Effect of CPAP, Weight Loss, or CPAP Plus Weight Loss on Central Hemodynamics and Arterial Stiffness

Snigdha Jain, Indira Gurubhagavatula, Raymond Townsend, Samuel T. Kuna, Karen Teff, Thomas A. Wadden, Jesse Chittams, Alexandra L. Hanlon, Greg Maislin, Hassam Saif, Preston Broderick, Zeshan Ahmad, Allan I. Pack, Julio A. Chirinos

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Abstract—Obesity and obstructive sleep apnea tend to coexist. Little is known about the effects of obstructive sleep apnea, obesity, or their treatment on central aortic pressures and large artery stiffness. We randomized 139 adults with obesity (body mass index >30 kg/m^2) and moderate-to-severe obstructive sleep apnea to (1) continuous positive airway pressure (CPAP) therapy (n=45), (2) weight loss (WL) therapy (n=48), or (3) combined CPAP and WL (n=46) for 24 weeks. We assessed the effect of these interventions on central pressures and carotid–femoral pulse wave velocity (a measure of large artery stiffness), measured with arterial tonometry. Central systolic pressure was reduced significantly only in the combination arm (−7.4 mm Hg; 95% confidence interval, −12.5 to −2.4 mm Hg; *P*=0.004), without significant reductions detected in either the WL-only (−2.3 mm Hg; 95% confidence interval, −7.5 to 3.0; *P*=0.39) or the CPAP-only (−3.1 mm Hg; 95% confidence interval, −8.3 to 2.0; *P*=0.23) arms. However, none of these interventions significantly changed central pulse pressure, pulse pressure amplification, or the central augmentation index. The change in mean arterial pressure (*P*=0.008) and heart rate (*P*=0.027) induced by the interventions was significant predictors of the change in carotid–femoral pulse wave velocity. However, after adjustment for mean arterial pressure and heart rate, no significant changes in carotid–femoral pulse wave velocity were observed in any group. In obese subjects with obstructive sleep apnea, combination therapy with WL and CPAP is effective in reducing central systolic pressure. However, this effect is largely mediated by changes in mean, rather than central pulse pressure. WL and CPAP, alone or in combination, did not reduce large artery stiffness in this population.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00371293.

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Obstructive sleep apnea (OSA) is associated with an elevated risk of cardiovascular disease.[1,2] Blood pressure (BP) is an important determinant of cardiovascular risk. Prior studies have examined the effects of continuous positive airway pressure (CPAP) therapy or weight loss (WL) on BP independently in both observational and randomized controlled settings. However, they were not designed to account for the comparative or simultaneous effect of these interventions.[3–11] Accounting for the effect of OSA versus obesity is important, given that OSA and obesity are strongly associated and often have overlapping associations with cardiovascular risk factors. We recently reported the primary results of the COSA trial (Cardiovascular Effects of Obstructive Sleep Apnea), which aimed to assess the independent effect of obesity and OSA on various cardiovascular risk factors in an experimental design.[12] In COSA trial, subjects with moderate-to-severe OSA were randomized to WL alone, CPAP alone, or combined therapy with CPAP and WL for 24 weeks, to assess the incremental effects of combination therapy over each individual therapy.[12] This trial demonstrated an incremental benefit of combination therapy over CPAP alone

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From the Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX (S.J.); Divisions of Sleep Medicine (I.G., G.M., S.T.K, A.I.P.), Nephrology (R.T) and Cardiovascular Medicine (J.A.C., Z.A.), Department of Medicine and Center for Weight and Eating Disorders, Department of Psychiatry (T.A.W), University of Pennsylvania Perelman School of Medicine, Philadelphia; Hospital of University of Pennsylvania, Philadelphia (R.T., S.T.K., T.A.W., A.I.P., J.A.C.); Corporal Michael Crescenz VA Medical Center, Philadelphia, PA (I.G.); Division of Diabetes, National Institutes of Health, Bethesda, MD (K.T.); Departments of Biostatistics Consulting Unit (J.C.) and Family and Community Health, (A.L.H.), School of Nursing, University of Pennsylvania, Philadelphia; Department of Cardiology, Lehigh Valley Health Network, Allentown, PA (H.S.); and Johns Hopkins University Technology and Innovation Center, Johns Hopkins University, Baltimore, MD (P.B.).

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Correspondence to Julio A. Chirinos, Perelman Center for Advanced Medicine, Hospital of the University of Pennsylvania, S Tower, Rm 11-138, 3400 Civic Center Blvd, Philadelphia, PA 19104. E-mail Julio.chirinos@uphs.upenn.edu

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(but not compared with WL alone) in reducing serum C-reactive protein levels, insulin resistance, and dyslipidemia. These results indicated that obesity (but not OSA) was the primary causal factor in these abnormalities. However, a secondary analysis of BP changes demonstrated that systolic BP (SBP) was reduced in all study arms. Although no significant between-group differences were present in intention-to-treat (ITT) analyses, a greater reduction in the combined intervention group than either of the monotherapy groups was observed in per-protocol analyses that included subjects compliant with therapy, suggesting that both OSA and obesity independently contribute to hypertension.

In general, BP is determined by a steady component (mean arterial pressure [MAP]), which is strongly dependent on microvascular resistance, and a pulsatile component, which is strongly dependent on conduit artery properties. The pulsatile component, often represented by pulse pressure, is increasingly recognized as an important determinant of cardiovascular risk. However, pulse pressure (and systolic pressure) is different in the arm compared with the central aorta.[13] Central aortic pulse pressure, in particular, is impacted by wave reflections from the peripheral arterial tree returning to the heart.[14–17] Central pulsatile hemodynamics and arterial stiffness are independent predictors of cardiovascular risk.[13,18–20] Whereas arterial stiffness has been linked to OSA in multiple observational studies,[21–25] little experimental data are available on the effect of CPAP, WL, or both, on either central hemodynamics or arterial stiffness.

In this study, we report on the results of an ancillary study of the COSA trial, in which changes in central BP and carotid–femoral pulse wave velocity (CF-PWV) were assessed, in response to randomized CPAP therapy, WL therapy, or both.

Methods

Study Design

This was a randomized, parallel-group, 3-armed trial comparing the effects of CPAP, WL, or both (CPAP plus WL) among subjects with (1) obesity, defined as body mass index ≥30 kg/m^2; (2) moderate-to-severe OSA, defined as the presence of an apnea–hypopnea index ≥15 events/h; and 3) serum C-reactive protein level ≥1 mg/dL. The study design, along with the detailed inclusion and exclusion criteria, has been described previously.[12] In brief, study participants were initially screened with a home-based sleep monitor. For those with apnea–hypopnea index ≥10 events/h, this was followed by diagnostic polysomnography. Subjects with apnea–hypopnea index ≥15 on polysomnography were randomized using a permuted block design with stratification according to enrollment site (Hospital of University of Pennsylvania and VA Medical Center), sex, and statin use.

This ancillary study was initiated with funding awarded by the American Heart Association several months after the primary National Heart, Lung and Blood Institute–funded trial was initiated. Once the ancillary trial was implemented, however, all subjects in the main trial were also enrolled in this ancillary study.

Interventions

The primary interventions for this trial were CPAP therapy and WL, either alone or in combination. For subjects in the CPAP-only and the combined intervention arms, CPAP was initially calibrated in the laboratory followed by continued therapy with either a fixed pressure or an auto-adjusting CPAP. Adherence was monitored weekly with the help of a router attached to the device. Subjects in the WL and the combined intervention arm received individual weekly counseling sessions targeted toward a goal caloric intake and progressively increasing durations of unsupervised exercise. Cognitive behavioral strategies including self-monitoring, goal setting, and problem-solving were used to promote compliance to WL recommendations.

Outcome Assessments

Assessments were performed at baseline, 8 weeks, and 24 weeks after the initiation of therapy and are detailed further in the online-only Data Supplement. Central pressure waveforms were obtained with applanation tonometry of the carotid artery, using a high-fidelity Millar tonometer (Millar Instruments, Houston, TX) and a SphygmoCor PWV Vx System (Atcor Medical; Sydney, Australia). We recorded radial artery waveforms from the wrist of the dominant arm. Radial waveforms were calibrated according to sphygmomanometric systolic and diastolic pressures measured in the brachial artery. MAP was obtained via integration of the radial pressure waveform. Carotid pressure waveforms were calibrated using radial MAP and diastolic BP, which varies minimally along the arterial tree. Because some amplification of the pulse pressure occurs between the aorta and the carotid artery, we performed a second set of sensitivity analyses, in which we obtained central (aortic) pressures using a generalized transfer function applied to the radial pressure waveform, as previously described.[26,27]

CF-PWV, considered the noninvasive gold standard index of large artery stiffness,[19,28] was measured using the SphygmoCor system. In brief, carotid-to-femoral transit time (ΔT) was computed from the foot-to-foot time difference between sequentially acquired carotid and femoral waveforms, using the intersecting tangents method, and the QRS complex of the ECG as a fiducial point. The distance between the sternal notch and the carotid artery was subtracted from the distance between the sternal notch and the femoral artery, to estimate the path length (L), and PWV was computed as L/ΔT. Distance measurements were performed using a rigid caliper, to avoid an artificial effect of obesity in distance measurements that can occur with flexible tape measures.

Statistical Analysis

Continuous data are described as mean±SD or counts (percentages) as appropriate. Statistical analyses were performed (1) on a primary modified ITT population, defined as all participants who were randomized to a study group and had at least 1 outcome assessment observation after randomization, and (2) in a per-protocol analysis restricted to participants who met prespecified minimum requirements for WL (at least 5% of baseline weight) and adherence to CPAP therapy (use for an average of at least 4 hours per night on at least 70% of the total number of nights). The ITT analysis best represents the expected therapeutic effects of our interventions as implemented in the trial. The per-protocol analysis is most informative about causal relationships between OSA or obesity on the end points; this is based on the fact that any incremental benefit of effective combination therapy (WL combined with effective CPAP treatment), relative to effective CPAP alone, must be because of the effects of obesity that are independent of the effects of OSA. Conversely, any incremental benefit of effective combination therapy, when compared with effective WL alone, must be because of the effects of OSA that are independent of the effects of obesity.[12] The effects of the interventions on end points were analyzed with the use of general linear mixed models, with all measurements available used to estimate intervention effects at 24 weeks. Estimates are presented as mean (95% confidence interval [CI]). Analyses were performed with SAS software, version 9.2 (SAS Institute).

Results

Study Participants

Of the 181 total participants who underwent randomization in the parent trial, 139 participated were included in this substudy (CPAP: n=45, WL: n=48, CPAP+WL: n=46). Seventy-one participants were found to meet adherence criteria and were included in the per-protocol analysis. A flowchart of study participants at each stage is shown in Figure S1 in the online-only Data Supplement.

Baseline characteristics of the tonometry subsample of study participants when compared with those without tonometry

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Table 1. Comparison of Baseline Characteristics of Subjects With and Without Tonometry Measurements

Characteristic	No Tonometry (n=42)	Tonometry (n=139)	*P* Value
Demographic parameters			
Age, y; mean±SD	47.7±11.0	49.2±11.2	0.367
% Female	43.2%	42.3%	0.921
Race			0.007
Black	60.5%	34.3%	
White	39.5%	61.9%	
Other	…	3.7%	
Comorbidities and medication use			
Tobacco use			0.272
Never smoker	77.3%	68.6%	
Current/Past	22.7%	31.4%	
Alcohol use			0.120
None	43.2%	29.2%	
<3 drinks	50.0%	51.1%	
3–7 drinks	6.8%	14.6%	
7–14 drinks	…	5.1%	
Statin use	20.5%	20.6%	0.985
Antihypertensive use	43.2%	37.2%	0.480
Days/week exercise; mean±SD	1.7±2.3	1.3±1.6	0.184
BMI; mean±SD	39.4±6.7	38.6±6.4	0.475
Hemodynamic parameters			
SBP; mean±SD	129.4±12.7	127.4±10.4	0.322
DBP; mean±SD	81.3±8.29	78.6±7.19	0.044
MAP; mean±SD	100.5±9.3	98.1±7.6	0.095
Pulse pressure; mean±SD	48.1±9.2	48.8±8.8	0.632
Heart rate; mean±SD	76.0±10.7	69.8±9.9	0.001

BMI indicates body mass index; DBP, diastolic blood pressure; MAP, mean arterial pressure; and SBP, systolic blood pressure.

measurements are shown in Table 1. The mean age of the participants was 49.4±11.2 years, and 42.3% of the subjects were female. The age and sex distribution of the substudy population was not significantly different from those not included in the substudy. However, there was a significantly higher proportion of Whites and lower proportion of Blacks among subjects enrolled in this substudy. Diastolic BP and heart rate were significantly but slightly lower among subjects enrolled in this substudy. There were no other significant differences between the 2 populations with respect to tobacco use, alcohol consumption, or use of antihypertensive agents or statins.

General baseline characteristics of the tonometry subsample of study participants randomized to WL, CPAP, or both are shown in Table 2. No significant differences were observed in various characteristics, except for a slightly greater body mass index at baseline among subjects randomized to CPAP. Changes in body weight, body mass index, and

Table 2. Baseline Characteristics of Study Participants With Tonometry Measurements

Characteristic	Weight Loss (n=48)	CPAP (n=45)	Weight Loss+CPAP (n=46)	*P* Value
Age, y; mean±SD	49.0±10.7	48.9±11.3	49.8±12.1	0.921
Male sex, n (%)	30 (62.5)	27 (60)	23 (50)	0.416
Race, n (%)				0.657
White	29 (60.4)	26 (57.8)	31 (67.4)	
Black	16 (33.3)	18 (40)	14 (30.4)	
Mixed or other	3 (6.2)	1 (2.2)	1 (2.2)	
Height, cm	172.6±10.5	171.7±9.1	171.4±9.4	0.826
Weight, kg	111.4±21.1	119.5±21.5	112.5±25.2	0.180
Waist size, cm	117.0±14.2	124.4±14.3	120.5±15.3	0.055
Body mass index	37.2±4.9	40.7±7.5	38.1±6.3	0.026
Hypertension, n (%)	18 (37.5)	18 (40)	16 (34.8)	0.948
Percentage of time SpO_2 <90%	4.2±6.2	8.2±15.3	6.4±11.6	0.262
AHI events/h	38.3±18.5	43.1±21.3	45.3±26.0	0.304
Oxygen desaturation index, no. of events/h				
>3% drop from baseline	22.8±18.2	29.1±23.5	27.9±26.5	0.381
>4% drop from baseline	18.5±16.3	23.9±21.9	23.3±25.6	0.418
Medication use, n (%)				
Statin	10 (21.3)	10 (22.2)	9 (24.3)	0.951
Antihypertensive	19 (39.6)	17 (37.8)	16 (34.8)	0.889
Hemodynamics (mean±SD)				
Peripheral SBP	124.8±10.2	129.1±10.6	128.4±10.2	0.099
Peripheral MAP	96.6±7.6	99.3±7.3	98.6±7.7	0.204
Carotid SBP	110.6±17.0	113.3±14.6	113.2±13.8	0.624
Carotid MAP	89.9±9.8	92.9±9.6	92.2±9.3	0.287
Peripheral Augmentation Index	78.5±16.2	74.1±13.5	75.5±17.5	0.409
Central Augmentation Index	117.5±32.2	116.3±22.5	116.2±26.6	0.964
CF-PWV	7.8±1.4	8.1±1.7	8.2±1.4	0.633
Peripheral PP	46.9±7.6	49.7±9.9	49.6±7.6	0.201
Central PP	34.8 (14.4)	34.9 (12.4)	36.0 (10.6)	0.892

Plus-minus values are mean±SD. AHI indicates apnea–hypopnea index; CF-PWV, carotid–femoral pulse wave velocity; CPAP, continuous positive airway pressure; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; and SpO_2, oxygen saturation level as measured by oximetry.

peripheral BP are summarized in Table S1 in the online-only Data Supplement.

Systolic Blood Pressure

In ITT analyses, central SBP assessed with carotid arterial tonometry was reduced significantly only in the combination arm (−7.4 mm Hg; 95% CI, −12.5 to −2.4 mm Hg; *P*=0.004),

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without significant reductions detected in either the WL-only (−2.3 mm Hg; 95% CI, −7.5 to 3.0; *P*=0.39) or the CPAP-only (−3.1 mm Hg; 95% CI, −8.3 to 2.0; *P*=0.23) arms (Figure 1A). Similarly, in the per-protocol compliant subsample, central SBP decreased significantly in the combination arm (−10.6 mm Hg; 95% CI, −17.4 to −2.8; *P*=0.003), without significant reductions detected in either the WL-only (−4.3 mm Hg; 95% CI, −11.0 to 2.4; *P*=0.20) or the CPAP-only (−3.6 mm Hg; 95% CI, −9.3 to 2.1; *P*=0.21; Figure 1B) arm. These differences were not seen at 8 weeks (Figure 1).

Central SBP assessed by radial tonometry in conjunction with a generalized transfer function revealed similar results. In these analyses, central SBP was reduced significantly only in the combination arm (−7.0 mm Hg; 95% CI, −12.0 to −2.1; *P*=0.006), without significant reductions detected in either the WL-only (−1.9 mm Hg; 95% CI, −7.0 to 3.1; *P*=0.45) or the CPAP-only (−3.5 mm Hg; 95% CI, −8.5 to 1.5; *P*=0.17) arms (Figure 1C). Similarly, in the per-protocol compliant subsample, central SBP decreased significantly in the combination arm (−9.9 mm Hg; 95% CI, −16.7 to −3.2; *P*=0.004), without significant reductions detected in either the WL-only (−4.3 mm Hg; 95% CI, −10.9 to 2.3; *P*=0.20) or the CPAP-only (−3.7 mm Hg; 95% CI, −9.3 to 1.9; *P*=0.20) arms (Figure 1D).

We analyzed the relationship between central and peripheral SBP and between change in central SBP and change in peripheral SBP. On regression analysis, we found both the baseline and the change in central and peripheral SBP to be highly correlated with correlation coefficient of 0.935 and 0.928, respectively.

Mean and Diastolic Blood Pressure

MAP was reduced significantly in the combination therapy arm and the CPAP arm in ITT analysis (CPAP+WL: −6.9 mm Hg; 95% CI, −10.2 to −3.6; *P*<0.0001; CPAP: −3.7 mm Hg; 95% CI, −6.9 to −0.5; *P*=0.02; WL, −1.8 mm Hg; 95% CI, −5.2 to 1.6; *P*=0.29) and in per-protocol analysis (CPAP+WL: −9.1 mm Hg; 95% CI, −13.0 to −5.3; *P*<0.0001; CPAP: −3.1; 95% CI, −6.3 to −0.02; *P=0.*05; WL: −1.9; 95% CI, −5.8 to 2.0; *P*=0.34). After adjustment for heart rate, significant reductions in MAP were noted in the CPAP and CPAP+WL group in the ITT analysis (CPAP: −3.4; 95% CI, −6.6 to −0.2; *P*=0.04; CPAP+WL: −6.0; 95% CI, −9.1 to −3.0; *P*=0.0002; WL: −0.8; 95% CI, −4.0 to 2.4; *P*=0.62) and only in the combined therapy arm in per-protocol analysis (CPAP: −2.8; 95% CI, −6.2 to 0.5; *P*=0.09; CPAP+WL: −8.8; 95% CI, −12.7 to −4.9; *P*<0.0001; WL: −1.9; 95% CI, −5.9 to 2.0; *P*=0.33).

The effect of the interventions in the 3 arms was similar with regards to change in diastolic BP. In both ITT and per-protocol analysis, diastolic BP decreased significantly in the combined CPAP+WL group but not in the CPAP- and WL-only arms. (ITT: CPAP: −3.4 mm Hg; 95% CI, −5.0 to 2.3; *P*=0.07; WL: −1.1; 95% CI, −3.6 to 1.8; *P*=0.43; CPAP+WL: −5.2; 95% CI, −7.9 to −2.6; *P*=0.0001. Per-protocol analysis: CPAP: −2.3; 95% CI, −5.0 to 0.4; *P*=0.09; WL: −1.3; 95% CI, −4.5 to 1.8; *P*=0.40; CPAP+WL: −6.9; 95% CI, −10.1 to −3.7; *P*<0.0001.)

Pulse Pressure

In the ITT analyses, the reduction in central (carotid) pulse pressure (Figure 2A) compared with baseline did not reach statistical significance in any of the 3 groups at 24 weeks (CPAP: −3.8 mm Hg; 95% CI, −8.3 to 0.7; *P*=0.09; WL: −2.7 mm Hg; 95% CI, −7.5 to 2.2; *P*=0.27; CPAP+WL: −4.1; 95% CI, −8.7 to 0.6; *P*=0.08). In per-protocol analyses (Figure 2B), subjects in the CPAP arm were found to have a significant reduction in central pulse pressure at 24 weeks compared with baseline (CPAP: −4.1 mm Hg; 95% CI, −8.2 to −0.04; *P*=0.048; WL: −1.7; 95% CI, −6.8 to 3.4; *P*=0.50; CPAP+WL: −3.2 mm Hg; 95% CI, −8.3 to 1.8; *P*=0.21), although no between-group differences were demonstrated. These results did not appreciably change after adjustment for MAP and heart rate (ITT: CPAP: −3.7; 95% CI, −8.0 to 0.6; *P*=0.09; CPAP+WL: −2.9; 95% CI,

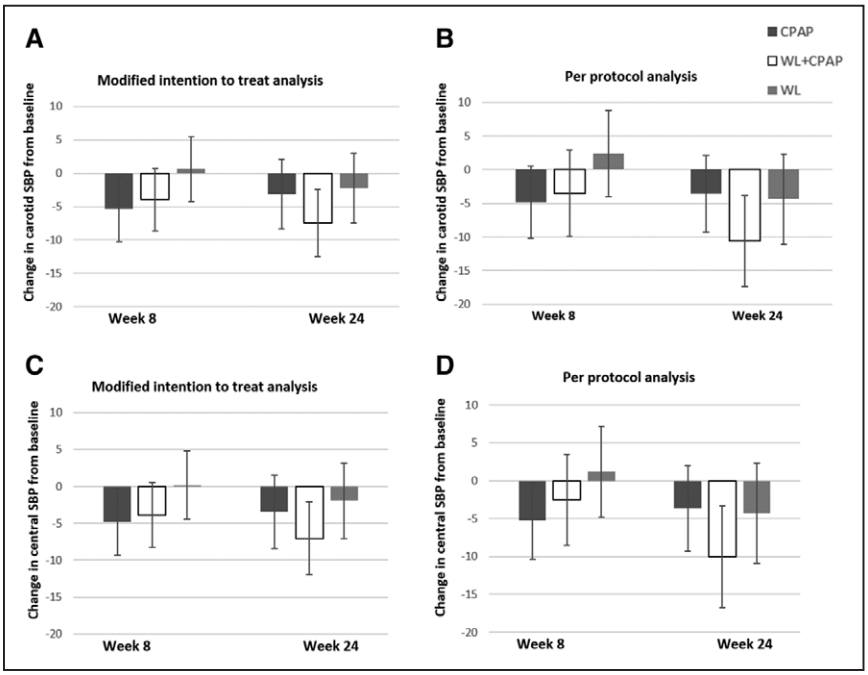

Figure 1. Change in central systolic blood pressure (SBP) from baseline derived from carotid tonometry in modified intention-to-treat analysis (**A**) and per-protocol analysis including only subjects who met prespecified adherence criteria (**B**). Change in central SBP from baseline derived from application of a generalized transfer function to radial tonometry in modified intention-to-treat analysis (**C**) and per-protocol analysis including only subjects who met prespecified adherence criteria (**D**). Error bars represent 95% confidence intervals. CPAP indicates continuous positive airway pressure; and WL, weight loss.

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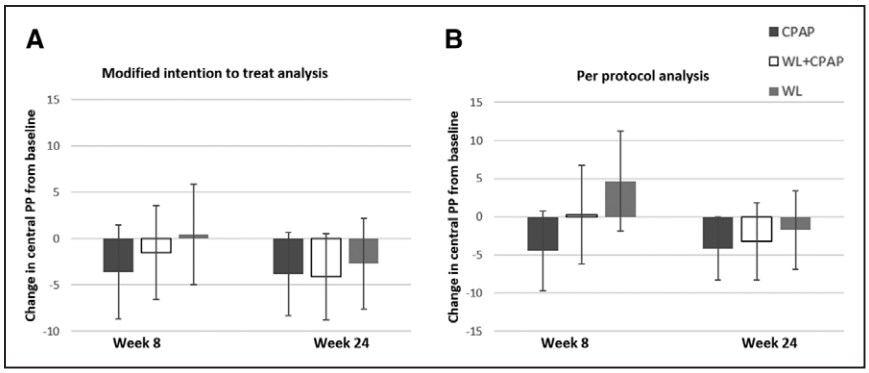

Figure 2. Change in central pulse pressure (PP) from baseline derived from carotid tonometry in modified intention-to-treat analysis (**A**) and per-protocol analysis including only subjects who met prespecified adherence criteria (**B**). Error bars represent 95% confidence intervals. CPAP indicates continuous positive airway pressure; and WL, weight loss.

−7.2 to 1.5; *P*=0.19; WL: −3.7; 95% CI, −8.3 to 0.9; *P*=0.11; per-protocol analysis: CPAP: −4.2; 95% CI, −8.2 to −0.3; *P*=0.04; CPAP+WL: −1.8; 95% CI, −6.8 to 3.1; *P*=0.46; WL: −2.2; 95% CI, −7.1 to 2.7; *P*=0.37).

Pulse Pressure Amplification

Pulse pressure amplification, assessed as the ratio of carotid over brachial artery pressure, did not significantly change from baseline in any of the 3 arms in ITT analysis (Figure 3A; CPAP: −0.3 mm Hg; 95% CI, −3.2 to 2.7; *P*=0.86; WL: −0.1 mm Hg; 95% CI, −2.9 to 3.2; *P*=0.92; CPAP+WL: −2.4 mm Hg; 95% CI, −5.4 to 0.6; *P*=0.11). Findings were very similar in per-protocol analysis (Figure 3B; CPAP: −0.5 mm Hg; 95% CI, −3.9 to 2.8; *P*=0.76; WL: 0.1 mm Hg; 95% CI, −3.8 to 4.1 mm Hg; *P*=0.94; CPAP+WL: −2.7; 95% CI, −6.8 to 1.3; *P*=0.18). Results were similar with the use of radial tonometry and application of a generalized transfer function (not shown).

Augmentation Index

The central augmentation index did not significantly change from baseline in any of the 3 arms in ITT analysis (Figure 3C; CPAP: 2.5; 95% CI, −4.7 to 9.7; *P*=0.48; WL: −5.7; 95% CI, −13.5 to 2.0; *P*=0.14; CPAP+WL: 2.1; 95% CI, −5.3 to 9.5; *P*=0.58). Similar findings were noted in per-protocol analysis (Figure 3D; CPAP: 4.7; 95% CI, −2.5 to 11.9; *P*=0.19; WL: −4.0; 95% CI, −13.0 to 5.0; *P*=0.38; CPAP+WL: −0.7; 95% CI, −10.0 to 8.2; *P*=0.88). Adjustment for MAP and heart rate did not reveal any significant changes in these results (ITT: CPAP: −3.1; 95% CI, −4.3 to 10.5; *P*=0.40; WL: −7.0; 95% CI, −14.9 to 0.9; *P*=0.09; CPAP+WL: 3.2; 95% CI, −4.4 to 10.7; *P*=0.41; per-protocol analysis: CPAP: 4.0; 95% CI, −3.1 to 11.2; *P*=0.26; WL: −4.3; 95% CI, −13.2 to 4.5; *P*=0.33; CPAP+WL: 1.6; 95% CI, −7.3 to 10.6; *P*=0.72). Results were also similar with the use of radial tonometry and application of generalized transfer function (not shown).

Carotid–Femoral Pulse Wave Velocity

In ITT analyses, no significant changes in CF-PWV were observed in any of the 3 study arms (CPAP: −0.13 m/s; 95% CI, −0.65 to 0.39; WL: −0.04 m/s; 95% CI, −0.55 to 0.47; WL+CPAP: 0.05 m/s; 95% CI, −0.45 to 0.54; Figure 4A). There were no significant differences in the change in

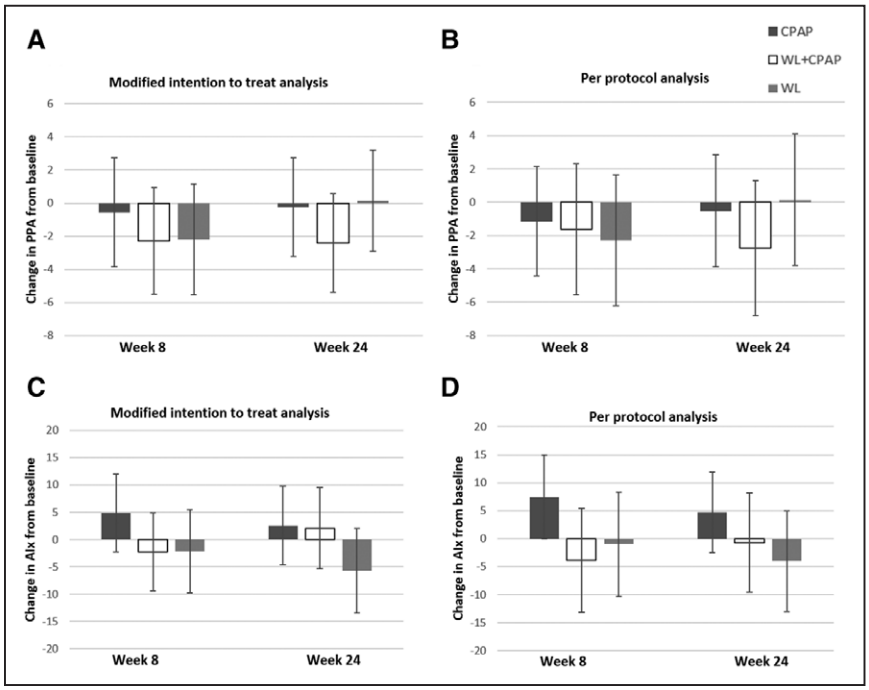

Figure 3. Change in pulse pressure amplification (PPA), ratio of central over radial artery pulse pressure from baseline in modified intention-to-treat analysis (**A**) and per-protocol analysis including only subjects who met prespecified adherence criteria (**B**). Error bars represent 95% confidence intervals. Change in aortic augmentation index (AIx) from baseline in modified intention-to-treat analysis (**C**) and per-protocol analysis including only subjects who met prespecified adherence criteria (**D**). Error bars represent 95% confidence intervals. CPAP indicates continuous positive airway pressure; and WL, weight loss.

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CF-PWV between the groups (*P* value for all pairwise comparisons >0.05). In prespecified per-protocol analyses restricted to subjects who complied with randomized therapy, these results were not appreciably different (Figure 4B).

The change in MAP induced by the intervention was a significant predictor of the change in CF-PWV (Pearson *R*=0.31; *P*=0.008). Similarly, the change in heart rate was weakly related to the change in CF-PWV (Pearson *R*=0.23; *P*=0.027). After adjustment for MAP and heart rate, no significant changes in CF-PWV were observed in either group, without significant between-group differences, in either ITT analyses or prespecified analyses in subjects who met compliance criteria.

Discussion

In this study, we found that, in obese individuals with moderate-to-severe OSA, combination therapy with WL and CPAP (but not CPAP or WL monotherapy) reduced central SBP. These results were consistently found when either carotid tonometry (without a transfer function) or radial tonometry (with the use of a generalized transfer function) was used. However, the reduction in central SBP was largely the result of a larger reduction in MAP in the combination arm because central pulse pressure or large artery stiffness (measured as CF-PWV) was not significantly reduced in either arm in ITT analyses. Among participants who complied with therapy, a significant reduction in central pulse pressure in the CPAP-only arm was observed, which was not seen in either the WL arm or the combined intervention arm. Overall, however, pulse pressure amplification was not significantly changed by WL, CPAP, or combination therapy, suggesting that brachial systolic (and pulse) pressure remains a good surrogate of central pulse pressure changes in response to these interventions.

Previous randomized controlled trials have studied the effect of CPAP therapy on BP in comparison to splinting devices, sham CPAP, or supplemental nasal oxygen, with variable results. Whereas most trials in patients with resistant hypertension have shown a significant improvement with CPAP, trials in normotensive subjects or those with nonresistant hypertension, similar to our population, have shown conflicting results.[3–6,11,29–31] However, the negative results have largely been from trials reporting effects of CPAP in subjects with mild OSA[30] or shorter durations of therapy,[29,31] and recent meta-analyses of randomized controlled trial data have confirmed a small but statistically significant reduction in BP with CPAP therapy.[32,33] In our study, we noted a significant reduction in MAP with CPAP in both ITT and per-protocol analyses, consistent with the notion that sleep apnea leads to hypertension, and that CPAP monotherapy can achieve a small BP effect. Furthermore, because the combined CPAP and the WL intervention achieved a significantly higher reduction in MAP compared with CPAP alone, it follows that both obesity and OSA have independent effects on BP and concurrent treatment of both achieves a larger BP reduction. This is in concordance with the results of the primary study measuring peripheral pressures, where compliant subjects in all 3 arms achieved significant MAP reduction with the highest effect in the combination intervention arm.[12]

We report, for the first time, the effect of CPAP, WL, or the combination of CPAP and WL on central hemodynamics and large artery stiffness. We found a significant reduction in central systolic pressure only in the combined CPAP+WL arm. Interestingly, we also observed a reduction in central pulse pressure in compliant subjects randomized to CPAP therapy. This finding, although interesting, should be interpreted with caution. First, this is a finding in a subsample of individuals enrolled in the parent trial, who had both available tonometry measurements (for estimation of central pressures) and adequate compliance to therapy. Furthermore, the analyses overall suggest that pulse pressure amplification does not change with CPAP, WL, or the combination, suggesting that peripheral pulse pressure is an adequate surrogate of central pulse pressure with regards to the response to these interventions. Of note, in the parent trial, pulse pressure was reduced in the combined intervention group in the ITT analysis, and in per-protocol analyses including compliant subjects, it was reduced in the combined CPAP+WL and the WL monotherapy arm.

OSA has also been linked to increased arterial stiffness and a recent meta-analysis summarizing 18 studies confirmed this association.[25] Evidence from prior studies on the impact of CPAP therapy in reducing arterial stiffness is less concrete with only a few randomized controlled trials evaluating this effect,[7,34–36] of which 3 studied the gold standard measure of large artery stiffness, CF-PWV.[7,35,36] Contrary to our results, Drager et al[7] and Litvin et al[36] described striking reductions in CF-PWV with 4 months and 3 weeks of CPAP therapy, respectively, whereas Jones et al[24] did not find a significant difference in CF-PWV with 12 weeks of CPAP therapy in patients with mild OSA. In our study, we did not observe any significant reduction in arterial stiffness with CPAP, WL, or

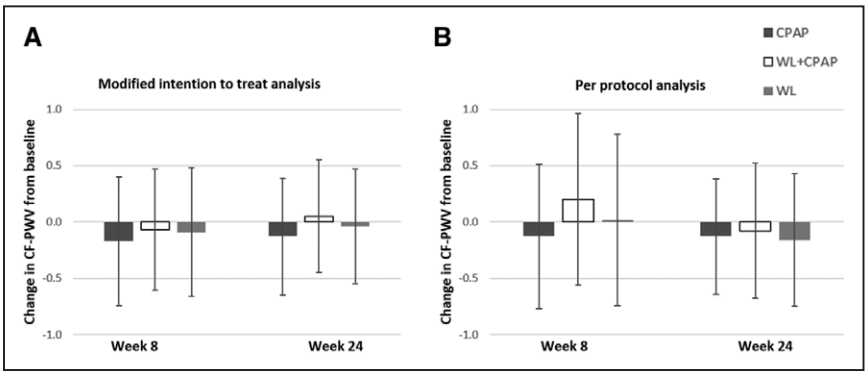

Figure 4. Change in carotid–femoral pulse wave velocity (CF-PWV) from baseline in modified intention-to-treat analysis (**A**) and per-protocol analysis including only subjects who met prespecified adherence criteria (**B**). Error bars represent 95% confidence intervals. CPAP indicates continuous positive airway pressure; and WL, weight loss.

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both interventions combined even in subjects who demonstrated compliance with therapy. Of note, both the reduction in MAP and heart rate were significant predictors of the change in CF-PWV (as is expected from physiological principles).[19] However, none of the interventions reduced CF-PWV independently of MAP or heart rate, indicating that they do not modify the material properties of the aortic wall. It remains to be determined whether greater WL and more prolonged periods of CPAP therapy exert favorable effects on large artery stiffness.

Our study should be interpreted in the context of its strengths and limitations. Strengths of our study include its prospective randomized experimental design, the assessment of central hemodynamics with high-fidelity carotid tonometry, and the design to assess the effects of WL, CPAP, and their combination, thus separating the effect of CPAP versus OSA treatment on the study end points. There are also limitations to our study. The study was not blinded for treatment assignment or outcome assessment. We did not include a sham CPAP or placebo control group; however, both sham CPAP and absence of CPAP therapy are accepted as adequate controls for an active CPAP intervention.[37] We did not assess ambulatory BP and included a nondiabetic population with significant obesity and moderate-to-severe OSA. Our results are therefore not necessarily generalizable to patients with milder OSA, milder obesity, or those with diabetes mellitus. The magnitude of BP reduction in the monotherapy arms was relatively small. Although it is possible that this was partially because of the inclusion of both hypertensive and normotensive participants in the study, the mean magnitude of BP reduction with CPAP observed in our study is comparable to the BP reduction seen in previous trials with CPAP in hypertensive populations.[32,38] We performed single, rather than duplicate arterial tonometry measurements at each visit. Despite the randomized nature of the study, we encountered imbalances in baseline characteristics which may have influenced the results. Furthermore, this analysis represented a subsample of the parent trial, with a lower representation of Black participants.

Perspectives

Our study provides evidence that both OSA and obesity have independent causal relationship with elevated central SBP and that among obese subjects with OSA, combination therapy with WL and CPAP is effective in reducing central systolic pressure. However, this effect is largely mediated by changes in mean, rather than central pulse pressure. WL and CPAP, alone or in combination, did not reduce large artery stiffness in this population. Our study adds support to the concept that in obese patients with OSA, combination therapy with CPAP and WL is required to address the increased cardiovascular risk factor burden of this population.

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Disclosures

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Novelty and Significance

What Is New?

- This is the first randomized controlled trial to examine the effect of continuous positive airway pressure (CPAP), weight loss (WL), or the combination of CPAP and WL on central hemodynamics and large artery stiffness.

What Is Relevant?

- Among obese subjects with obstructive sleep apnea, combination therapy with WL and CPAP is effective in reducing central systolic pressure.
- Reduction in central systolic pressure is largely mediated by changes in mean, rather than central pulse pressure.
- WL and CPAP, alone or in combination, did not reduce large artery stiffness in this population.

Summary

In obese individuals with moderate-to-severe obstructive sleep apnea, combination therapy with WL and CPAP but not CPAP or WL monotherapy reduced central systolic blood pressure.

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Effect of CPAP, Weight Loss, or CPAP Plus Weight Loss on Central Hemodynamics and Arterial Stiffness

Snigdha Jain, Indira Gurubhagavatula, Raymond Townsend, Samuel T. Kuna, Karen Teff, Thomas A. Wadden, Jesse Chittams, Alexandra L. Hanlon, Greg Maislin, Hassam Saif, Preston Broderick, Zeshan Ahmad, Allan I. Pack and Julio A. Chirinos

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Online Supplement

TITLE: Effect of CPAP, Weight Loss or CPAP Plus Weight loss on Central Hemodynamics and Arterial Stiffness

Snigdha Jain, MD[1]; Indira Gurubhagavatula, MD[2,3]; Raymond Townsend, MD[2]; Samuel T. Kuna, MD[2,3]; Karen Teff, PhD[4]; Thomas Wadden, PhD[2]; Jesse Chittams, MS[5]; Alexandra L. Hanlon, PhD[5]; Greg Maislin, MS, MA[2]; Hassam Saif, MD[6]; Preston Broderick, MBA[7]; Zeshan Ahmad, MD[2], Allan I. Pack, MBChB, PhD[2], Julio Chirinos, MD, PhD[2]

1. UT Southwestern Medical Center, Dallas, TX
2. University of Pennsylvania Perelman School of Medicine and Hospital of the University of Pennsylvania, Philadelphia, PA
3. Corporal Michael J. Crescenz VAMC, Philadelphia, PA
4. National Institutes of Health, Bethesda, MD
5. University of Pennsylvania School of Nursing, Philadelphia, PA
6. Lehigh Valley Health Network, Allentown, PA
7. Johns Hopkins University

CPAP therapy:

Patients randomized to receive CPAP therapy received a full night CPAP titration study, with the goal being to completely abolish all apneas, hypopneas, snoring and arousals. This was performed in a certified sleep lab with trained technicians experienced in titrating CPAP therapy. CPAP therapy was provided through either a fixed pressure or auto-adjusting CPAP device (ResMed Corp., Poway, CA), depending on the titration study. The auto-adjusting device was designed to provide the minimum pressure at each time point of treatment to eliminate apneas. Subjects assigned to CPAP therapy were instructed in the use of their CPAP device by study personnel and CPAP use was monitored by a wireless reporting system that transmitted data through a router attached to the back of the CPAP device. Information on CPAP adherence was retrieved weekly.

Weight loss therapy

Weight loss sessions were organized by the Weight and Eating Disorders Clinic at the University of Pennsylvania. Dieticians at this clinic possessed expertise in nutrition and behavioral modification, particularly within the context of weight loss trials, including diet therapy among diabetic subjects. Each patient assigned to weight loss therapy received 24 weekly individual counseling sessions during the entire 24-week period. Calorie goals were set at 1200-1500 kcal/day for those who weigh <250 pounds, or 1500-
1800 kcal/day for those whose weight exceeds 250 pounds. Physical activity consisted of unsupervised exercise and was initiated at week 4 with four 15 minute sessions per
week and increased progressively to four 50 minute sessions per week by week 15. Cognitive behavioral strategies were used to help facilitate and maintain weight loss, such as recording daily calorie and fat intake.

Tonometry measurements

We used a commercially available system (SphygmoCor Pulse Wave Velocity Vx System, AtCor Medical; Sydney, Australia) that uses the principle of applanation tonometry (Millar tonometer, Millar Instruments; Houston, Texas) and appropriate acquisition and analysis software for noninvasive recording and analysis of the arterial pulse. This system allows determinations of aortic PWV from carotid and femoral pressure waveforms that are signal-averaged using the ECG R-wave as a fiducial point. Carotid to femoral transit time (ΔT) is computed from the foot to foot time difference between carotid and femoral waveforms. The distance between the surface markings of the sternal notch and femoral artery was used to estimate the path length between the carotid and femoral arteries (L), and PWV computed as $L/\Delta T$.

The Sphygmocor system was also used to record radial artery waveforms from the wrist of the dominant arm. Waveforms of radial pressure were calibrated according to sphygmomanometric systolic and diastolic pressures measured in the brachial artery because there is practically negligible pressure pulse amplification between the brachial and radial arteries. Pulse wave analysis was then used to generate a corresponding central (ascending aortic) waveform with a generalized transfer function which has been prospectively validated for the assessment of ascending aortic blood pressure (reference). Parameters related to the central aortic pressure waveform were automatically provided by

the device software, including augmented pressure and augmentation index. Mean arterial pressure (MAP), which is the same along the arterial tree, was also obtained by the software by integration of the radial waveform.

Blood pressure measurements were performed with the oscillometric method in the fasting state, between 8:00 and 9:00 AM, before any blood draws and the initiation of the frequently-sampled intravenous glucose tolerance test. Subjects were asked to fast from food and liquid for at least 12 hours prior to the visit.

S1. Change in characteristics of 3 groups presented as mean change from baseline (95% CI) at 24 weeks. ITT: Intent to treat analysis, BMI: Body mass index, BP: Blood pressure.

Characteristic	**CPAP**		**Weight loss + CPAP**		**Weight loss**	
	Mean (95% CI)	P value	Mean (95% CI)	P value	Mean (95% CI)	P value
Body weight (kg)						
ITT	0.73 (-1.07, 2.53)	0.42	-7.08 (-8.94, -5.22)	<0.0001	-6.92 (-8.81,-5.04)	<0.0001
Per protocol	0.48 (-1.04, 1.99)	0.53	-11.76 (-13.81, -9.71)	<0.0001	-10.54 (-12.34, -8.73)	<0.0001
BMI						
ITT	0.47 (-0.19, 1.13)	0.16	-2.31 (-3.00, -1.63)	<0.0001	-2.40 (-3.09, -1.71)	<0.0001
Per protocol	0.41 (-0.20, 1.03)	0.19	-4.03 (-4.87, -3.19)	<0.0001	-3.64 (-4.38, -2.90)	<0.0001
Peripheral Systolic BP						
ITT	-3.34 (-9.06, 2.37)	0.25	-8.28 (-13.94, -2.62)	0.004	-1.71 (-7.57, 4.14)	0.56
Per protocol	-3.65 (-10.09, 2.78)	0.26	-11.07 (-18.72, -3.42)	0.005	-4.86 (-12.42, 2.71)	0.20
Peripheral Diastolic BP						
ITT	-2.40 (-5.04, 0.24)	0.07	-5.24 (-7.87, -2.62)	0.0001	-1.09 (-3.79, 1.62)	0.43
Per protocol	-2.31 (-4.98, 0.36)	0.09	-6.89 (-10.11, -3.69)	<0.0001	-1.33 (-4.47, 1.81)	0.40
Peripheral Mean BP						
ITT	-2.60 (-5.78, 0.57)	0.11	-6.23 (-9.39, -3.08)	0.0002	-1.57 (-4.83, 1.69)	0.34
Per protocol	-2.69 (-5.98, 0.60)	0.11	-8.92 (-12.86, -4.99)	<0.0001	-2.71 (-6.58, 1.15)	0.17
Peripheral Pulse Pressure						
ITT	-0.94 (-6.13, 4.25)	0.72	-3.18 (-8.33, 1.97)	0.22	-0.66 (-5.98, 4.67)	0.81
Per protocol	-1.34 (-7.34, 4.65)	0.65	-4.22 (-11.36, 2.91)	0.24	-3.52 (-10.57, 3.51)	0.32

Supplemental Figure S1. Flow chart of study participant selection. WL= Weight loss, CW= CPAP + weight loss, C= CPAP, ITT = Intent to treat, PP = Per protocol