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SHORT REPORT

A Cross-Sectional Study Evaluating the Association of Brachial Artery Flow Mediated Vasodilation with Physical Activity Measured by Accelerometry in Patients with the Overlap of Obstructive Sleep Apnea and Chronic Obstructive Pulmonary Disease

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Abstract: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in Overlap Syndrome (OS), the co-occurrence of Obstructive Sleep Apnea and Chronic Obstructive Pulmonary Disease. Clustering of patients in subgroups with similar pre-clinical manifestations (ie, endothelial dysfunction) may identify relevant therapeutic phenotype categories for patients with OS who are at high risk of CVD. We therefore conducted a cross-sectional pilot study of endothelial function in 7 patients with OS (Forced Expiratory Volume in 1 second/Forced Vital Capacity < 0.7) on continuous positive airway pressure therapy (n = 7) to assess the relationship between FMD and physical activity. We found a strong association between FMD and step counts (rho = 0.77, p = 0.04); and FMD and moderate physical activity (rho = 0.9, p = 0.005). Further, larger studies are needed to confirm that FMD may identify patients with OS at high risk of CVD who benefit from increased physical activity.

Keywords: flow-mediated dilation, chronic obstructive pulmonary disease, obstructive sleep apnea, physical activity

Introduction

Both chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) are recognized as complex and heterogeneous disorders, ranging from mild symptoms to severe comorbid conditions. The term "Overlap Syndrome" (OS) is used to describe the simultaneous presence of both COPD and OSA in the same patient. Despite variations in clinical spectrum, the treatment decisions in OS are based on the forced expiratory volume in 1 second (FEV_1) and the apnea hypopnea index (AHI) only and lack stratification by other clinical characteristics. In contrast, classification of patients with OS into phenotypes with similar clinical manifestations may identify treatments aimed at reducing cardiovascular risk, in addition to the standard of care therapies that include inhaled medications and continuous positive airway pressure (CPAP). Phenotypes that predict CVD specifically in OS are not known.

Vascular endothelial dysfunction is a known pathophysiologic antecedent of clinical atherosclerosis and a valuable early therapeutic target for reducing CVD risk.[1] Studies suggest that patients with OS have endothelial dysfunction that can improve with short term (3 months) CPAP therapy.[2] It is unclear if endothelial dysfunction persists in most OS

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patients who are on long-term CPAP, which may explain the lack of CPAP treatment effects on CVD events in recent randomized trials.[3] The endothelial function can be measured by ultrasound, called flow-mediated vasodilation (FMD), which measures the increase in brachial artery diameter that occurs with inflation of an upper arm blood pressure cuff.

Habitual physical activity (PA) attenuates endothelial aging through increased endothelial shear stress and function.[4] A meta-analysis showed that individuals who engage in the equivalent of 150 minutes per week of moderate intensity PA have 20% decreased risk of developing coronary artery disease compared to those who are sedentary.[5] Despite that finding, patients with OS have low levels of PA, a mean of 2000 steps per day, which is far below the recommended threshold of 10,000 steps per day.[6] Thus, a physically active lifestyle in addition to CPAP may attenuate the development of CVD in patients with OS and endothelial dysfunction.

In summary, the objective of our study was to investigate endothelial dysfunction and its association with PA in patients with OS treated with long-term CPAP (mean length of CPAP therapy of 78 months), with the goal of identifying relevant prognostic and therapeutic phenotype categories for this population at high risk of CVD.

Methods

Participants

Participants were enrolled from Pulmonary Clinics into a 12-week home-based single-arm pilot. FMD testing was added to the protocol and performed in the last 8 of the 18 total participants. Inclusion criteria included a diagnosis of COPD ($FEV_1/FVC < 0.7$) and OSA on CPAP for at least 4 hours nightly for 70% of the days in the prior month. Patients were excluded if they had 1) symptomatic CVD, 2) limited ambulation or fall-risk, 3) participation in structured exercise, 4) weight above 330 lbs., 5) recent hospitalization or acute COPD exacerbations, and 6) daytime home oxygen. Written informed consent was obtained from all subjects.

Ethics

This study was conducted in accordance with the provisions of the Declaration of Helsinki. The study was initiated after approval from the Salem Veterans Affairs Medical Center (Salem, Virginia) Research and Development Committee and Institutional Review Board on December 5th, 2016. An information sheet with study details was provided to the patients, and they were enrolled in the study after providing written informed consent for study participation.

Clinical Evaluation

Medical history and medication use were extracted from the Electronic Medical Record. Dyspnea severity was graded using Modified Medical Research Council Dyspnea Scale (mMRC).[7]

CPAP Compliance

CPAP compliance data were downloaded from AirView, a secure cloud-based patient management system for online CPAP monitoring. The following variables were obtained from these data: monthly number of days of CPAP usage and nightly average hours of CPAP use prior to and after the intervention period.

Physical Activity

Participants were instructed on the proper wear of an accelerometer (Actigraph GT3X+, Actigraph, Pensacola, FL). Patients wore the accelerometer for more than 10 hours daily, for a mean of 9 days. The daily step counts and daily time spent in PA of different intensity levels were downloaded and analyzed with ActiLife software (Actigraph, Pensacola, FL).[8]

Flow-Mediated Vasodilation

Flow-mediated dilatation (FMD) of the brachial artery was noninvasively examined by 2D high-resolution ultrasound machine (Logiq E9, GE, USA) with a 9-MHz linear array transducer in the Ultrasound Department at the Salem VAMC, Salem, VA by a method previously described.[9] All patients underwent FMD measurements at noon, 1 hour prior to the CPET. A sphygmomanometer cuff was first placed above the antecubital fossa. After baseline longitudinal image of

brachial artery was acquired, the surface of the skin was marked, and the arm and the ultrasound probe the cuff were inflated to 50 mmHg for 5 minutes. Brachial artery diameter was measured again in the baseline longitudinal image 1 minute after cuff deflation at the marked sign. Brachial artery diameter percent change from baseline was computed from the formula [(maximum diameter-baseline diameter)/baseline diameter×100] and recorded as the FMD of the patient. The variability of the diameter measurement was minimized by repeating the measurements 3 times along the longitudinal segment of brachial artery and selecting the median value. All measurements were done by the same physician who trained with an ultrasound technician prior to the study.

Statistical Analyses

Data were expressed as mean±SD for continuous variables. The Shapiro–Wilk test was used as test of normality. Relationships between variables were assessed using two-way scatter plots and Spearman correlation test. A 2-sided $p < 0.05$ was considered statistically significant.

Results

Population Characteristics

Seven out of the 8 participants who had FMD measured also had accelerometry data. There were no significant differences between the groups with FMD data (n = 8) or without (n = 10), in terms of age, baseline disease severity, CPAP usage or daily PA ($p > 0.2$). The participants' characteristics are shown in Table 1.

Daily Physical Activity and Endothelial Function

Mean FMD was 6.5%±2.3. Daily step counts and time spent in PA of different intensity levels (sedentary, light, and moderate) are described in Table 1.

There was a strong association between higher FMD (better endothelial function) and daily step counts as shown in Figure 1 Scatter plot of the correlation between Endothelial Function and Daily Step Count (rho = 0.77, p = 0.04); and

Table 1 Participants' Characteristics

Clinical Parameter (n=7)	Mean Value ± SD
Age (years)	65 ± 6
Body Mass Index (kg/m2)	33 ± 3
FEV_1 (% predicted)	68 ± 9
Charlson Comorbidity Index	3 ± 1
Dyspnea Scale (n) Modified Medical Research Council 0 Modified Medical Research Council 1 Modified Medical Research Council 2	 2 4 1
Quality of Life (Q-LES-Q-SF)	58 ± 6
COPD Severity (% total participants) Mild (FEV_1>80% predicted) Moderate (50%<FEV_1<80% predicted)	 14% 86%
OSA Compliance Apnea Hypopnea Index on CPAP Total length of CPAP therapy (months) CPAP usage (minutes/night) CPAP usage > 4 hours/night (% nights)	 1.8 ± 2.2 78 ± 48 427 ± 118 90 ± 12

(*Continued*)

Table 1 (Continued).

Clinical Parameter (n=7)	Mean Value ± SD
Cardiovascular Risk Factors	
Hypertension (%)	42%
Diabetes (%)	0
Dyslipidemia (%)	42%
Active smoker (%)	57%
Endothelial Function	
Baseline Artery Diameter (mm)	57 ± 4
Post-dilation Artery Diameter (mm)	60 ± 4
Flow Mediation Dilation (%)	6.5 ± 2.3
Physical Activity	
Daily Step Count	8782 ± 2333
Sedentary Time (minutes/day)	549 ±175
Light Physical Activity (minutes/day)	280 ± 66
Moderate Physical Activity (minutes/day)	143 ± 60

Abbreviations: SD, Standard Deviation; mm, Millimeter; %, Percentage; CPAP, Continuous Positive Airway Pressure; OSA, Obstructive Sleep Apnea; COPD, Chronic Obstructive Pulmonary Disease; FEV1, Forced Expiratory Volume in 1 Second; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire.

FMD and daily moderate PA as shown in Figure 2. Scatter plot of the correlation between Endothelial Function and Daily Physical Activity (rho = 0.9, p = 0.005).

Discussion

To our knowledge, these preliminary results are the first to suggest that FMD may help identify a relevant OS phenotype category that is at greatest risk for CVD and in need of specific treatments, in addition to those measures currently considered standard of care.

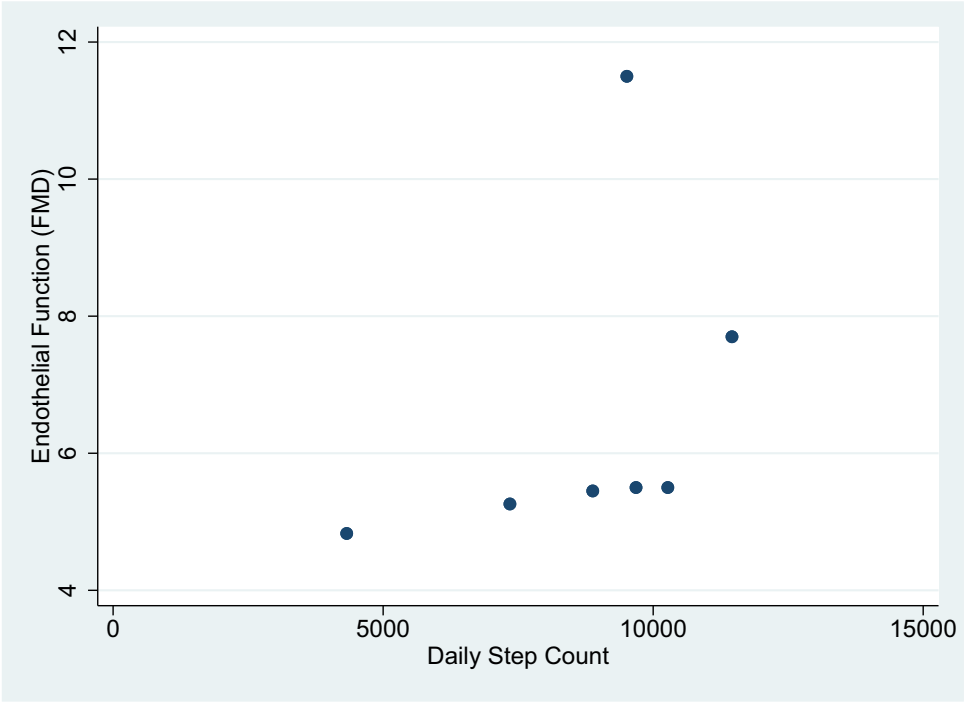

Figure 1 Scatter plot of the correlation between Endothelial Function and Daily Step Count.

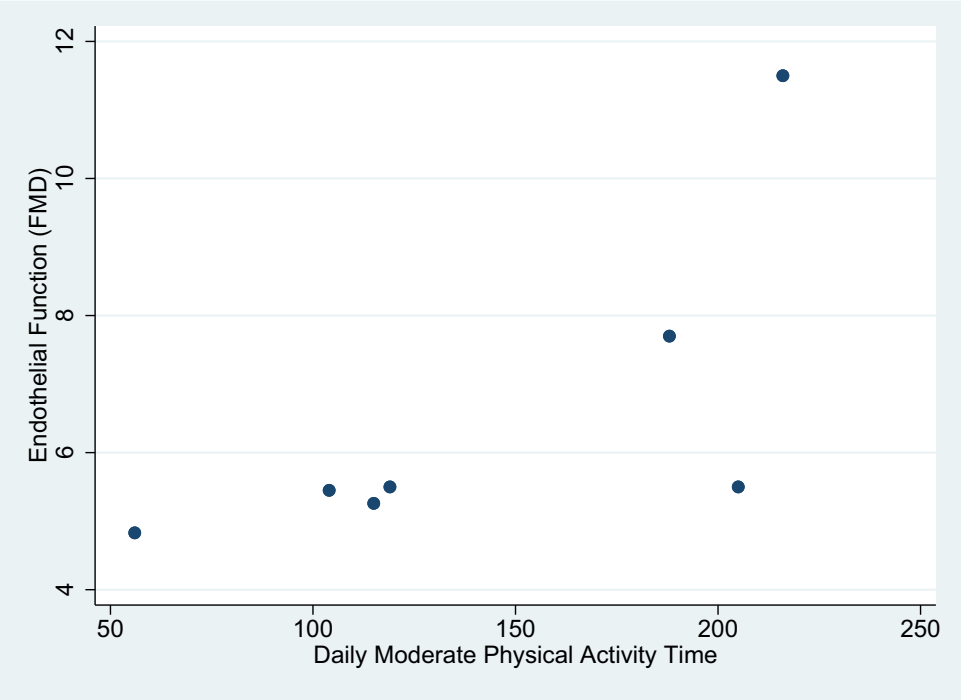

Figure 2 Scatter plot of the correlation between Endothelial Function and Daily Physical Activity.

The cutoff values of brachial artery FMD for endothelial dysfunction subjects in OS are not yet established. Shechter et al[1] showed that the best independent predictor of long-term cardiovascular adverse events was an FMD of less than 11.3%. In our small OS cohort, all except one patient had an FMD lower than 11.3%.

In our study, we found a strong positive association between FMD and average daily step counts, and between FMD and daily moderate PA. This finding could be perhaps best explained by Goto et al[10] who compared the effect of a 12-week exercise training at low (25% VO2peak), moderate (50% VO2peak) and high (75% VO2 peak) intensity. The moderate intensity group had the greatest increase in FMD. Such results suggest that low PA may fall below the threshold for improvement in FMD and that the vigorous PA may fail to increase FMD due to a decreased nitric oxide production as a result of concomitant increase in oxidative stress.

Finally, we found no association between FMD and FEV1 or traditional CVD risk factors (ie, obesity, dyslipidemia, smoking habit, diabetes and hypertension). Our results agree with those of Bernardi et al,[11] who similarly showed that in moderate COPD, the PA was the only determinant independently associated with FMD activity, while traditional CVD risk factors were not. Our findings could be due to the limitations of our study that included a small sample size and mostly OS patients who had moderate COPD.

Our study has several limitations. First, as a small pilot study lacking a control group, the findings may be influenced by insufficient power and potential confounders of the FMD, such as blood pressure, diabetes mellitus and smoking.[12] Second, as we included a sample of patients with OS who mostly had moderate COPD, our findings apply to this select population only.

Our novel preliminary results focus on patients with OS, who have been largely excluded from landmark CPAP trials due to severity of nocturnal hypoxia. Although the association between endothelial function and physical activity is plausible in this population, our study limitations preclude a clear evidence of a causal link between endothelial dysfunction and activity. Future trials that address the impact of CPAP treatment on the primary and secondary prevention of CVD in this population are critically needed.

Conclusion

To our knowledge, these preliminary results are the first to suggest an association between FMD between FMD and step counts and FMD and moderate physical activity in OS. Further larger study are needed to confirm that FMD may be used as biomarkers of susceptibility that selects an OS phenotype at high risk of CVD who benefits from increased physical activity.[13]

Abbreviations

AHI, Apnea Hypopnea Index; COPD, Chronic Obstructive Pulmonary Disease; CPAP, Continuous Positive Airway Pressure; CPET, Cardiopulmonary Exercise Testing; CVD, Cardiovascular Disease; FMD, Flow mediation dilatation; mMRC, Modified Medical Research Council Dyspnea Scale; OS, Overlap Syndrome; OSA, Obstructive Sleep Apnea; PA, Physical Activity; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire Short Form; VAMC, Veterans Affairs Medical Center.

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Disclosure

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