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BRIEF COMMUNICATION

Optimal Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea Reduces Daytime Resting Heart Rate in Prediabetes: A Randomized Controlled Study

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BACKGROUND: It has been widely recognized that obstructive sleep apnea (OSA) is linked to cardiovascular disease. Yet, randomized controlled studies failed to demonstrate a clear cardiovascular benefit from OSA treatment, mainly because of poor adherence to continuous positive airway pressure (CPAP). To date, no prior study has assessed the effect of CPAP treatment on daytime resting heart rate, a strong predictor of adverse cardiovascular outcomes and mortality.

METHODS AND RESULTS: We conducted a randomized controlled study in 39 participants with OSA and prediabetes, who received either in-laboratory all-night (ie, optimal) CPAP or an oral placebo for 2 weeks. During daytime, participants continued daily activities outside the laboratory. Resting heart rate was continuously assessed over 19 consecutive days and nights using an ambulatory device consisting of a single-lead ECG and triaxis accelerometer. Compared with placebo, CPAP reduced daytime resting heart rate (treatment difference, −4.1 beats/min; 95% CI, −6.5 to −1.7 beats/min; P=0.002). The magnitude of reduction in daytime resting heart rate after treatment significantly correlated with the magnitude of decrease in plasma norepinephrine, a marker of sympathetic activity (r=0.44; P=0.02), and the magnitude of decrease in OSA severity (ie, apnea-hypopnea index [r=0.48; P=0.005], oxygen desaturation index [r=0.50; P=0.003], and microarousal index [r=0.57; P<0.001]).

CONCLUSIONS: This proof-of-concept randomized controlled study demonstrates, for the first time, that CPAP treatment, when optimally used at night, reduces resting heart rate during the day, and therefore has positive cardiovascular carry over effects. These findings suggest that better identification and treatment of OSA may have important clinical implications for cardiovascular disease prevention.

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Key Words: cardiovascular ■ continuous positive airway pressure adherence ■ resting heart rate ■ sleep apnea

Resting heart rate is a readily accessible clinical measure and prognostic marker of cardiovascular health. Large, prospective, epidemiologic studies indicate that a higher resting heart rate is an independent predictor of cardiovascular and all-cause mortality.[1]

Obstructive sleep apnea (OSA) is a highly common and often overlooked sleep disorder in the general population.[2] Numerous epidemiologic and clinical studies have indicated that OSA is strongly associated with cardiovascular disease and mortality.[3]

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In addition, detailed clinical studies have revealed that untreated OSA increases sympathetic activity,[4] which is a key trigger for provoking adverse cardiovascular events. Despite such a strong association between OSA and cardiovascular disease, randomized controlled studies failed to demonstrate a clear cardiovascular benefit from OSA treatment, mainly because of poor adherence to continuous positive airway pressure (CPAP).[5] Essentially, rigorous studies investigating the effect of optimal CPAP treatment on cardiovascular outcomes are lacking. To date, no prior study has assessed the effect of CPAP treatment on daytime resting heart rate.

We conducted a randomized controlled study in patients with OSA and prediabetes, who received either in-laboratory all-night (ie, optimal) CPAP or an oral placebo for 2 weeks.[6] From this proof-of-concept randomized controlled study, we have previously reported that all-night CPAP improves glucose metabolism and 24-hour blood pressure, and reduces plasma norepinephrine, a marker of sympathetic activity.[6] Using data collected in this previous study, herein we examined the effect of all-night CPAP treatment of OSA on daytime resting heart rate.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Participants

This was a secondary analysis of a randomized, placebo-controlled study that investigated the effects of all-night CPAP treatment on cardiometabolic outcomes in overweight or obese (body mass index ≥25 kg/m^2) patients, aged ≥45 years, with prediabetes and OSA. Details of the study sample, eligibility criteria, and protocol design have been described previously.[6] Participants were randomly assigned (2:1 ratio) to receive either 2 weeks of all-night CPAP treatment or oral placebo every night in a laboratory setting. Block randomization was performed using computer-generated random numbers. Randomization assignments were prepared by a statistician in opaque, sealed envelopes. During the daytime, participants continued their daily routine activities outside and returned to the laboratory at night to receive their assigned treatment. CPAP treatment was applied at optimal therapeutic settings (determined from in-laboratory CPAP titration), and all-night adherence was ensured by continuous supervision.[6] Participants assigned to the oral placebo group were given a placebo capsule 30 minutes before bedtime and were told that it was intended to improve upper airway function and OSA. The choice of an oral placebo as a control has been discussed elsewhere.[6] Both groups spent each night in the laboratory with enforced 8-hour bedtimes (from 11 PM to 7 AM), while sleep was recorded by attended polysomnography. The study was approved by the University of Chicago Institutional Review Board, and all participants provided informed consent.

A small, lightweight, and waterproof device (Actiwave Cardio, CamNtech, UK) consisting of a single-lead ECG channel (sampled at 128 Hz) and a triaxis accelerometer (sampled at 32 Hz) was used to monitor heart rate, physical activity, and posture throughout the entire study period (ie, 19 consecutive days and nights). Participants wore this device on their chest using 2 disposable ECG electrodes, which was replaced with a fully charged unit every 24 hours.

Heart Rate Analysis

The ECG and accelerometer recordings from each 24-hour period were exported as EDF files, and processed using PRANA software (PhiTools, Strasbourg, France). The data processing included analyses of motion and posture using triaxis accelerometer signals from actigraphy,[7] and heart rate analyses from the ECG signal. Active (ie, nonsedentary) periods were excluded from analyses to account for the influence of intensity of physical activity on heart rate. Thus, daytime data included only rest periods (ie, sedentary periods), and nighttime data included only sleep periods. An automated artifact detection was performed on ECG signal, band pass filtered between 5 and 45 Hz, and scanned using automated artifact detection algorithms. Any residual artifacts were removed by visual inspection, as necessary. Artifact-free ECG signals were then processed to obtain beat-to-beat (ie, R-R) intervals. All ectopic beats and arrhythmias were excluded, and aberrant beats were corrected using cubic spline interpolation.[8] The heart rate analyses of the R-R intervals were performed using a 5-minute moving window with 30-second interval to match the visual sleep-wake stage scoring. A composite quality index based on the percentage of segments with aberrant beats or artifacts was calculated for all 5-minute windows, and those with a quality index ≤50% were excluded.[9]

There were 602 nighttime recordings and 572 daytime recordings included in the final analyses after considering missing or technically uninterpretable recordings, as well as excluding any recording with a quality index ≤50% or a recording duration ≤120 minutes. Daytime data in the CPAP group are reported in n=25 subjects as 1 individual had invalid data on 3 baseline days. The duration of daytime recordings during rest periods was similar between CPAP and placebo groups at baseline (575.0±84.9 versus 498.0±109.5 minutes) and did not significantly change with treatment. The mean percentage of time spent at rest during the entire daytime recording was 54±9% compared with 48±8% in the CPAP versus placebo groups.

Statistical Analysis

Linear mixed effects models were used to determine the treatment differences between the CPAP and placebo groups. These models included random effect for participant; treatment group, day of treatment (as a categorical variable), and treatment group by day interaction; and baseline value (average of days 1–3), baseline OSA severity (ie, apnea-hypopnea index [AHI]), age, and sex as covariates. These covariates were selected on the basis of their known influence on resting heart rate.[10] In addition, covariate adjustment offers the potential for more precise estimates of the treatment effect. To confirm the robustness of primary findings, mixed models simply adjusted for baseline values were also fit. These models included postbaseline values as outcomes and were fit with residual maximum likelihood and small sample adjustment made using the Kenward-Roger method. The treatment difference (95% CI) was calculated as the average of the CPAP–oral placebo contrasts over the corresponding treatment days. From the same model, the change during treatment was calculated for each group as the average change from the first day of treatment. A Spearman rank correlation coefficient was calculated to assess the relationships between the changes (from baseline) in heart rate and the changes (from baseline) in OSA indexes (ie, AHI, oxygen desaturation index, and microarousal index), as well as daytime plasma norepinephrine levels.[6] The changes in outcomes for each subject were calculated by subtracting the corresponding baseline value from the average of all postbaseline values. A $P<0.05$ was considered statistically significant. Statistical analyses were performed using Stata version 15.

RESULTS

Study Participants

A total of 39 participants with OSA and prediabetes were randomized (Figure 1).[6] 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. Of the entire randomized sample, approximately two thirds were men, 72% were obese, 82% had moderate-to-severe OSA, and 46% reported excessive daytime sleepiness. Baseline characteristics of the participants did not differ significantly between groups, with the exception of lower physical activity in the CPAP group (Table).

Polysomnographic Data

The total sleep time between CPAP and placebo groups was similar at baseline (6.7 versus 6.9 hours) and did not change after treatment. In the CPAP group, the mean duration of CPAP use was approximately 8 hours per night, as participants wore the CPAP mask all night, except for rare bathroom breaks.[6] Over the

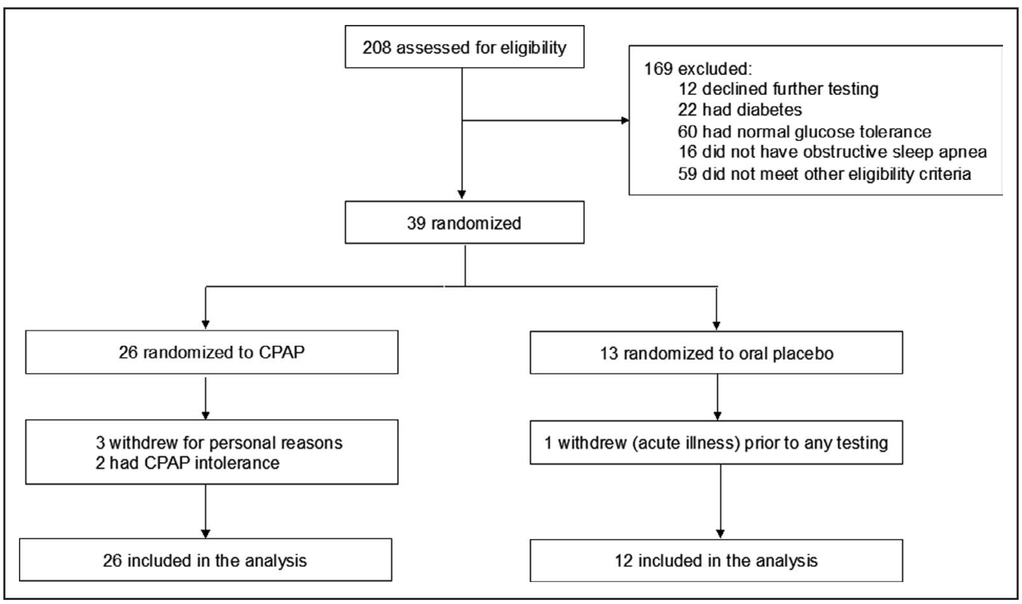

Figure 1. Participant flow diagram.
CPAP indicates continuous positive airway pressure.

entire treatment period, CPAP group compared with placebo had significantly lower mean residual AHI (event/hour; 3.3±2.3 versus 39.3±21.6; *P*<0.001), lower mean residual oxygen desaturation index (event/hour; 1.2±1.4 versus 29.5±22.3; *P*<0.001), and lower mean residual microarousal index (event/hour; 12.8±5.2 versus 38.6±20.1; *P*<0.001).

Resting Heart Rate Data

Mean profiles of resting heart rate at baseline (days 1–3) and over the entire treatment period (days 4–19) in the CPAP and placebo groups are shown in Figure 2. CPAP compared with placebo significantly reduced the daytime resting mean heart rate (treatment difference, −4.1 beats/min; 95% CI, −6.5 to −1.7 beats/min; *P*=0.002) in addition to sleeping mean heart rate (treatment difference, −4.2 beats/min; 95% CI, −6.4 to −2.0 beats/min; *P*<0.001). Similar treatment effects were observed during nonrapid eye movement sleep and rapid eye movement sleep. Over treatment days, the change in daytime resting mean heart rate was −4.2 beats/min (95% CI, −6.2 to −2.2 beats/min) in the CPAP group versus 0.9 beats/min (95% CI, −2.0 to 3.7 beats/min) in the placebo group. The treatment effect on daytime resting mean heart rate was of greater magnitude during the second half of treatment (days 12–19; treatment difference, −4.7 beats/min; 95% CI, −7.3 to −2.2 beats/min; *P*=0.001) compared with first half (days 4–11; treatment difference, −3.4 beats/min; 95% CI, −5.9 to −0.9 beats/min; *P*=0.01; Figure 2). Findings were similar when daytime resting maximum (or minimum) heart rate was considered.

We have previously reported that daytime plasma norepinephrine levels, a marker of sympathetic activity, were markedly lower after CPAP treatment compared with placebo.[6] In the current analysis, the magnitude of reduction in daytime resting heart rate after treatment correlated with the magnitude of reduction in plasma norepinephrine levels (*r*=0.44; *P*=0.02). In addition, the magnitude of reduction in daytime resting heart rate after treatment correlated with the magnitude of decrease in OSA indexes (ie, AHI [*r*=0.48; *P*=0.005], oxygen desaturation index [*r*=0.50; *P*=0.003], and microarousal index [*r*=0.57; *P*<0.001]).

DISCUSSION

To our knowledge, this is the first study investigating the effects of CPAP treatment of OSA on daytime resting heart rate. Using a proof-of-concept randomized controlled trial design, we demonstrated that CPAP treatment, when optimally used at night, reduces resting heart rate during the day in patients with OSA, and thus has significant positive carryover effects on cardiovascular health. These findings have substantial clinical implications for cardiovascular disease prevention, particularly in high-risk populations. Furthermore, given the negative findings in prior CPAP trials on cardiovascular outcomes,[5] our rigorous study design with optimal CPAP adherence provides strong rationale for recommending longer duration of CPAP use than the currently advised adherence target of 4 hours per night, to achieve clinically significant cardiovascular benefit.

We observed an average of 4.1-beat/min decrease in daytime resting heart rate over 2-week CPAP treatment compared with placebo. In addition, the magnitude all-night CPAP effect was larger during the second half of treatment, suggesting cumulative cardiovascular benefits of optimal therapy over time. Our effect sizes are comparable to, if not exceeding, that of exercise-induced decreases in resting heart rate in healthy subjects.[11] Our findings may also have important implications for reducing mortality if regular and optimal CPAP use can be achieved over long-term. Indeed, strong epidemiologic evidence indicates that higher resting heart rate is an independent predictor of cardiovascular and all-cause mortality, even in people

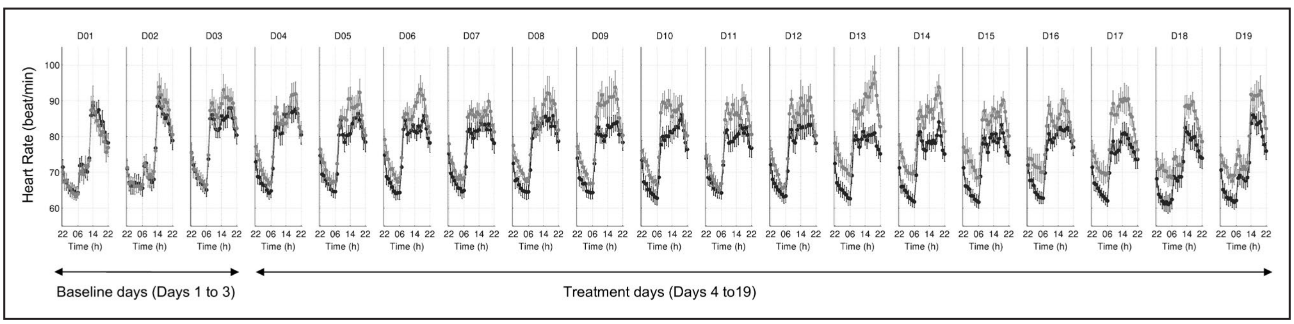

Figure 2. Resting heart rate profiles.
Hourly average profiles of resting heart rate (beats/min) during the entire study period (ie, 19 consecutive days). Time (*x* axis) represents 24-hour clock time. Data are mean±SEM. Bedtimes in the sleep laboratory were from 11 PM to 7 AM. Participants continued their daily routine activities outside the sleep laboratory during the daytime and returned to the laboratory each night. D01 to D03 indicates baseline days 1 to 3; and D04 to D19, treatment days 4 to 19.

without significant cardiac disease.[1] In a middle-aged population cohort, every 1-beat/min increase in resting heart rate was associated with 3% higher mortality.[12]

Our study is the first to assess the effect of CPAP treatment on daytime resting heart rate. One prior study found that the average heart rate during daily activities (not measured at rest) was reduced after 1 month of CPAP treatment.[13] Heart rate is primarily modulated by the opposing autonomic influences of parasympathetic activity, which slows heart rate, and sympathetic activity, which accelerates it. Under normal resting conditions, parasympathetic activity predominates. Previous studies have proposed sympathetic overactivity as a key mechanism for driving increased cardiovascular risk with higher resting heart rate.[1,14] Sympathetic (adrenergic) overactivity has been shown in experimental studies of intermittent hypoxia[15–18] and has been recognized as a key mediator of adverse cardiovascular consequences in OSA.[3] Seminal studies using microneurography recordings have demonstrated that sympathetic overactivity in OSA, elicited by breathing events during sleep, persists into daytime, which subsequently reduces with CPAP treatment in short- and long-term.[4,19] We found that the CPAP-induced decrease in daytime resting heart rate correlated with the decrease in daytime norepinephrine levels,[6] a marker for sympathetic activity. Furthermore, CPAP-induced reduction in resting heart rate was more pronounced in patients who showed greater reductions in markers of OSA severity, as reflected by positive correlations between changes in daytime heart rate and apnea-hypopnea events, intermittent hypoxia, and sleep fragmentation, all of which can increase sympathetic activity.[3] These findings suggest that beneficial effects of CPAP on daytime resting heart rate may be mediated, at least in part, by a decrease in sympathetic output carrying over into the daytime.

Several studies have shown an association between the presence and severity of OSA and altered heart rate variability,[20] a predictor of cardiovascular risk and mortality.[21–24] Some, but not all, studies have reported favorable effects of CPAP treatment on indexes of heart rate variability with reductions in both parasympathetic and sympathetic tone during sleep.[25–27] When we have examined heart rate variability as a surrogate marker of autonomic control, CPAP treatment compared with placebo significantly reduced overall heart rate variability (SDNN; SD of normal-to-normal interval index) during sleep, but not during the daytime period (data not shown). This is likely because of correction of abnormal breathing pattern during sleep with CPAP, which is consistent with several prior reports.[28] We found no significant treatment effect on heart rate variability indexes of parasympathetic or sympathetic tone. We postulate that the mechanisms for our CPAP-induced decrease in resting heart rate are likely to be multiple, including autonomic modulation, baroreflex- or chemoreflex-induced cardiac responses, and intrinsic factors, such as sinoatrial node plasticity, which are all operating in different time scales for short- and long-term regulation of heart rate.[29] The underlying molecular and cellular pathways responsible for our findings on heart rate remain to be elucidated.

A major strength is our rigorous study design and continuous ECG and activity monitoring over multiple days in real-life conditions. More important, although the subjects continued their usual daily activities outside the laboratory, we carefully identified daytime rest periods.[7] Thus, our analysis accounted for the influence of physical activity on heart rate. Moreover, sleep was assessed using gold standard in-laboratory polysomnography simultaneous with all-night CPAP administration so that optimal adherence was ensured.[6] Notably, our participants had no history of significant heart disease (eg, coronary artery disease, heart failure, or arrhythmias) or other chronic illness. They were not

Table. Baseline Characteristics of Participants

Characteristic	CPAP Group (n=26)	Oral Placebo Group (n=13)
Age, y	53.8±6.2	55.2±8.4
Men, n (%)	16 (62)	10 (77)
Race/Ethnicity, n (%)		
Black	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
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, n (%)	12 (46)	6 (46)
Apnea-hypopnea index, events/h	34.2±24.5	39.0±22.9
Sleeping heart rate, beats/min[†]	66.4±9.3	67.5±6.0
Daytime resting heart rate, beats/min[‡]	77.6±10.6	81.3±8.5
Physical activity, counts/min[§]	139.5±29.4	151.1±18.7

Data are mean±SD unless otherwise specified. Dyslipidemia was defined by any of the following: medical history, any abnormal lipid value, or antilipid therapy. Hypertension was considered to be present if any of the following were satisfied: history of hypertension, antihypertensive use, or systolic or diastolic blood pressure >140 or >90 mm Hg, respectively. CPAP indicates continuous positive airway pressure.

*n=24 CPAP and n=10 oral placebo, using 1-week wrist actigraphy recordings before baseline.

[†]n=26 CPAP and n=12 oral placebo.

[‡]n=25 CPAP and n=12 oral placebo.

[§]n=25 CPAP and n=11 oral placebo, using daytime triaxis accelerometer data at baseline.

taking prescription medications with the exception of 4 patients who were on antihypertensive and/or lipid-lowering agents (not on β-blockers). Thus, we minimized the confounding effects of poor cardiac or overall health status or pharmacologic treatment on resting heart rate. Finally, our statistical models accounted for the confounding effects of OSA severity (ie, AHI), age, and sex, given their influence on resting heart rate.

Our study also has some limitations. This was a study in a small number of overweight or obese individuals with prediabetes and selective eligibility criteria, including no major history of cardiac disease, which may limit the generalizability to more diverse populations (eg, lean patients with OSA and those with known cardiovascular disease or other comorbidities). Resting heart rate may also depend on exercise habits and physical fitness level. Although we did not have objective assessments of cardiorespiratory fitness, most of our participants did not report engaging in regular exercise. Furthermore, we continuously monitored activity throughout the entire study and found that physical activity levels were similar between CPAP and placebo groups in response to treatment, which is in agreement with prior CPAP studies.[30,31] Resting heart rate appears to be a stronger marker of cardiovascular disease and mortality in men compared with women.[32] Our small sample size did not allow sex-stratified analyses, and thus future studies investigating sex effects on resting heart rate response to CPAP would be warranted.

In this study with a proof-of concept design, the CPAP intervention was limited to 2 weeks. However, we demonstrated clinically meaningful and cumulative effects over the course of treatment, suggesting that if CPAP therapy is used regularly for longer periods, there may be additive cardiovascular benefits.

In conclusion, we have demonstrated that CPAP, when optimally used at night, has important cardiovascular benefits carrying over into the daytime. These findings provide novel insights into the impact of OSA treatment on cardiovascular health. Future large-scale clinical trials in real-life settings are needed to investigate the role of optimal CPAP treatment in diverse patient populations. Our findings also highlight the importance of a better identification and treatment of OSA in at-risk populations, which may have substantial clinical implications for cardiovascular risk reduction.

ARTICLE INFORMATION

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Disclosures

None.

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