (Beaver et al., 1986). Results for peak $\dot{V}O_2$ are reported as milliliters per kilogram per minute and relative to Wasserman's formula-predicted value, (Wasserman et al., 1999) which accounts for age, weight, and gender, to allow comparison across subjects with different baseline characteristics. Maximal heart rate was predicted using the formula 220 – age. Peak oxygen pulse was calculated by dividing peak $\dot{V}O_2$ by peak heart rate. Immediately following termination of the cardiopulmonary exercise test, the subject was moved to an adjacent examining table and post-exercise echocardiographic parameters were obtained.

Echocardiogram results were scored by a cardiologist blinded to the study outcomes. Cardiac output was calculated from the left ventricular outflow velocity-time integral, outflow area, and heart rate. Pulmonary artery systolic pressure (PASP) was calculated using the standard formula: PASP = 4*[Tricuspid regurgitant velocity] ^2 + [Right atrial pressure]. Since increased cardiac output can lead to increases in pulmonary artery pressure, the total pulmonary resistance (TPR = mean PA pressure divided by cardiac output) has been advocated as a means to identify accurately exercise-induced pulmonary hypertension (Herve et al., 2015a). Mean PA pressure (MPAP) was estimated using the formula: MPAP = 0.61 × PASP +2 mmHg (Bossone et al., 2013; Chemla et al., 2004). To assess right ventricular diastolic function, pulsed waved Doppler was utilized to measure the tricuspid valve inflow velocities through the passive (E) and active (A) filling phases of diastole at end expiration via the apical 4-chamber view. Tissue doppler was used to measure the tricuspid annular velocities (E' and A'). Estimation of right atrial pressure was measured by IVC diameter and its collapsibility with inspiration. Diastolic function was measured utilizing the E to A ratio and E to E' ratio.

2.3. Echocardiogram 2-D speckle tracking

Standard grayscale 2D images in the apical 4-chamber view were used for speckle tracking analysis. All images were analyzed with Epsilon Imaging EchoInsight® software. The RV myocardium was separated into six standard segments and traced along the endocardial border at end-systole. The software then employed an automated, speckle tracking algorithm to trace the endocardial border continuously throughout the cardiac cycle. Strain was calculated for each of the individual RV free wall and septal segments—base, mid, and apex.

2.4. Statistical analysis

Statistics were performed using SPSS 24. Continuous variables were summarized as mean ± SD or median [interquartile interval limits] if the data were skewed. Normality was assessed visually with Q-Q plot and with Kolmogorov-Smirnov and Shapiro-Wilk tests. Echocardiographic measurements from pre- and post-exercise were compared using paired t-tests. Correlations between variables were evaluated using Spearman correlation coefficient. Association between continuous variables was analyzed using general linear modeling. A $p \leq 0.05$ was considered statistically significant; all tests were two-sided.

In an exploratory secondary analysis, multivariable linear regression was used to determine the association between percent predicted peak $\dot{V}O_2$ (primary outcome measure) and AHI or ODI (both are a priori predictors of interest), and to identify other independent predictors of exercise performance. The potential predictor variables were baseline characteristics, polysomnogram results, and exercise echocardiogram findings. Univariable analysis was done first to identify the potential important predictors of the percent predicted peak $\dot{V}O_2$, and those predictor variables with $p < 0.20$ were included in the multivariable linear regression analysis. However, given the small sample size of our study (n = 22), we decided to only include at most three predictor variables in our multivariable linear regression models to avoid over-fitting, Analysis of covariance (ANCOVA) was performed to

determine the proportion of total variability in percent predicted peak $\dot{V}O_2$ explained by the predictor variables.

3. Results

3.1. Baseline characteristics

Twenty-two subjects were enrolled, and all completed the testing session. As shown in Table 1, our subjects were mainly middle age male with moderate obstructive sleep apnea (8 mild, 9 moderate, 5 severe). The majority of these subjects were symptomatic from their OSA (54.5 % of subjects with ESS > 10; 81 % of subjects with PSQI > 5, which is considered indicative of a poor sleeper). Hypertension was present in 10 subjects, hyperlipidemia in 4 subjects, and diabetes in 3 subjects. No subjects took beta-blockers at the time of the CPET study. Only 7 out of 22 subjects had endothelial dysfunction as assessed by EndoPAT. Based on the IPAQ questionnaire, the subjects had a wide variety of baseline activity levels (32 % inactive, 32 % minimally active, and 36 % of active).

3.2. Cardiopulmonary exercise testing

All subjects exercised to symptom limited maximum and cardiopulmonary exercise testing data are shown in Table 2. Percent predicted peak $\dot{V}O_2$ and percent predicted peak heart rate were not significantly different from normal values (99.7 ± 17.3 %; $p = 0.93$ and 99.7 ± 5.6 %; $p = 0.79$, respectively).

3.3. Echocardiography

Pre- and post-exercise echocardiography data for LV and RV function are presented in Table 3. LV systolic and diastolic function were not significantly changed post-exercise except cardiac output, which is a normal response to exercise. RV systolic, RV diastolic function and pulmonary artery pressure changed as a normal response to exercise with increased cardiac output. 2D myocardial speckle tracking data are presented in Table 4. RV systolic function except TAPSE has shown similar changed with exercise as shown in Table 3. The discrepancy may be caused by the different techniques used to measure TAPSE by routine echocardiography and 2D speckle tracking.

3.4. Effects of OSA severity on cardiopulmonary performance

There was no statistically significant correlation between AHI and peak $\dot{V}O_2$, expressed as percent predicted ($R^2 = 0.031$; $\beta = -0.25$, 95 % CI: −0.92 to 0.41; $p = 0.44$) or mL/kg/min ($R^2 = 0.008$; $\beta = 0.03$, 95 % CI: −0.14 to 0.20; $p = 0.69$). Similarly, there was no correlation between percent time with SpO_2 < 90 % (T < 90 %), mean SpO_2, oxygen desaturation index (ODI) and percent predicted $\dot{V}O_2$ ($p = 0.80$, $p = 0.55$ or, $p = 0.48$) or mL/kg/min peak $\dot{V}O_2$ ($p = 0.86$, $p = 0.79$, or $p = 0.74$) respectively. Neither AHI, ODI, T < 90 %, nor mean SpO_2 were significantly associated with other cardiopulmonary exercise performance parameters such as percent predicted peak heart rate, peak oxygen pulse, $\dot{V}_E/\dot{V}CO_2$ slope, ventilatory threshold, peak dyspnea, or leg fatigue scores.

3.5. Effects of endothelial dysfunction on exercise in OSA

RHI was not significantly correlated with cardiopulmonary exercise performance including peak $\dot{V}O_2$ as percent predicted ($p = 0.13$) or mL/kg/min ($p = 0.95$), percent predicted heart rate ($p = 0.35$), peak oxygen pulse ($p = 0.27$), $\dot{V}_E/\dot{V}CO_2$ slope ($p = 0.64$), ventilatory threshold ($p = 0.63$), peak dyspnea ($p = 0.71$), or leg fatigue score ($p = 0.70$). There was no statistically significant association between RHI on EndoPAT and AHI, ODI, T<90 %, or mean SpO_2.

EndoPAT augmentation index at heart rate of 75 beats per minute (AI@75), which is a marker of arterial stiffness and an independent risk factor of cardiovascular disease, showed borderline correlation with peak $\dot{V}O_2$ as percent predicted ($R^2 = 0.16$, $p = 0.06$), but not mL/kg/min ($R^2 = 0.08$, $p = 0.20$). AI@75 was negatively associated with peak $\dot{V}CO_2$ ($R^2 = 0.20$, $p = 0.03$) and $\dot{V}_E$ ($R^2 = 0.22$, $p = 0.03$), but not significantly correlated with the $\dot{V}_E/\dot{V}CO_2$ slope ($R^2 = 0.01$, $p = 0.66$). AI@75 was also negatively associated with peak oxygen pulse ($R^2 = 0.25$, $p = 0.02$); AI@75 was positively correlated with peak leg fatigue score ($R^2 = 0.22$, $p = 0.03$). There was no statistically significant association between AI@75 on EndoPAT and AHI, ODI, T<90 %, or mean SpO_2.

3.6. Association between OSA severity and post exercise pulmonary hypertension

Post-exercise echocardiography data were obtained on all 22 subjects. Pre- or post-exercise mean PAP or TPR were not associated with $\dot{V}O_2$ as a percent predicted or in mL/kg/min. There was an association between pre-exercise TPR and AHI ($R^2 = 0.24$, p = 0.03). T < 90 % was significantly correlated with pre-exercise TPR, post-exercise MPAP and post-exercise TPR ($R^2 = 0.34$, $p = 0.01$; $R^2 = 0.27$, $p = 0.01$; $R^2 = 0.25$, $p = 0.02$), respectively.

3.7. Effects of cardiac function evaluated by echography on exercise in OSA

Pre-exercise RV diastolic function measured by lateral RV e' and post-exercise RV apex strain were significantly correlated with $\dot{V}O_2$ as percent predicted ($R^2 = 0.36$, $p = 0.002$; $R^2 = 0.32$, $p = 0.01$). Pre-exercise LV diastolic function measured by E/A ratio and pre-exercise LV volume index are correlated with $\dot{V}O_2$ as mL/kg/min ($R^2 = 0.28$, $p = 0.02$; R2 = 0.21, $p = 0.03$). Pre-exercise RV diastolic function measured by RV A' was correlated with the $\dot{V}_E/\dot{V}CO_2$ slope ($R^2 = 0.20$, $p = 0.04$). Other echocardiographic measurements did not have statistically significant association with $\dot{V}O_2$ as percent predicted or as mL/kg/min, or $\dot{V}_E/\dot{V}CO_2$ slope.

Pre-exercise LV systolic function measured as cardiac output was significantly correlated with AHI ($R^2 = 0.20$, $p = 0.03$) and ODI ($R^2 = 0.22$, $p = 0.03$). Pre-exercise LV diastolic function measured as E/e' is correlated with AHI ($R^2 = 0.20$, $p = 0.03$) and ODI ($R^2 = 0.20$, $p = 0.03$). Other echocardiographic measurements did not have statistically significant associations with AHI, ODI, T<90 %, or mean SpO_2.

3.8. Predictors of CPET performance

The relationship between the percent predicted peak V. O_2 and severity of obstructive sleep apnea (measured by AHI or ODI), adjusting for other potential predictor variables was explored with multivariable linear regression analysis. After adjusting for AHI or ODI, the association between pre-exercise RV diastolic function measured as lateral RV e' and predicted peak $\dot{V}O_2$ remained significant, respectively (see Table 5). BMI, which was significantly correlated with peak $\dot{V}O_2$ and a known predictor of exercise capacity, was included in the linear multivariable linear regression analysis to explore further the relationship between sleep apnea, RV diastolic function and exercise performance. ODI was found to be associated significantly with exercise performance after adjusting for lateral RV e' and BMI (as shown in Table 5). ODI, pre-exercise lateral RV e', and BMI together explained 59.3 % of the variability observed ($p < 0.001$).

4. Discussion

In summary, the findings of this study were that 1) Exercise performance in this group of untreated OSA patients was not significantly different from population normative values, 2) Severity of OSA (ODI), RV diastolic dysfunction, and BMI may predict exercise performance, 3) Endothelial dysfunction measured as AI@75 predicts leg fatigue during exercise, and a marker of cardiac output, oxygen pulse. However, AI@75 was not associated with OSA severity, 4) post exercise pulmonary hypertension was not associated with exercise performance but was associated with OSA severity.

4.1. Potential predictors of exercise performance

Our findings are important as they add to the literature regarding the potential interactions between sleep disorders, vascular dysfunction and exercise performance. Although we observed normal exercise capacity in our participants, we did find important predictors of maximal exercise which could be mechanistically important. In particular, the independent roles of sleep apnea, RV dysfunction and BMI are predictive of $\dot{V}O_2$ max which has implications for the notion that diet, exercise, and sleep are critical to optimal health.

The fact that we observed normal exercise performance in our participants is at odds with prior work (Mendelson et al., 2018) including our own (Beitler et al., 2014). The sleep fragmentation of OSA frequently leads to excessive daytime sleepiness and reduced physical activities. Furthermore, obesity is present in roughly 70 % of OSA patients (Vgontzas et al., 1994). However, previous meta-analysis has demonstrated larger reduction of $\dot{V}O_2$ max in non-obese OSA patients (BMI < 30 kg/m^2) than obese OSA patients (BMI ≥ 30 kg/m^2), (Mendelson et al., 2018) and this finding suggests that reduced exercise performance in OSA patients is not caused by obesity alone. Previous studies also have demonstrated several distinct exercise response characteristics in OSA, including chronotropic incompetence (Kaleth et al., 2007), exaggerated blood pressure (Tryfon et al., 2004), and delayed heart rate recovery (Maeder et al., 2008).

The reason for the normal exercise performance in our study is unclear but may reflect relatively healthy participants compared to prior studies. Given the study location in

Southern California, participants may have a greater baseline level of activity as locals are health conscious and because the weather is conducive to outdoor activity. This assertion is supported by our IPAQ results: 32 % participants are inactive, which is lower than reported literature (43.3 % of Americans are inactive) (Hallal et al., 2012). Although subjective evaluation of physical activity through IPAQ has been reported to over-estimate the activity recorded by objective measurement, this observation still provides some insights into the relatively normal CPET results we have. In addition, low levels of physical activity have been observed in OSA patients and attributed to fatigue and somnolence that characterize OSA (Hong and Dimsdale, 2003). Lastly, the sample size for many of these studies has been quite modest leading to potential discrepancies in the literature. Nonetheless, we found important predictors of exercise performance which we view as potential early markers of exercise impairment, a topic which requires further study.

Although more data are needed to examine our findings given the limitation of our sample size, our exploratory analysis showed the interesting observation that the severity of OSA, right ventricular diastolic dysfunction, and BMI may predict exercise performance. A prior study has shown right ventricular diastolic dysfunction is more prevalent than systolic dysfunction in non-obese OSA patient (Çetin, 2018). This finding may suggest that right ventricular diastolic dysfunction is the earliest sign of cardiac dysfunction secondary to untreated OSA. Furthermore, this change may be reversible as shown in a study that 6-month of CPAP treatment improved right ventricular diastolic function in OSA patients (Dursunoglu et al., 2006). On the other hand, RV diastolic dysfunction has also been associated with diabetes mellitus (DM) and hypertension (Karamitsos, 2007; Eweda, 2017; Cicala et al., 2002). Diabetes, OSA, and hypertension share risk factors, obesity, with all these conditions contributing to the risk of developing cardiovascular diseases (Surani, 2014). The pathophysiological links between RV diastolic dysfunction and OSA are still unclear, and may be partially contributed to by concomitant DM or/and hypertension. Of note, a prior study demonstrated right ventricular diastolic dysfunction may be associated with impaired exercise capacity in COPD patients (Fenster et al., 2015). A larger study to assess the right ventricular function and exercise capacity may define the early cardiac changes caused by OSA, and identify those who are at high risk for cardiovascular consequence from untreated OSA.

4.2. Association of endothelial dysfunction with OSA

Prior literature has shown endothelial dysfunction in OSA although again this finding has been variable (Ip et al., 2004; Atkeson et al., 2009). In our study, reactive hyperemia index (RHI), which is a measure for endothelial function, was not significantly correlated with cardiopulmonary exercise performance. In addition, RHI was not associated with markers of OSA severity such as AHI or ODI. One of the potential explanations for this observation may be due to the method of endothelial function testing. There are several noninvasive methods to test for endothelial dysfunction. Flow-mediated dilatation (FMD), which is considered as the “gold-standard” of noninvasive technique to assess endothelial function, is a nitric oxide–dependent ultrasound-based test of large artery endothelial function. FMD reflects atherosclerosis risk and is predictive of cardiovascular outcomes (Flammer et al., 2012). Reactive hyperemia peripheral arterial tonometry (PAT) such as EndoPAT is a test of

microvascular endothelial function and is well correlated with traditional and metabolic cardiovascular risk factors such as hypertension (Hamburg et al., 2011a). These two tests correlate only modestly with each other, and probably reflect different but complementary aspects of vascular physiology (Schnabel et al., 2011; Hamburg et al., 2011b). A recent review suggested that microvascular function evaluated by EndoPAT might be more relevant in subjects without overt CV disease and may be an earlier indicator of CV risk than macrovascular function assessed by FMD (Flammer et al., 2012). However, previous studies of treatment effects on endothelial function of OSA implied there might be difference in response to treatment based on the different endothelial function test techniques such as FMD vs EndoPAT (Gagnadoux et al., 2017).

In our study, EndoPAT augmentation index at heart rate of 75 beats per minute (AI@75), which is a marker of arterial stiffness and a surrogate indicator of left ventricular systolic loading, was positively correlated with peak leg fatigue score ($R^2 = 0.22$, $p = 0.03$) and negatively associated with peak oxygen pulse ($R^2 = 0.25$, $p = 0.02$). This finding suggests that increased peripheral arterial stiffness is associated with increased perceived muscle fatiguability and decreased cardiac output during exercise. A recent systematic review has confirmed the significant association between vascular health and skeletal muscle health (Dvoretskiy et al., 2020). A study in older adults also observed a correlation between arterial stiffness and perceived leg fatigability during exercise and it hypothesized that increased arterial stiffness (such as measured as augmentation index) serves an early marker of generalized atherosclerosis (Gonzales et al., 2015). Prior literature has not definitively shown an association between augmentation index and left ventricular contractility (Sharman et al., 2009). Furthermore, the need to correct augmentation index for heart rate is still under debate. Although our study showed a correlation between AI@75 and oxygen pulse, there was no significant association between AI@75 with OSA disease severity markers such as AHI. This result may suggest that other factors such as age, diabetes or/and medications play a role in this observation. For example, a recent study demonstrated that vascular function is a strong predictor of overall cardiac function in older but in not younger people (Houghton et al., 2016). Our study was not designed or powered to examine this correlation while controlling for relevant covariates.

4.3. Association of pulmonary hypertension, exercise, and OSA

Prior studies have shown 20–40 % prevalence of pulmonary vasoreactivity in OSA compared to carefully matched controls, with most of the pulmonary hypertension associated with OSA tending to be mild (Golbin et al., 2008; Sajkov and McEvoy, 2009). The participants in our study were relatively healthy without major comorbidities, so we expected to find a low prevalence of (and mild) pulmonary hypertension at rest if any. Therefore, we aimed to assess the presence of exercise-associated pulmonary hypertension as some have suggested that this mechanism may precede pulmonary hypertension at rest and may be an early sign of pulmonary vasoreactivity. We chose stress echocardiography as we could not ethically justify the risk of invasive pulmonary pressure assessment to our relatively healthy participants. Although invasive criteria for diagnosis of exercise-induced PH have been proposed, (Herve et al., 2015b) specific, validated, consensus diagnostic criteria of exercise-induced PH through stress echocardiography has not been established as

there are limited exercise echocardiographic data concerning standards for right atrial pressure (RAP) and their prognostic implications (Rudski et al., 2018).

In healthy subjects, moderate exercise induces mild increases in pulmonary arterial pressure that are linear with increased cardiac output and decreases in pulmonary vascular resistance secondary to the dilation of compliant small vessels and/or the recruitment of additional vessels in the normal lungs (Naeije and Chesler, 2012). A subset of patients with pathologic response of increased pulmonary arterial pressure (PAP) during exercise (i.e. increased PAP is thought to impair exercise capacity) and normal pulmonary pressure at rest; this is referred to as exercise-induced or associated pulmonary hypertension. In OSA, there is evidence that exercise-associated pulmonary hypertension is more prevalent than pulmonary hypertension at rest, and this may be largely due to left sided heart disease, rather than pulmonary vasculopathy (Hetzel et al., 2003). Our study did not demonstrate significant pulmonary vasoreactivity, or any association of pulmonary vasoreactivity to exercise capacity. This result may be partially explained by the fact that our participants were relatively healthy with minimal comorbidities. On the other hand, association of vasoreactivity with severity of OSA including AHI and T < 90 % were observed, as supported by prior studies (Kholdani et al., 2015). Part of the rationale to undertake this study was to assess whether endothelial dysfunction measured with EndoPAT would be predictive of pulmonary vasoreactivity given the literature that exercise induced pulmonary hypertension can limit exercise in some patients (Tolle et al., 2008).

4.4. Limitations

Despite our study's strengths we acknowledge a number of limitations. First, this study had a small sample size given that it was labor intensive and required sophisticated equipment and analyses. Thus, we may be underpowered but believe we have adequate sample for important mechanistic findings. Second, we enrolled a cohort which was relatively healthy which limited our ability to define predictors of impaired exercise performance. Thus, we view some of our analyses as exploratory and would be careful to suggest that they may generalize to other OSA patients. We excluded patients with obvious clinical cardiovascular disease or history; thus, our enrollment of relatively healthy patients was to some extent by design. Our conclusions are limited to the population studied but do speak to the possibility of early markers of exercise impairment which could be 'actionable' prior to full blown disease. Third, we did not perform invasive hemodynamic monitoring which some might argue is the gold standard for assessing exercise induced pulmonary hypertension. Indeed, doppler echocardiography can be challenging at peak exercise or immediately thereafter. We chose this approach as we did not feel we could ethically justify pulmonary artery catherization in relatively healthy participants. Nonetheless questions remain regarding how our findings may have been affected had we used a more invasive approach. Lastly, our study did not have a matched control group for the main risk factors such as BMI, affecting our ability to control for common comorbidities such as interpret the result as obesity, hypertension, and diabetes. Despite these limitations we view our findings as important and worthy of subsequent study.

5. Conclusions

Although exercise capacity was not impaired in our cohort of patients with OSA, our exploratory analysis suggested that severity of OSA, right ventricular diastolic dysfunction, and BMI may predict exercise performance. A larger study to assess right ventricular function and exercise capacity may be able to identify the early cardiac changes caused by OSA, and those are at higher risk for cardiovascular consequence from untreated OSA.

Acknowledgements

The authors thank the study participants who volunteer for the study and the research staff at Dr. Malhotra's research laboratory.

Funding sources

Supported by NIHR01HL129990 and R01HL119201. Dr. Malhotra is funded by NHLBI

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Table 1

Subject Characteristics (N = 22).

	Mean ± SD / Median [Interquartile limits]
Age (years)	55.8 ± 7.7
Male, n (%)	17 (77.3 %)
BMI (Kg/m^2)	29.4 ± 3.4
Typical Physical Activity (MET-minutes/week)	2706 [1694, 5441]
Home Sleep Test Results	
AHI (events / hr)	22.3 ± 11.9
ODI (events / hr)	19.6 ± 11.2
Awake SpO_2	98.0 ± 1.1
Nadir SpO_2	81.0 [74.8, 83.3]
TST% SpO_2 < 90%	16.5 ± 12.2
Sleep Quality	
Epworth Sleepiness Scale (ESS)	10.3 ± 6.5
Pittsburgh Sleep Quality Index (PSQI)	7.1 ± 4.0
EndoPAT	
RHI	2.1 ± 0.5
% RHI ≤ 1.67	6 (31.8 %)
AI@75	1.64 ± 12.76

BMI: body mass index; MET: metabolic equivalent of task; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; SpO_2: oxygen saturation; TST: total sleep time; RHI: reactive hyperemia index; AI@75: augmentation index adjusted to standard heart rate of 75 beats per minute.

Table 2

Cardiopulmonary Exercise Data (N = 22).

	Mean ± SD
Peak V. O_2 (L/min)	2.45 ± 0.57
Peak V. O_2 (% predicted)	99.7 ± 17.3
Peak V. O_2 (mL/kg/min)	26.4 ± 4.4
Peak V. CO_2 (L/min)	2.7 ± 0.6
Ventilatory threshold (% predicted peak O_2)	56.5 ± 15.7
Ventilatory threshold (% actual peak O_2)	58.9 ± 8.9
Maximal V. $_E$ (L/min)	85.5 ± 19.2
Ventilatory efficiency (V. $_E$/V. CO_2 slope)	29.6 ± 4.5
Peak respiratory exchange ratio	1.19 ± 0.08
Peak dyspnea score (scale 0–10)	5.2 ± 2.4
Peak leg fatigue score (scale 0–10)	4.6 ± 2.4
Peak systolic blood pressure (mm Hg)	204.0 ± 22.5
Peak diastolic blood pressure (mm Hg)	83.1 ± 13.4
Peak heart rate (% predicted)	99.7 ± 5.6
Peak oxygen pulse (mL O_2/beat)	14.9 ± 3.6

VO_2: oxygen uptake; VCO_2: carbon dioxide output; V_E: ventilation; V_E/VCO_2: ventilatory equivalents for carbon dioxide.

Table 3

Standard 2D, Doppler Exercise Echocardiographic Results (N = 22).

	Pre-exercise (Mean ± SD)	Post-exercise (Mean ± SD)	Mean Difference	t	*p*
LV Systolic Function					
LVEF (%)	66.0 ± 5.7	–	–	–	–
LVOT (mm)	25.8 ± 4.8	26.9 ± 6.8	− 1.1	1.219	0.236
CO (L/min)	6.3 ± 1.1	11.8 ± 2.6	− 5.6	− 13.081	<0.001
LV Diastolic Function					
E/A	1.0 ± 0.4	0.9 ± 0.3	0.1	1.622	0.123
E/e’	11.3 ± 3.5	10.0 ± 2.9	1.3	1.922	0.074
RV Systolic Function					
TAPSE (mm)	19.8 ± 6.8	25.5 ± 4.5	− 5.7	− 3.421	0.003
RV S’ (cm/s)	14.1 ± 2.8	19.1 ± 4.6	− 5.0	− 5.777	<0.001
RV Diastolic Function					
RV E’ (cm/s)	55.2 ± 11.6	69.3 ± 15.6	− 14.1	− 3.951	0.001
RV A’ (cm/s)	46.3 ± 8.3	68.9 ± 17.0	− 22.6	− 6.738	<0.001
Lateral RV e’ (cm/s)	11.9 ± 3.3	14.7 ± 4.6	− 2.8	− 2.990	0.008
Volume Measurement					
LA volume index (mL/m^2)	46.6 ± 16.8	–	–	–	–
Pulmonary Hemodynamics					
SPAP (mmHg)	24.2 ± 6.3	36.4 ± 9.9	− 12.2	− 6.920	<0.001
MPAP (mmHg)	16.8 ± 3.8	24.2 ± 6.0	− 7.4	− 6.920	<0.001
TPR (mmHg•min/L)	2.7 ± 0.5	2.1 ± 0.6	0.6	4.899	<0.001

LVEF: left ventricular ejection fraction; LVOT: Left ventricular outflow tract velocity time integral; CO: cardiac output; RV E/A: ratio of early to late diastolic trans-tricuspid flow velocity; RV E/e’: ratio early diastolic trans-tricuspid flow velocity to tricuspid annular tissue velocity; TAPSE: tricuspid annual plane systolic excursion; RV S’: systolic excursion velocity by tissue Doppler; RV E’: tricuspid annular early diastolic velocity; RV A’: annular velocity with atrial contraction; lateral RV e’: early diastolic velocity of lateral tricuspid annulus; LA: left atrium; SPAP: systolic pulmonary artery pressure; MPAP: mean pulmonary artery pressure; TPR: total pulmonary resistance.

Table 4

2-D Speckling Exercise Echocardiographic Results (N = 22).

	Pre-exercise (Mean ± SD / Median [Interquartile limits])	**Post-exercise (Mean ± SD / Median [Interquartile limits])**	***p***
RV Longitudinal Strain			
Global	− 23.6 [−25.0, −20.5]	− 27.5 [−31.0, −21.3]	0.003
Base	− 25.4 ± 11.2	− 34.0 ± 9.8	0.001
Mid	− 27.2 ± 8.8	− 27.8 ± 10.9	0.52
Apex	− 17.8 ± 10.3	− 21.1 ± 13.6	0.16
RV Systolic Function			
TAPSE (mm)	2.3 ± 0.4	2.4 ± 0.6	0.15
RV S’ (mm/s)	10.1 ± 1.8	14.9 ± 2.3	<0.001
RVFAC (%)	39.4 ± 6.8	46.3 ± 13.1	0.005

RV S’: systolic excursion velocity by tissue Doppler; RVFAC: right ventricular fractional area change.

Table 5

Multivariable Linear Regression Analyses of Percent Predicted Peak $\dot{V}O_2$.

	Model 1 (R^2 = 0.43)		**Model 2 (R^2 = 0.57)**		**Model 3 (R^2 = 0.42)**		**Model 4 (R^2 = 0.59)**	
	β	95 % CI	β	95 % CI	β	95 % CI	β	95 % CI
Pre- Lateral RV e’	3.33 ǂ	1.59 to 5.07	2.48 ǂ	0.83 to 4.13	3.24 *	1.52 to 4.96	2.35 *	0.76 to 3.94
AHI	− 0.39	− 0.89 to 0.10	− 0.42	− 0.85 to 0.01				
ODI					− 0.41	− 0.94 to 0.11	− 0.49 ǂ	− 0.93 to −0.04
BMI			− 2.17 ǂ	− 3.87 to −0.47			− 2.30 ǂ	− 3.97 to −0.63

* $p < 0.01$;

ǂ $p < 0.005$.