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A pilot study of the effects of bariatric surgery and CPAP treatment on vascular function in obese subjects with obstructive sleep apnea

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INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by intermittent hypoxemia, recurrent arousals, and intra-thoracic pressure swings, all of which can contribute to sympathetic activation and/or cardiovascular risk. The intermittent hypoxemia can lead to inflammation and oxidative stress, while pressure swings can place shear stress on the myocardium and intrathoracic vessel walls.¹ Taken together, these pathways can result in endothelial dysfunction, a recognized early marker of cardiovascular disease.²

At the macrovascular level, cross-sectional studies have reported impaired brachial artery flow-mediated dilation (FMD), increased carotid intima-media thickness, and arterial stiffness quantified by the augmentation index (AIx) in OSA subjects compared with controls.³⁻⁸ This association is strengthened by reports of a dose-response relationship between these outcomes and OSA severity and duration.^{3,8,10} Microvascular reactivity has been less studied in OSA; an association between OSA and reduced capillary density has been demonstrated,¹¹ and two small studies have reported differences between OSA subjects and controls in microcirculatory flow following administration of the endothelium-dependent vasodilator acetylcholine (ACh) delivered either non-invasively¹² or via intra-arterial infusion.¹³ Two studies conducted in our laboratories, however, have not replicated these findings in the microvasculature.^{4,14}

In addition to this observational evidence, a number of randomized controlled trials have found improvements in FMD and the AIx with continuous positive airway pressure (CPAP),¹⁵⁻¹⁸ while CPAP-withdrawal studies have demonstrated a deterioration.^{15,19,20} Again, the effects of CPAP on endothelium-dependent microvascular reactivity have not been widely studied. Only one study has reported a significant improvement with CPAP in

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AUTHOR CONTRIBUTIONS

JPB – data collection, data analysis, interpretation, manuscript preparation; JSB - data collection, data analysis, interpretation, manuscript preparation; FT - data collection, data analysis, interpretation; PDY - data collection, data analysis, interpretation, manuscript preparation; AV – study design, data analysis, interpretation, manuscript preparation; AM – study design, data analysis, interpretation, manuscript preparation.

microvascular reactivity measured non-invasively;¹² this trial was of a short duration (two months) and the average BMI was $<30\text{kg/m}^2$. The association between OSA and endothelial dysfunction is complicated by the presence of obesity as a potential confounder;¹ thus, the independent contributions of OSA and obesity on vascular functioning – at the cellular, microvascular, and macrovascular levels – are as yet unclear. In an attempt to elucidate the mechanisms by which obesity and OSA may contribute to endothelial dysfunction, we sought to follow-up a sample of obese subjects who, since completing our aforementioned cross-sectional study,¹⁴ have undergone either bariatric surgery resulting in substantial weight-loss, or begun CPAP treatment to eliminate obstructive respiratory events. We hypothesized improved vascular function with both therapeutic approaches, consistent with a reversible OSA effect on the circulation. Such pilot data would be critical to the design of subsequent randomized comparative effectiveness trials.

METHODS & PROCEDURES

Subjects

Subjects in the current study represent a sub-sample of $n=27$ from our original cross-sectional study,¹⁴ which consisted of 72 non-smoking, obese subjects (body mass index $>30\text{kg/m}^2$) aged 18-70 years who were free from any cardiovascular, endocrine or sleep comorbidities other than OSA. OSA subjects who were scheduled to undergo either bariatric surgery or CPAP treatment were approached for potential inclusion immediately after completing the aforementioned cross-sectional study. The study was approved by the Brigham & Women's Hospital institutional review board, and all subjects gave written informed consent. Data collection began in 2005, pre-dating the requirement for listing on the clinicaltrials.gov website.

Protocol

Subjects underwent attended polysomnography (PSG) in a research setting as described below. All vascular tests occurred the following day in the fasting state between 8:00 and 11:00 in temperature-controlled rooms ($24\text{-}26^\circ\text{C}$). Subjects who chose to undergo CPAP treatment via our local clinical sleep laboratory were managed in the clinical rather than research setting. As such, the type of CPAP device and mask varied across subjects, but a fixed therapeutic pressure was always applied (that is, no auto-adjusting or flexible pressure delivery was used). Subjects who chose to undergo bariatric surgery (either gastric banding or gastric bypass) underwent the procedure at Brigham & Women's Hospital. All subjects were CPAP-naïve at baseline, and those undergoing surgery did not receive CPAP during the course of the study. Six months after intervention, subjects returned for a follow-up PSG, as well as repeat vascular testing under the same conditions as baseline. The CPAP group used therapy during the follow-up PSG.

Diagnostic & follow-up polysomnographic studies

PSG consisted of electroencephalogram (C4-A1, C3-A2, O2-A1, O1-A2), bilateral electrooculogram, bilateral chin and tibial electromyogram, electrocardiogram, airflow using thermistor and nasal pressure sensors, abdominal and thoracic respiratory excursion measured by piezo bands, pulse oximetry, and body position. PSGs were scored by experienced sleep technicians blinded to treatment allocation according to the Chicago scoring criteria.²¹ OSA was diagnosed as an apnea-hypopnea index (AHI) of at least 10 events/hour. Follow-up PSGs were conducted with nasal pressure measured at the CPAP mask using a pneumotachometer, where applicable.

Assessment of macrovascular reactivity

Images of the brachial artery in the left arm were obtained using a high-resolution ultrasound with a 10.0-MHz linear array transducer and an HDI Ultramark 9 system (Advanced Technology Laboratories, Signal Hill, CA) as previously described.^{14,22} Surface electrocardiogram was measured simultaneously, and each image was captured at the peak of the R-wave. Four images were obtained during rest in the supine position, before a blood pressure cuff was inflated to supra-systolic pressure to occlude brachial artery blood flow for five minutes. A further four images were obtained following cuff release (endothelium-dependent FMD). Separated by at least thirty minutes, another set of four images were obtained during rest, followed by sublingual administration of 400µg nitroglycerin and a further four images (endothelium-independent nitroglycerin-induced dilation, NID). The media-to-media brachial artery diameter was measured by two independent investigators, blinded to both treatment allocation (CPAP or surgery) and condition (before/after cuff release or nitroglycerin). The average percentage change for each condition was then calculated.

Assessment of microvascular reactivity

Following at least 15 minutes rest after completion of the macrovascular testing, skin blood flow was measured on the ventral surface of the right forearm using LASER Doppler flowmetry (Lisca PIM 2.0, Lisca Development AB, Linköping, Sweden) as previously described,^{14,23} after ten minutes of seated rest. Measurements were obtained before and after iontophoresis of ACh, and before and after iontophoresis of sodium nitroprusside (SNP) (endothelium-dependent and -independent microvascular reactivity, respectively) using a MICI iontophoresis system (Moor Instruments, Millwey, Devon UK). The percentage change with each drug was calculated.

Assessment of blood pressure and arterial stiffness

Peripheral blood pressure was measured at the brachial artery using an automatic sphygmomanometer.²⁴ Ten-second pulse wave readings were obtained at the radial artery using a SphygmoCor applanation tonometry device (AtCor Medical, NSW Australia). The average radial pulse waveform was converted to an estimate of the central pulse waveform by the SphygmoCor software, which was then used to calculate central systolic and diastolic blood pressure (SBP, DBP), and the AIx corrected to a heart rate of 75 beats per minute. Two measurements meeting manufacturer-defined quality control values were averaged. This technique has demonstrated satisfactory inter- and intra-operator reproducibility in previous studies.^{25,26}

Statistical analysis

All analyses were performed using SPSS (Version 20, IBM, NY USA). Statistical analyses were undertaken using non-parametric tests due to the small sample size in each group, and data are presented as the median with 25th and 75th percentile. Within-group comparisons were made using Wilcoxon Matched-Pairs tests. Univariate linear regression models were used to investigate predictors of vascular reactivity measurements. Standardized residuals of the regression models were assessed, in order to ensure that the assumptions for linear regression were met. All statistical analyses were considered statistically significant when $p < 0.05$ (2-sided).

RESULTS

Of the 72 subjects in the original cohort, 27 were scheduled to undergo either CPAP treatment ($n=15$) or bariatric surgery ($n=12$) based on clinical indications independent from

this study. Descriptive characteristics of the study sample at baseline and post-intervention are summarized in Table 1. Both groups showed significant improvements in the AHI, SpO₂ nadir, arousal index, and sleep efficiency, while the surgery group also exhibited significant reductions in both BMI and neck circumference. Objective CPAP adherence data were available for seven of the 15 subjects (median 7.1 hours/night, interquartile range [6.5, 7.6]). Comparing subjects for whom CPAP adherence data were available vs. absent, there were no significant differences in baseline BMI, neck circumference, AHI, oxygen saturation (SpO₂) nadir, % of total sleep time with SpO₂<90%, or arousal index (all $p>0.05$). The median therapeutic CPAP level was 11cmH₂O, interquartile range [8, 12].

Microvascular reactivity and pulse wave analysis measurements were obtained for all subjects. Two subjects in the CPAP group did not tolerate the cuff inflation during FMD measurements, and high quality brachial artery ultrasound images were not obtained in a further two subjects in each group. The surgery group showed a significant reduction in both central and peripheral DBP despite being normotensive at baseline; there were no significant BP changes in the CPAP group. The percent change in skin blood flow following ACh (endothelium-dependent microvascular reactivity) improved with CPAP but not with surgery. There were no significant changes in skin blood flow following SNP (endothelium-independent microvascular reactivity), FMD (endothelium-dependent macrovascular reactivity), or NID (endothelium-independent macrovascular reactivity).

In separate univariate linear regression models with all subjects combined, the change in skin blood flow with ACh between baseline and post-intervention was predicted by the SaO₂ nadir ($\beta = -1.6$, SE=0.8, $p=0.047$), but not the AHI. Multivariate analysis was not conducted due to the small sample size.

DISCUSSION

The major finding of this pilot study is that obese OSA subjects undergoing CPAP treatment demonstrate a significant improvement in endothelium-dependent microvascular reactivity despite experiencing no weight loss, an effect which was not observed in OSA subjects undergoing weight-loss surgery. Although both the CPAP and surgery group experienced statistically significant reductions in OSA severity, the change in AHI in the CPAP group was far greater than the surgery group (decreases in AHI of 31.2 and 7.6 events/hour respectively), which we believe is likely the reason for the greater improvement in microvascular reactivity with CPAP. As expected, there were no significant differences in endothelium-independent microvascular reactivity, demonstrating that the impairment in vasodilation in OSA and the subsequent improvement with CPAP is due to endothelial rather than vascular smooth muscle dysfunction. The fact that we did not observe any concurrent changes in macrovascular reactivity suggests that these improvements may take a longer duration of therapy to occur; although our analyses of macrovascular reactivity may be under-powered due to the pilot nature of the study.

As mentioned, the evidence of microvascular improvements with CPAP is limited and our methodology differs from previous studies. We have reported a 45.6% response to ACh at baseline and a 69.1% response post-CPAP; the latter is similar to the response in an obese control group of a prior study (70.7%).¹⁴ The predictive value of SaO₂ nadir in determining endothelium-dependent microvascular reactivity is consistent with previous publications, which have reported that the degree of vascular impairment in OSA is proportional to the degree of oxygen desaturation during sleep.²⁷⁻²⁹ Although improvements in microvascular reactivity with weight loss in presumably non-OA subjects have been demonstrated using invasive methodology,³⁰ few previous studies using non-invasive administration of ACh are available for comparison. Our results are consistent with those

reported by Hamdy *et al.*, who found no significant improvement in microvascular reactivity resulting from a 6-month weight-loss program.³¹

To our knowledge, this study is the first to attempt to separate the influences of obesity and sleep-disordered breathing on vascular functioning by quantifying the effects of CPAP treatment and bariatric surgery. It is also the longest study of CPAP investigating non-invasive microvascular reactivity published to date that we are aware of. We do, however, acknowledge a number of important limitations, most notably the small sample size which did not allow us to investigate further predictors of the microvascular response (such as age¹⁴), as well as our non-randomized design. By choosing to study subjects who volunteered to undergo treatment in a clinical setting our aim was to investigate real-world clinical effectiveness of each therapy; however, this approach did not allow us to make treatment comparisons as would be possible in a randomized trial. This approach also meant that the two treatment groups were not balanced at baseline in aspects such as gender, age, BMI and AHI; the groups resemble usual CPAP and weight-loss clinic populations and as mentioned, our aim was not to make direct comparisons between treatments. Having subjects undergo treatment clinically resulted in a large amount of missing CPAP adherence data, and thus we were unable to investigate the ‘dose’ of treatment applied over the follow-up period. The average CPAP adherence level in the subjects with available data was high, and there is no reason to believe that the missing data for the remaining subjects was selective. Although subjective reporting of CPAP adherence is notoriously unreliable, we have observed reasonably high subjective adherence levels amongst the highly motivated subjects in our research studies. We are therefore fairly confident that non-adherence did not have a major effect on our results. We also acknowledge that because treatment assignment was not random, selection bias may have contributed to unexplained variance between our two intervention groups (for example, more severe OSA in the CPAP group compared with the surgery group at baseline). Despite these limitations, we believe our findings are a useful addition to the literature and will be critical to the design and power calculation/s of comparative effectiveness trials in the future.

In summary, we have demonstrated that six months of CPAP is sufficient to improve endothelium-dependent microvascular reactivity. Further research should be directed towards randomized trials using these novel surrogate outcomes, as well as hard cardiovascular outcomes.

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Table 1

Subject characteristics at baseline and six months following CPAP or surgery.

	CPAP GROUP (n=15)		SURGERY GROUP (n=12)	
	<i>Baseline</i>	<i>Post-CPAP</i>	<i>Baseline</i>	<i>Post-surgery</i>
<i>Male gender (number)</i>	11 (73%)		2 (17%)	
<i>Age (years)</i>	48 (range 26-60)		43 (37, 49)	
<i>BMI (kg/m²)</i>	33.8 (31.3, 37.9)	34.1 (31.7, 39.1)	43.7 (42.0, 51.4)	32.7 (30.1, 38.7) **
<i>Neck circumference (cm)</i>	44.0 (41.9, 46.0)	43.1 (41.5, 45.0)	41.1 (39.6, 47.97)	37.8 (35.1, 41.1) **
<i>AHI (events/hour)</i>	36.5 (24.7, 77.3)	5.3 (1.6, 10.9) **	18.1 (16.3, 67.5)	10.5 (5.0, 20.8) **
<i>SaO₂ nadir (%)</i>	73.0 (53.0, 81.0)	84.0 (81.0, 89.0) **	78.0 (72.8, 82.8)	79.0 (74.0, 88.0) **
<i>Arousal index (events/hour)</i>	37.2 (19.4, 72.6)	16.2 (11.1, 28.6) **	36.5 (27.2, 54.5)	29.5 (18.6, 35.7) **
<i>Sleep efficiency (%)</i>	84.1 (78.1, 92.8)	85.4 (81.5, 90.3)	86.7 (77.9, 91.9)	92.7 (89.1, 95.3) *
<i>Glycated hemoglobin (%)</i>	5.7 (5.4, 6.3)		5.7 (5.4, 6.0)	
<i>Total cholesterol (mg/dL)</i>	164 (149, 202)		181 (167, 230)	
<i>Low-density lipoprotein (mg/dL)</i>	103 (86, 128)		116 (105, 148)	
<i>High-density lipoprotein (mg/dL)</i>	44 (36, 50)		43 (34, 55)	
<i>Triglycerides (mg/dL)</i>	107 (83, 132)		117 (77, 166)	
<i>Plasma glucose (mg/dL)</i>	93 (82, 103)		95.5 (88.3, 99.0)	
<i>Follow-up duration (days)</i>	161 (141, 217)		204 (174, 245)	

Data are presented as median (lower quartile, upper quartile) unless indicated otherwise.

AHI = apnea-hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; SaO₂ = oxygen saturation.* *p* 0.05 compared to baseline,** *p* 0.01 compared to baseline.

Table 2

Changes in micro- and macro-vascular reactivity and arterial stiffness with CPAP and surgery

	CPAP GROUP (n=15)		SURGERY GROUP (n=12)	
	<i>Baseline</i>	<i>Post-CPAP</i>	<i>Baseline</i>	<i>Post-surgery</i>
Pulse wave analysis				
<i>Office brachial SBP (mmHg)</i>	118 (110, 132)	122 (114, 128)	123 (116, 137)	117 (109, 131)
<i>Office brachial DBP (mmHg)</i>	72 (67, 85)	75 (65, 80)	75 (71, 81)	71 (67, 78)*
<i>Central SBP (mmHg)</i>	109 (101, 122)	108 (104, 117)	109 (105, 128)	106 (101, 118)
<i>Central DBP (mmHg)</i>	73 (68, 86)	76 (66, 80)	76 (72, 82)	72 (68, 79)*
<i>Augmentation index (%)</i>	20.0 (14.5, 26.0)	15.5 (10.5, 23.0)	21.5 (16.4, 31.9)	20.3 (15.6, 26.9)
Microvascular reactivity				
<i>Change in skin blood flow with ACh (%)</i>	45.6 (24.4, 61.9)	69.1 (36.2, 98.5)*	57.7 (33.4, 108.8)	57.5 (34.3, 75.1)
<i>Change in skin blood flow with SNP (%)</i>	59.0 (35.5, 92.1)	44.0 (32.1, 68.2)	64.1 (29.3, 82.7)	57.5 (42.1, 73.5)
Macrovascular reactivity				
<i>Flow-mediated dilation (%)</i>	5.5 (2.2, 10.5)	2.8 (-0.06, 4.4)	4.8 (-0.5, 8.9)	5.2 (1.7, 7.4)
<i>Nitroglycerin-induced dilation (%)</i>	17.0 (11.5, 22.1)	13.0 (5.7, 19.6)	11.6 (7.2, 15.0)	16.5 (9.7, 24.4)

Data are presented as median (lower quartile, upper quartile).

ACh = acetylcholine; CPAP = continuous positive airway pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure; SNP = sodium nitroprusside.

* p 0.05 compared to baseline.