Eight Hours of Nightly Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea Improves Glucose Metabolism in Patients with Prediabetes

A Randomized Controlled Trial

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Abstract

Rationale: Although obstructive sleep apnea (OSA) is associated with impaired glucose tolerance and diabetes, it remains unclear whether OSA treatment with continuous positive airway pressure (CPAP) has metabolic benefits.

Objectives: To determine the effect of 8-hour nightly CPAP treatment on glucose metabolism in individuals with prediabetes and OSA.

Methods: In a randomized controlled parallel group study, 39 participants were randomly assigned to receive either 8-hour nightly CPAP (n = 26) or oral placebo (n = 13). Sleep was polysomnographically recorded in the laboratory on each night. CPAP adherence was ensured by continuous supervision. Participants continued their daily routine activities outside the laboratory. Glucose metabolism was assessed at baseline and after 2 weeks of assigned treatment using both the oral and intravenous glucose tolerance tests. The primary outcome was the overall glucose response as quantified by the area under the curve for glucose during 2-hour oral glucose tolerance testing. Secondary outcomes included fasting and 2-hour glucose and insulin, the area under the curves for insulin and insulin secretion, norepinephrine, insulin sensitivity, acute insulin response to glucose, and 24-hour blood pressure.

Measurements and Main Results: The overall glucose response was reduced (treatment difference: −1,276.9 [mg/dl] · min [95% confidence interval, −2,392.4 to −161.5]; $P = 0.03$) and insulin sensitivity was improved (treatment difference: 0.77 $[\text{mU/L}]^{-1} \cdot \text{min}^{-1}$ [95% confidence interval, 0.03–1.52]; $P = 0.04$) with CPAP as compared with placebo. Additionally, norepinephrine levels and 24-hour blood pressure were reduced with CPAP as compared with placebo.

Conclusions: In patients with prediabetes, 8-hour nightly CPAP treatment for 2 weeks improves glucose metabolism compared with placebo. Thus, CPAP treatment may be beneficial for metabolic risk reduction.

Clinical trial registered with www.clinicaltrials.gov (NCT 01156116)

Keywords: obstructive sleep apnea; CPAP; metabolic; glucose; norepinephrine

Prediabetes is an intermediate state between normal glucose tolerance and type 2 diabetes. It is a highly common condition characterized by insulin resistance and glucose intolerance (1). Individuals with prediabetes are at high-risk for cardiovascular disease and up to 70% eventually develop diabetes (2, 3). Because the onset of diabetes can be prevented or delayed, identifying reversible risk factors and additional preventive strategies is of utmost

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At a Glance Summary

Scientific Knowledge on the Subject: Observational studies have suggested that obstructive sleep apnea (OSA) is associated with impaired glucose tolerance and diabetes. Experimental animal and human models mimicking OSA have demonstrated insulin resistance and glucose intolerance. To date, it remains unclear whether OSA treatment with continuous positive airway pressure (CPAP) is beneficial for glucose metabolism. A common drawback of prior studies is limited CPAP use.

What This Study Adds to the Field: This is the first study to investigate the effects of 8 hours of nightly CPAP treatment. In this proof-of-concept study, we demonstrate that all-night CPAP adherence for 2 weeks in the laboratory reduces overall glucose response during oral glucose tolerance testing and improves insulin sensitivity in individuals with prediabetes. Additionally, 8-hour nightly CPAP use decreases norepinephrine levels and 24-hour blood pressure as compared with placebo. Our findings suggest that CPAP treatment, if used 8 hours per night, may provide cardiometabolic benefit to patients with prediabetes, a potentially reversible state in which the development of overt diabetes and its cardiovascular complications may be prevented or delayed.

importance in trying to control the current diabetes epidemic.

Obstructive sleep apnea (OSA) is a treatable disorder linked to increased cardiovascular disease and mortality (4–9). Observational studies have also demonstrated that OSA is an independent risk factor for prediabetes and incident diabetes (10–13). Both animal and human models of intermittent hypoxia and sleep fragmentation acutely mimicking OSA show evidence of insulin resistance and glucose intolerance (14–17). Despite this strong association between OSA and alterations in glucose metabolism, there is still controversy as to whether treatment of OSA with continuous positive airway pressure (CPAP) has metabolic benefits (18, 19). Prior randomized controlled trials investigating the effects of CPAP on measures of glucose metabolism yielded mostly negative results (20–30). The average duration of CPAP use in these trials ranged from 3.3 to 6.2 hours per night. A common drawback in most of these trials was limited CPAP use. Interestingly, some studies (29, 31) have reported positive correlations between the hours of CPAP usage and metabolic benefit following CPAP treatment of OSA.

We performed a randomized controlled clinical trial to rigorously test the hypothesis that CPAP treatment, when applied for 8 hours on a nightly basis, can improve glucose metabolism in individuals with prediabetes and OSA. Participants were randomized to receive either 8-hour CPAP treatment or oral placebo on each night. In this proof-of-concept study, all-night CPAP adherence was ensured by direct observation and laboratory polysomography with 8-hour bedtimes during the 2-week treatment period. Glucose metabolism was assessed at baseline and after 2 weeks of assigned treatment using both the oral glucose tolerance test (OGTT) and the intravenous glucose tolerance test (ivGTT). Additionally, norepinephrine levels during OGTT and 24-hour ambulatory systolic and diastolic blood pressures were measured. Preliminary results of this study have been previously reported in the form of abstracts at the American Thoracic Society meeting (32, 33).

Methods

Participants

Overweight or obese (body mass index [BMI] ≥ 25 kg/m^2) adults aged greater than or equal to 45 years, who had OSA (apnea–hypopnea index ≥ 5) and prediabetes were recruited between November 2009 and October 2012 through flyers and advertisements seeking volunteers for a "research study about sleep and prediabetes." The advertisements were posted at the University of Chicago campus, local neighborhoods, and newspapers in the Chicago area. Participants who met the American Diabetes Association criteria for impaired fasting glucose (fasting plasma glucose of 100–125 mg/dl) and/or impaired glucose tolerance (2-hour plasma glucose of 140–199 mg/dl) were diagnosed as having prediabetes (34). They were excluded if they smoked cigarettes, had diabetes, had a history of significant cardiac or other chronic illness, or were taking prescription medications other than antihypertensives or lipid-lowering agents. Detailed inclusion and exclusion criteria are provided in the online supplement. A complete medical history and physical examination was conducted in all participants. Overnight laboratory polysomnography was performed to establish the presence and the severity of OSA. A fasting blood sample was drawn for routine laboratory tests and a standard 75-g OGTT was performed to assess glucose tolerance. The study was approved by the University of Chicago Institutional Review Board. All participants provided written informed consent.

Study Protocol

This was a randomized (2:1), placebo-controlled, parallel-group study. Participants were randomly assigned to receive either 2 weeks of 8-hour CPAP treatment or 2 weeks of oral placebo every night. Block randomization was performed using computer-generated random numbers. Randomization assignments were prepared by a statistician using opaque, sealed envelopes. During the entire protocol, both groups spent each night in the laboratory with enforced 8-hour bedtimes (from 11:00 P.M. to 7:00 A.M.), while sleep was recorded by attended polysomnography. During the daytime, participants continued their daily routine activities outside the laboratory. At baseline and after the 2-week treatment period, metabolic testing including a standard morning OGTT, a morning frequently sampled ivGTT, and ambulatory 24-hour blood pressure monitoring were performed in both groups on consecutive days (Figure 1). Participants continued their assigned treatment during the post-treatment testing period. During the 2-hour OGTT, glucose and insulin responses were assessed. Additionally, plasma norepinephrine levels were measured at each time point during the OGTT. The ivGTT was performed to estimate the

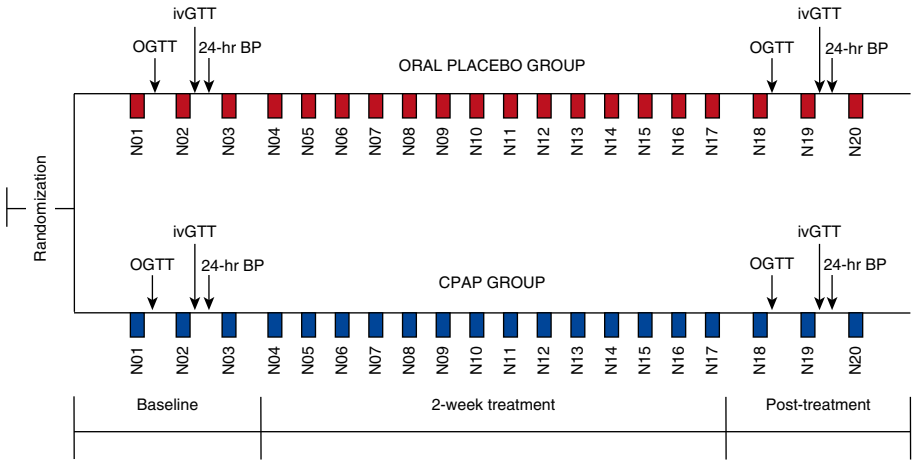

Figure 1. Study protocol. *Boxes* represent consecutive nights spent in the laboratory (i.e., nights N01–N20) for participants in the oral placebo group (*red*) and in the continuous positive airway pressure (CPAP) group (*blue*). At baseline and post-treatment, both groups underwent the same assessments: morning oral glucose tolerance test (OGTT), morning frequently sampled intravenous glucose tolerance test (ivGTT), and 24-hour ambulatory blood pressure (BP) monitoring.

insulin sensitivity and the acute insulin response to glucose using the minimal model approach (35).

Participants in the CPAP group initially underwent an overnight laboratory CPAP titration according to clinical guidelines to identify the optimal pressure needed (36). CPAP treatment was applied at the optimal therapeutic settings and all-night adherence was ensured by continuous supervision by a registered polysomnography technician. Participants were only allowed to take the CPAP off during bathroom use, if needed. Participants assigned to the oral placebo group were administered a placebo capsule 30 minutes before bedtime and were told, with the permission of the local ethics committee, that it was intended to improve upper airway function and OSA. All participants were fully debriefed regarding their treatment allocation following study completion, and were counseled on the diagnosis of OSA and given a referral for effective treatment of OSA. Further details of the study protocol are provided in the online supplement.

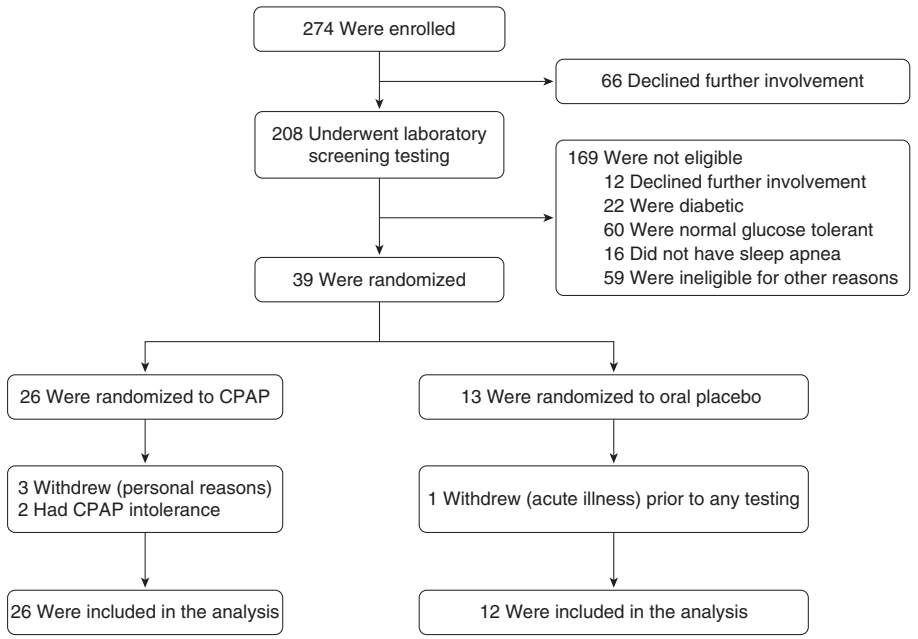

Figure 2. Participant flow diagram showing the number of participants who were enrolled, underwent laboratory screening testing to assess for eligibility, randomized to each treatment arm, and included in the analysis. CPAP = continuous positive airway pressure.

Statistical Analysis

The primary outcome was the overall glucose response as quantified by area under the curve for glucose (AUC_{glu}) during the 2-hour OGTT. Secondary outcomes included the fasting and 2-hour glucose and insulin levels; the AUCs for insulin (AUC_{ins}) and insulin secretion rate ($AUC_{insulin\ secretion}$); mean norepinephrine levels during the OGTT; insulin sensitivity and acute insulin response to glucose estimated from the ivGTT; and the 24-hour, daytime, and nighttime ambulatory blood pressure measurements.

The primary analysis was based on linear mixed-effect models to determine the treatment differences between the CPAP and placebo groups for all outcomes. These models included treatment group (CPAP vs. oral placebo); time (baseline vs. post-treatment); the treatment group–by-time interaction; a random effect for participant; and age, BMI, and ethnicity-based diabetes risk (high/low) as covariates. These covariates were preselected because they are well-established risk factors for diabetes that predict the primary outcome. These covariates were not included in the models predicting polysomnographic variables. The interaction was of particular interest to determine whether the change over time varied by treatment. Regression coefficients and 95% confidence intervals are reported. The mixed model was used because it permits inclusion of all available data and is a valid and advantageous approach for analysis of randomized controlled trials with missing data (37, 38). Further details on missing data are provided in the online supplement. Additionally, we performed sensitivity analyses using a fixed imputation approach (i.e., using the post-treatment value for those missing baseline and vice versa) or using only participants who had available data at both baseline and post-treatment.

Table 1. Baseline Characteristics of the Study Population

	CPAP Group (*n* = 26)	Oral Placebo Group (*n* = 13)
Age, yr	53.8 ± 6.2	55.2 ± 8.4
Men, n (%)	16 (62)	10 (77)
Ethnicity, n (%)		
African American	13 (50)	6 (46)
Asian	0 (0)	1 (8)
White	13 (50)	5 (38)
Hispanic	0 (0)	1 (8)
Body mass index, kg/m^2	36.8 ± 7.8	32.7 ± 4.3
Body fat, %	38.2 ± 9.3	33.1 ± 5.7
Waist circumference, cm	118.9 ± 24.7	112.1 ± 12.6
Ethnicity-based diabetes risk, high/low	13/13	8/5
Family history of diabetes, n (%)	10 (40)	4 (30)
Hypertension, n (%)	5 (19)	0 (0)
Dyslipidemia, n (%)	12 (46)	9 (69)
Hemoglobin A1c, %	5.8 ± 0.4	5.8 ± 0.3
Habitual sleep duration, h*	6.1 ± 0.9	5.8 ± 1.2
Epworth sleepiness score	10.0 ± 5.9	10.9 ± 5.0
Apnea–hypopnea index, events/h	34.2 ± 24.5	39.0 ± 22.9

Definition of abbreviation: CPAP = continuous positive airway pressure.
Data are mean ± SD unless otherwise specified. Ethnicity-based diabetes risk was categorized as "high" for African Americans, Hispanics, and Asians and "low" for white individuals. Family history of diabetes was considered positive if at least one first-degree relative had type 2 diabetes. Body fat percentage was estimated by bioimpedance. Dyslipidemia was defined by any of the following: prior medical history, any abnormal lipid value, antilipid therapy. Hypertension was considered to be present if any of the following were satisfied: prior history of hypertension, antihypertensive use, systolic or diastolic blood pressure greater than 140 or greater than 90 mm Hg, respectively.
*Habitual sleep duration data are reported in n = 34 from 1-week wrist actigraphy recordings prior to baseline assessments.

Associations between the changes in metabolic parameters were examined using Pearson correlation coefficients. A *P* value less than 0.05 was considered statistically significant. No adjustment for multiple comparisons was made. With a sample size of 39 subjects (26 in the CPAP group and 13 in the control group), the study had more than 80% power (two-sided $\alpha = 0.05$) to detect effect sizes of 1.0 for differences between treatment groups. Statistical analyses were performed using Stata Version 13 (Stata Corp., College Station, TX).

Results

Study Participants

A total of 208 individuals had laboratory screening testing to assess for eligibility and 39 participants underwent randomization (Figure 2). Of the entire randomized cohort, approximately two-thirds were men, 72% were obese, and 54% had high diabetes risk based on ethnicity. The degree of severity of OSA was moderate-to-severe (apnea–hypopnea index ⩾ 15 events/h) in 82% of the entire sample and 46% of all participants had excessive daytime sleepiness (Epworth sleepiness score >10). Baseline characteristics of the participants were similar between the groups with only trends toward higher BMI, percent body fat, and presence of hypertension in the CPAP group (Table 1). One participant who was assigned to the oral placebo group withdrew before any testing because of an acute illness, and thus was excluded from further analyses. In the CPAP group, three participants withdrew because of personal reasons and two had CPAP intolerance during the treatment period (Figure 2).

Sleep Characteristics

At baseline, total sleep time was similar between the CPAP and oral placebo groups and averaged approximately 6.7 hours in the CPAP group and approximately 6.9 hours in the placebo group. No significant differences in the changes in total sleep time or sleep efficiency were found between the CPAP and oral placebo groups after 2 weeks of treatment (Table 2). In the CPAP group,

Table 2. Effect of Treatment on Sleep Characteristics for CPAP versus Oral Placebo Groups*

Variable	CPAP Group (*n* = 26)		Oral Placebo Group (*n* = 12)		Treatment Difference	*P* Value
	Baseline	Change after 2 Weeks	Baseline	Change after 2 Weeks		
Total sleep time, h	6.7 (6.5 to 7.0)	−0.16 (−0.33 to 0.01)	6.9 (6.7 to 7.2)	−0.17 (−0.40 to 0.05)	0.01 (−0.27 to 0.29)	0.95
Sleep efficiency, %	84.1 (80.7 to 87.4)	−1.7 (−3.5 to 0.2)	86.7 (83.6 to 89.9)	−2.2 (−4.7 to 0.3)	0.5 (−2.6 to 3.6)	0.74
AHI, events/h	34.2 (24.3 to 44.1)	−31.6 (−40.0 to −23.2)	39.0 (24.4 to 53.5)	2.3 (−9.0 to 13.7)	−33.9 (−48.1 to −19.8)	<0.001
ODI (3%), events/h	22.5 (14.7 to 30.3)	−21.3 (−28.1 to −14.5)	29.9 (16.0 to 43.9)	1.6 (−7.5 to 10.8)	−22.9 (−34.4 to −11.5)	<0.001
Oxygen saturation < 90%, min	55.0 (25.8 to 84.2)	−49.7 (−72.9 to −26.5)	62.3 (19.9 to 104.7)	9.9 (−21.4 to 41.2)	−59.6 (−8.5 to −20.7)	0.003
Microarousal index, events/h	32.0 (24.0 to 39.9)	−19.7 (−26.9 to −12.6)	36.6 (22.6 to 50.6)	1.3 (−8.4 to 11.0)	−21.0 (−33.1 to −9.0)	0.001

Definition of abbreviations: AHI = apnea–hypopnea index; CPAP = continuous positive airway pressure; ODI = oxygen desaturation index.
Data are mean (95% confidence interval). Sleep variables were derived from the average of the three consecutive nights of polysomnographic recordings during baseline testing (i.e., baseline) and the three consecutive nights of polysomnographic recordings after 2 weeks of treatment during post-treatment testing (i.e., post-treatment). Change after 2 weeks (i.e., treatment effect) was calculated from the regression models as the post-treatment – baseline effect for each treatment group. Treatment difference between the two groups was also calculated from the regression models as the CPAP − oral placebo 2-week changes (i.e., the interaction effect from the model). *P* values for the treatment difference are from the test of the treatment group–by-time interaction using linear mixed model approach.
*All available data were used in the analyses (*see* online supplement for further details).

the mean duration of CPAP use approximated 8 hours per night, because participants wore the CPAP mask for the entire duration of 8-hour time-in-bed, except for rare bathroom breaks. As expected, the group receiving CPAP had significant reductions in all measures of OSA severity as compared with placebo (Table 2). The nightly total sleep time, apnea–hypopnea index, oxygen desaturation index, and microarousal index at baseline during the 2-week treatment period and post-treatment in the CPAP and oral placebo groups are shown in Figure 3.

Outcomes

The mean profiles of glucose, insulin, and insulin secretion rate during the OGTT at baseline and post-treatment are illustrated in Figure 4. The overall glucose response (AUC_{glu}) during OGTT (i.e., primary outcome) was significantly reduced with CPAP treatment as compared with oral placebo, whereas the effect of treatment on insulin response during OGTT was similar between the groups, suggesting improved insulin sensitivity (Table 3). No significant difference in treatment effect was found for fasting glucose between the groups, but the 2-hour glucose during the OGTT tended to decrease after CPAP treatment as compared with the treatment effect with placebo. After 2 weeks of treatment, fasting insulin levels were significantly reduced in the group receiving CPAP compared with the change in the placebo group, but the change in 2-hour insulin levels did not differ between the groups. Insulin sensitivity estimated by the ivGTT was significantly improved after CPAP treatment as compared with the treatment effect with placebo. The treatment effect for the acute insulin response to glucose

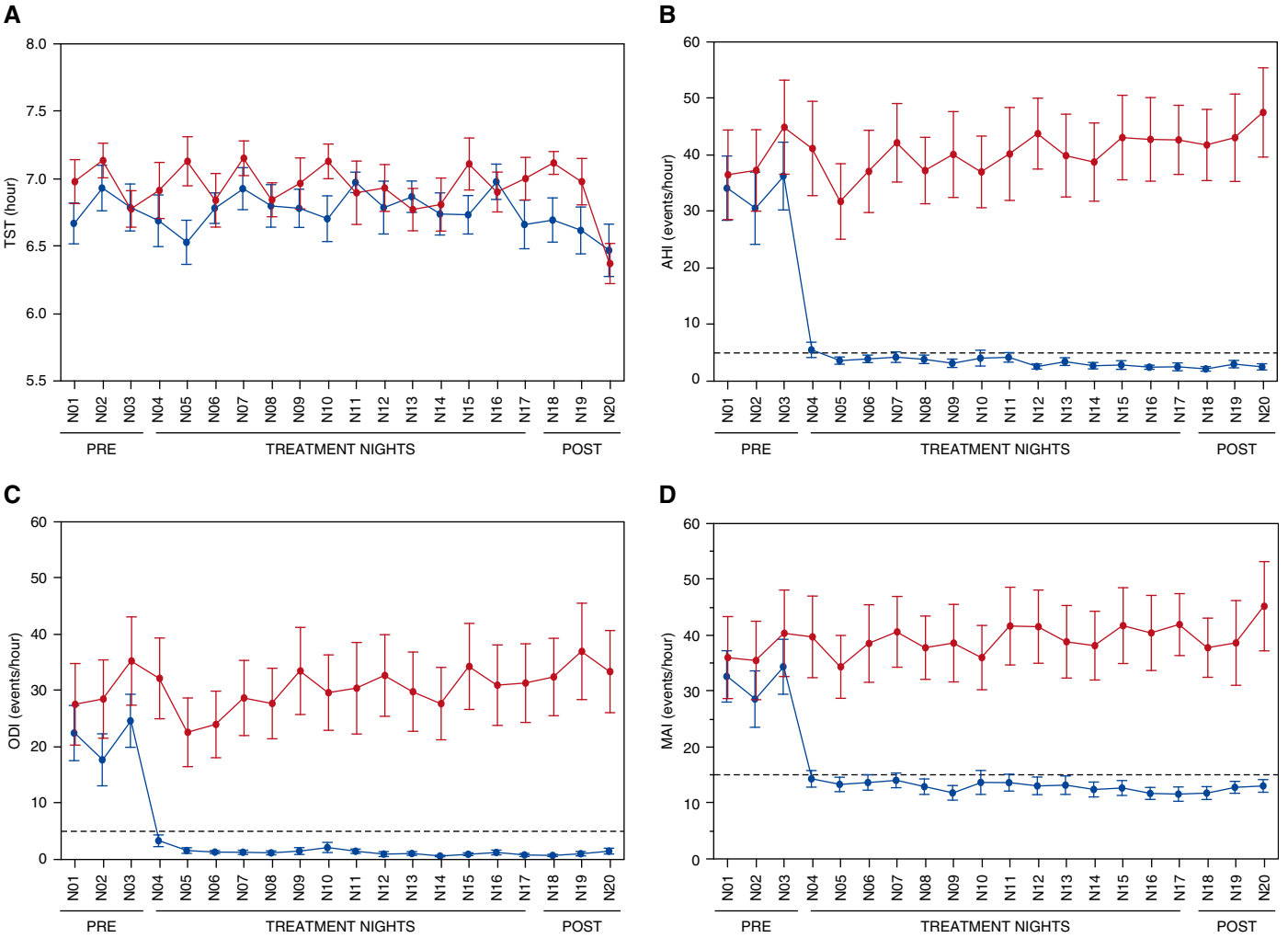

Figure 3. Night-by-night polysomnographic data. Average nightly total sleep time (TST; *A*), apnea–hypopnea index (AHI; *B*), 3% oxygen desaturation index (ODI; *C*), and microarousal index (MAI; *D*) for participants in the oral placebo group (*red lines*) and in the continuous positive airway pressure group (*blue lines*) are shown. PRE denotes the three nights recorded during baseline testing period (N01, N02, and N03), and POST denotes the three consecutive nights recorded after treatment during post-treatment testing period (N18, N19, and N20). Participants continued their assigned treatment during the post-treatment testing period. Data are shown in a total of n = 33 participants (excluding three in the continuous positive airway pressure group who withdrew for personal reasons and two who had continuous positive airway pressure intolerance during treatment period). *Error bars* represent SEM. *Dashed lines* indicate AHI = 5, ODI = 5, and MAI = 15 events per hour.

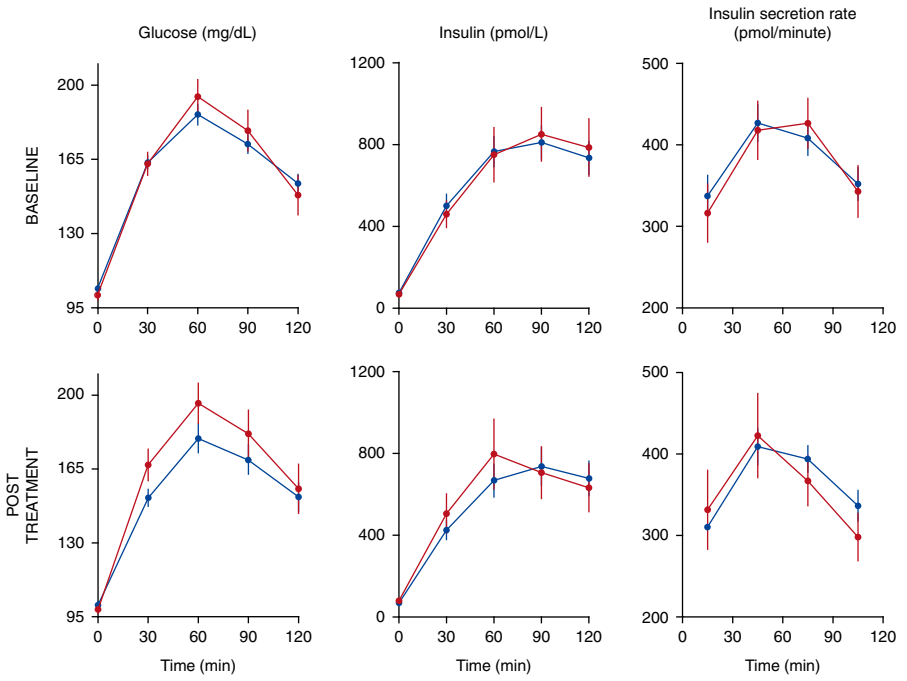

Figure 4. Mean profiles of glucose (*left*), insulin (*middle*), and insulin secretion rate (*right*) during the oral glucose tolerance test for participants in the oral placebo group (*red lines*) and in the continuous positive airway pressure group (*blue lines*). *Error bars* represent SEM.

did not differ significantly between the groups.

Norepinephrine levels were markedly lower after CPAP treatment as compared with the change with placebo (treatment difference, −111.4; 95% confidence interval, −175.5 to −47.4; $P = 0.001$) (Figure 5). There were no significant correlations between the magnitude of change in catecholamine levels and the magnitude of change in insulin sensitivity ($P = 0.76$) or the magnitude of change in AUC_{glu} ($P = 0.34$). After 2 weeks of treatment, the mean 24-hour, daytime and nighttime systolic and diastolic blood pressure were significantly reduced in the group receiving CPAP compared with the change in the placebo group (Table 4). Changes in daytime activity levels measured by continuous wrist actigraphy monitoring ($P = 0.68$) and self-reported food intake assessed by daily meal logs ($P = 0.66$) were not different between the groups. Additionally, in a mixed-effects (random slope and intercept) regression model with treatment group, day, and the group-by-day interaction, the interaction was not statistically significant for activity levels ($P = 0.55$) and food intake ($P = 0.51$), further indicating that the change over time in activity or food intake did not vary significantly between treatment groups.

Overall, the effect of treatment on outcomes for CPAP versus oral placebo groups using unadjusted models yielded similar findings (*see* Table E1 in the online supplement). In cases of nonnormality, the use of square root or log transformation did not change the findings. Sensitivity analyses using fixed imputation for missing values (data not shown) and using only participants who had data at both baseline and post-treatment also resulted in similar findings (*see* Table E2).

Discussion

We demonstrated that 8 hours of nightly CPAP treatment of OSA for 2 weeks reduces the overall glucose response during the OGTT and improves insulin sensitivity in individuals with prediabetes. Additionally, CPAP treatment reduced norepinephrine levels and 24-hour systolic and diastolic blood pressure as compared with placebo. To our knowledge, this is the first trial to investigate the effects of 8 hours of nightly CPAP treatment. In this proof-of-concept study, all-night CPAP use was ensured by continuous supervision in the laboratory with simultaneous 8-hour sleep recordings. Our findings suggest that CPAP treatment, if used for 8 hours per night, may provide cardiometabolic benefits patients with prediabetes, a potentially reversible state in which the development of overt diabetes and its cardiovascular complications could be prevented or delayed.

In our study, CPAP treatment resulted in reduced glucose levels without changes in insulin levels or insulin secretion during the OGTT, suggesting improved insulin sensitivity. Consistent with the OGTT findings, we also demonstrated a significant improvement in insulin sensitivity assessed by the ivGTT. In a prior randomized controlled trial in patients with prediabetes, no significant improvement overall was observed in glucose tolerance or insulin sensitivity indices derived from the OGTT after 2 months of CPAP treatment averaging approximately 4.6 hours per night (29). However, each hour of CPAP use led to a significant improvement in insulin sensitivity from baseline, suggesting a dose–response relationship. In our participants with prediabetes, we observed a significant metabolic benefit when CPAP was applied for 8 hours per night for 2 weeks.

Another randomized controlled CPAP trial in men with no diabetes showed no improvement in glucose and insulin indices derived from OGTT after 12 weeks of CPAP, but CPAP adherence was again low averaging approximately 3.6 hours per night (21). In a recent randomized controlled trial, 24 weeks of CPAP treatment alone (on average ~4 h per night) did not improve insulin sensitivity as assessed by ivGTT (27). Previous randomized controlled trials have found no benefit of CPAP treatment on measures of glucose metabolism when the duration of average CPAP use ranged from 3.3 to 6.2 hours per night (20–28). In one controlled study involving individuals with prediabetes, 2 months of CPAP use (on average ~4.8 h per night) led to an improvement in insulin sensitivity only in those who had severe OSA (29). Additionally, sleepy patients had larger improvements in insulin sensitivity as compared with nonsleepy patients (29).

These findings suggest that subgroups of OSA patients may derive some metabolic benefits even though the CPAP use is limited. In another controlled study, 1 week of higher CPAP adherence (~6.2 h per night) improved insulin sensitivity

Table 3. Effect of Treatment on Measures of Glucose Metabolism for CPAP versus Oral Placebo Groups*

	CPAP Group (*n* = 26)		Oral Placebo Group (*n* = 12)			
	Baseline	Change after 2 Weeks	Baseline	Change after 2 Weeks	Treatment Difference	*P* Value†
Fasting glucose, mg/dl	104.1 (100.7 to 107.5)	−4.1 (−7.2 to −1.0)	100.9 (95.8 to 105.9)	−1.3 (−5.6 to 3.1)	−2.8 (−8.1 to 2.5)	0.30
Fasting insulin, pmol/L	73.6 (60.0 to 87.3)	−5.7 (−16.5 to 5.1)	69.7 (49.4 to 90.0)	13.0 (−2.1 to 28.1)	−18.7 (−37.3 to −0.1)	0.05
2-h glucose, mg/dl	153.4 (141.2 to 165.7)	−3.8 (−12.4 to 4.8)	147.9 (129.7 to 166.2)	10.2 (−1.7 to 22.1)	−14.0 (−28.7 to 0.6)	0.06
2-h insulin, pmol/L	766.8 (603.9 to 929.7)	−73.2 (−192.7 to 46.4)	728.0 (485.9 to 970.0)	−118.6 (−284.7 to 47.5)	45.5 (−159.1 to 250.1)	0.66
$AUC_{glucose}$, (mg/dL) · min	19,564.9 (18,548.3 to 20,581.5)	−794.2 (−1,446.4 to −142.0)	19,723.4 (18,212.2 to 21,234.6)	482.7 (−422.2 to 1,387.7)	−1,276.9 (−2,392.4 to −161.5)	0.03
$AUC_{insulin}$, (pmol/L) · min	77,158.4 (62,515.6 to 91,801.2)	−9,506.9 (−19,161.9 to 148.0)	70,252.0 (48,486.6 to 92,017.4)	−2,228.9 (−15,628.3 to 11,170.5)	−7,278.1 (−23,792.9 to 9,236.7)	0.39
$AUC_{insulin\ secretion}$, pmol/min	35,773.1 (32,266.5 to 39,279.7)	−1,915.3 (−4,006.0 to 175.4)	34,954.3 (29,741.3 to 40,167.4)	−2,318.5 (−5,217.6 to 580.6)	403.2 (−3,171.0 to 3,977.4)	0.83
S_I, $(mU/L)^{-1} \cdot min^{-1}$	2.3 (1.9 to 2.7)	0.31 (−0.11 to 0.74)	2.8 (2.2 to 3.4)	−0.46 (−1.07 to 0.15)	0.77 (0.03 to 1.52)	0.04
AIRg, (mU/L) · min	445.7 (342.3 to 549.1)	26.2 (−35.1 to 87.5)	282.7 (129.2 to 436.2)	99.7 (10.6 to 188.8)	−73.5 (−181.6 to 34.7)	0.18

Definition of abbreviations: AIRg = acute insulin response to glucose; $AUC_{glucose}$ = area under the glucose curve during oral glucose tolerance test (OGTT); $AUC_{insulin}$ = area under the insulin curve during OGTT; $AUC_{insulin\ secretion}$ = area under the curve of the insulin secretion rate; CPAP = continuous positive airway pressure; S_I = insulin sensitivity.
Data are mean (95% confidence interval). Change after 2 weeks (i.e., treatment effect) was calculated from the regression models as the post-treatment – baseline effect for each treatment group. Treatment difference between the two groups was also calculated from the regression models as the CPAP − oral placebo 2-week changes (i.e., the interaction effect from the model). *P* values for the treatment difference are from the test of the treatment group–by-time interaction using linear mixed model approach. AUC was calculated according to the trapezoidal rule between the 0 and 120 minutes during the OGTT.
*All available data were used in the primary analysis (*see* online supplement for further details). Data are from n = 25 in CPAP and n = 12 in oral placebo for S_I and AIRg.
†Analyses were adjusted for age, body mass index, and ethnicity-based diabetes risk.

Table 4. Effect of Treatment on 24-Hour Blood Pressure for CPAP versus Oral Placebo Groups*

	CPAP Group (*n* = 22)		Oral Placebo Group (*n* = 10)			
	Baseline	Change after 2 Weeks	Baseline	Change after 2 Weeks	Treatment Difference	*P* Value†
24-h SBP, mm Hg	135.2 (129.4 to 140.9)	−1.9 (−6.2 to 2.3)	130.8 (122.2 to 139.4)	7.6 (1.9 to 13.3)	−9.5 (−16.6 to −2.4)	0.009
Daytime SBP, mm Hg	141.2 (135.4 to 147.0)	−3.8 (−8.1 to 0.5)	136.2 (127.5 to 144.8)	5.9 (0.2 to 11.6)	−9.7 (−16.8 to −2.5)	0.008
Nighttime SBP, mm Hg	122.2 (115.3 to 129.1)	1.7 (−4.3 to 7.7)	117.0 (106.7 to 127.4)	12.4 (4.4 to 20.4)	−10.8 (−20.7 to −0.8)	0.04
24-h DBP, mm Hg	79.3 (76.2 to 82.4)	−2.6 (−4.9 to −0.3)	75.6 (71.0 to 80.2)	4.5 (1.4 to 7.5)	−7.1 (−10.9 to −3.2)	<0.001
Daytime DBP, mm Hg	84.7 (81.3 to 88.1)	−4.7 (−7.3 to −2.1)	79.4 (74.4 to 84.4)	3.5 (0.04 to 7.0)	−8.2 (−12.5 to −3.9)	<0.001
Nighttime DBP, mm Hg	68.1 (64.6 to 71.6)	1.6 (−1.6 to 4.7)	65.7 (60.4 to 71.0)	7.7 (3.4 to 11.9)	−6.1 (−11.4 to −0.8)	0.02

Definition of abbreviations: CPAP = continuous positive airway pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.
Data are mean (95% confidence interval). Change after 2 weeks (i.e., treatment effect) was calculated from the regression models as the post-treatment – baseline effect for each treatment group. Treatment difference between the two groups was also calculated from the regression models as the CPAP − oral placebo 2-week changes (i.e., the interaction effect from the model). *P* values for the treatment difference are from the test of the treatment group–by-time interaction using linear mixed model approach.
*All available data were used in the primary analysis (*see* online supplement for further details). The blood pressure data were missing both at baseline and post-treatment in a total of n = 6 participants (n = 4 in the CPAP group and n = 2 in the oral placebo group).
†Analyses were adjusted for age, body mass index, and ethnicity-based diabetes risk.

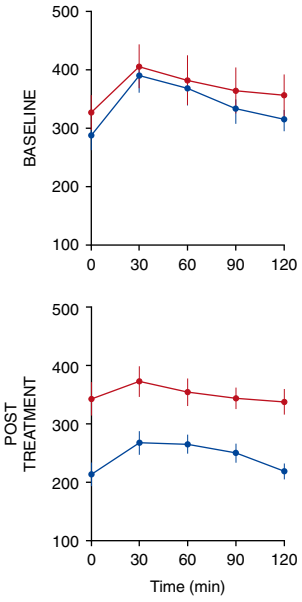

Figure 5. Mean profiles of norepinephrine measured during the oral glucose tolerance test for participants in the oral placebo group (*red lines*) and in the continuous positive airway pressure group (*blue lines*) are shown. *Error bars* represent SEM.

estimated by the short insulin tolerance test in Asian men with no diabetes (30). In our study, the participants used CPAP continuously (except for rare bathroom breaks) in the laboratory during the entire duration of the time in bed (i.e., from 11:00 P.M. to 7:00 A.M.), which is comparable with approximately 8 hours of nightly objective CPAP adherence downloaded from devices in a clinical setting.

Our finding that CPAP treatment reduces systolic and diastolic blood pressure as compared with placebo is consistent with prior randomized trials showing beneficial effects of CPAP on blood pressure in OSA patients (25, 28, 39–42). Most of our participants (~80%) were not hypertensive at baseline. Although the average decrease in blood pressure seems to be larger in our study as compared with the treatment effect in prior trials (28, 39–42), it has been reported that the effectiveness of CPAP in reducing blood pressure increases with higher adherence to treatment (28, 41–43). Within the CPAP group, we observed significant decreases in 24-hour and daytime diastolic blood pressure, whereas the nighttime systolic and diastolic blood pressure seemed to be higher after treatment, although these nighttime changes did not reach statistical significance. One potential explanation could be that the use of the blood pressure cuff itself may result in appreciable arousal from sleep and therefore alter the blood pressure readings at night. It is also possible that our intermittent blood pressure measurements at night (every 20 min) were not sufficient to capture the more rapid blood pressure changes that occur transiently after each obstructive respiratory event. Finally, unmeasured factors (e.g., diet with salt intake, stressful events) over the 2-week period may also have influenced the blood pressure findings.

We have found that CPAP treatment decreased norepinephrine levels, which is in agreement with prior reports (25, 44–47). The magnitude of decrease in norepinephrine levels after CPAP treatment was approximately 27% in our study, which is similar to the 26% reduction observed in earlier studies (47, 48). We did not find significant correlations between the magnitude of change in norepinephrine levels and the magnitude of changes in glucose metabolism. However, our finding of concomitantly lower overall norepinephrine levels and improved glucose levels suggests that a reduction in sympathetic activity could be a potential mediator of metabolic benefit from CPAP.

Although oral placebo has been used as a control group in several randomized controlled CPAP trials (49–55), an alternative, commonly used approach is sham-CPAP, a specially designed CPAP device with minimal and clinically ineffective airway pressure. We chose to use oral placebo rather than sham-CPAP in the control group for several reasons. First, because air pressure is the mechanism of action of CPAP, sham devices may feel different due to a markedly lower mask air pressure compared with the therapeutic device, which may adversely affect its tolerability and acceptance by patients. Indeed, several studies investigating the effects of CPAP on glucose metabolism have reported lower average duration of sham-CPAP adherence as compared with therapeutic CPAP (20, 21, 29, 30). A large randomized controlled multicenter trial (56), comparing the effects of therapeutic versus sham-CPAP, reported significantly lower adherence to sham-CPAP and a lower retention rate in the sham-CPAP group. Another large randomized controlled multicenter trial (57) also reported lower duration of sham-CPAP use as compared with active CPAP.

Second, in the study by Kushida and colleagues (56), about two-thirds of sham participants correctly guessed their treatment assignment, which raises the possibility of unblinding when sham-CPAP is used. In a recent randomized crossover trial of active versus sham-CPAP (58), when the patients were asked about their treatment experience before unblinding, most were able to identify the active CPAP as the more effective treatment. The authors (58) also concluded that investigator blinding is unlikely to be achieved in such trials with sham-CPAP. Finally, there is some evidence to suggest that sleep quality may worsen to a small degree by sham-CPAP (59). For all these reasons, we believed that oral placebo was an acceptable choice as a control group in our trial.

A major strength of our study is the unique and rigorous design to achieve 8-hour nightly CPAP compliance during the 2-week intervention period. Other strengths include the focus on a high-risk population with prediabetes and a comprehensive assessment of glucose metabolism using both OGTT and ivGTT, which provide dynamic and complementary information on metabolic pathways.

Our study also has several limitations. This was a study in a small number of individuals with prediabetes with selective eligibility criteria, which may limit the generalizability to more diverse populations. The investigators were unblinded to treatment allocation because of the use of oral placebo in the control group. The secondary outcomes should be considered exploratory and the borderline significant effects of CPAP observed with these outcomes not definitive. In this proof of concept study, the CPAP treatment was limited to 2 weeks, and thus the study does not provide information on the potential effects of CPAP on glucose metabolism over a longer period of time. Importantly, in our study, CPAP was applied in the laboratory under continuous supervision, but 8-hour nightly CPAP use may be difficult to achieve in real-life conditions. Thus, our findings should be interpreted with caution, particularly in regards to CPAP recommendations to patients in clinical settings. Our participants were treated with CPAP for 8 hours on a nightly basis, and thus the study cannot determine a specific

adherence threshold for beneficial effects on glucose metabolism. Similarly, the required dose of CPAP to observe a specific effect may be difficult to determine and may vary according to the outcome of interest.

One can argue that the apparent worsening in cardiometabolic parameters in the placebo group may have inflated the treatment effect in our study. However, in randomized trials, it is strongly recommended to perform a direct comparison between the groups rather than separate tests against baseline within the groups because such separate tests could be highly misleading (60). Nevertheless, because our participants continued their daily life under free-living conditions, additional environmental factors (unmeasured in our study) may have affected our findings. Although we did not find significant differences between the CPAP and oral placebo groups for daytime activity levels and self-reported food intake, we cannot exclude the possibility that changes in energy metabolism contributed to our findings.

In conclusion, we have demonstrated that all-night CPAP adherence (~8 h per night) for 2 weeks in the laboratory is beneficial for glucose metabolism in individuals with prediabetes and OSA. Future large-scale clinical trials in real-life settings, perhaps combining CPAP with lifestyle changes, are needed to determine the exact role of CPAP treatment of OSA in the management of prediabetes. Our data also provide some incentive to improve CPAP adherence in individuals with prediabetes for cardiometabolic risk reduction. ■

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