

Effect of One Week of 8-Hour Nightly Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea on Glycemic Control in Type 2 Diabetes: A Proof-of-Concept Study

To the Editor:

Obstructive sleep apnea (OSA) is both a risk factor for type 2 diabetes mellitus (T2DM) (1) and an exceptionally frequent comorbidity with an adverse effect on glycemic control (2–4). To date, it remains unclear whether continuous positive airway pressure (CPAP) treatment of OSA can improve glycemic control. Previous studies examining the effect of CPAP treatment on measures of glucose metabolism in individuals with T2DM have yielded conflicting results (5). In two randomized clinical trials, there was no effect of CPAP on hemoglobin A1c (HbA1c) when compared with either sham CPAP (6) or usual care (7). One potential reason for the failure of OSA treatment to improve chronic glycemic control is insufficient CPAP use. Notably, the mean nightly CPAP use in these two randomized controlled trials was 3.6 and 4.3 hours per night (6, 7). We recently reported a significant association between OSA during REM sleep and glycemic control in T2DM (4). Because REM sleep predominates in the early morning hours before typical awakening, the cardiometabolic benefits of CPAP therapy may not be achieved with the typical CPAP use of 3–4 hours per night (4, 8).

To obtain definite evidence regarding the clinical efficacy of CPAP treatment to improve glucose control in T2DM, we designed a proof-of-concept study to test the hypothesis that 1 week of full-night CPAP treatment of OSA in the laboratory, as compared with sham CPAP (placebo), results in improvement in glycemic control as assessed by mean plasma glucose levels from 24-hour blood sampling. Preliminary data from this study have been previously reported in the form of an abstract (9). This study is registered at ClinicalTrials.gov (NCT01136785).

Methods

Adults with T2DM and OSA were recruited at the University of Chicago between November 2009 and September 2014. Subjects were eligible if they were newly diagnosed and as-yet untreated for T2DM or were taking a stable oral antidiabetic regimen for at least the past 3 months. Exclusion criteria were use of insulin, unstable

medical conditions, being a shift worker, and current or past treatment with positive airway pressure or supplemental oxygen for OSA. The protocol was approved by the Institutional Review Board, and all participants gave informed consent.

Nightly bedtime duration in the laboratory was 8 hours, but bedtimes were individually tailored to habitual bedtimes derived from home actigraphy. In-laboratory baseline assessments were conducted over the course of 2 days under strictly controlled dietary conditions and nightly polysomnography. In the afternoon of the second day, blood sampling at 15- to 30-minute intervals for 24 hours was initiated to assess glucose and insulin levels. During the sampling periods, subjects were provided with identical meals served at 09:00 h, 14:00 h, and 19:00 h. Subjects were required to consume each meal within 20 minutes. No other caloric intake was allowed. Subjects were instructed to take their medications at the habitual time. During bedtime hours, the intravenous line was extended to allow blood drawing from an adjacent room.

After baseline assessments, subjects were assigned in a 2:1 ratio to 1 week of either active CPAP or sham CPAP treatment. Before starting treatment, all subjects underwent an overnight in-laboratory CPAP titration (10). The subjects who were assigned to sham CPAP underwent a sham titration night, using a customized CPAP device (11). During the 1-week treatment period, CPAP or sham CPAP adherence for a full 8 hours on each night was achieved by continuous supervision. During the first 5 days of treatment, subjects were allowed to leave the laboratory in the morning but had to return by approximately 20:00 h. In the evening of the fifth day, the subjects were admitted for 2 days to repeat all baseline assessments under the same laboratory conditions.

The primary endpoint was the change in mean 24-hour plasma glucose level after 1 week of active CPAP versus sham CPAP therapy for 8 hours per night. After verifying the distribution of the outcome measure, group differences were tested using two-sided unpaired Student's *t* tests with Welch unequal variances. Data are reported as mean \pm SEM.

Results

In a 2:1 ratio, 22 eligible subjects who had completed baseline assessments underwent 1 week of in-laboratory active CPAP or sham CPAP therapy and completed the post-treatment assessments. Two subjects assigned to the CPAP group and one subject assigned to the sham group were excluded for protocol violations. In two additional subjects, the sham CPAP device was found to have delivered therapeutic CPAP pressure that effectively treated OSA on each of the 7 treatment nights. Data from these two subjects were, therefore, included in the CPAP-treated group. In a per-treatment analysis, 13 subjects were analyzed in the treated group and six subjects were analyzed in the untreated group. Baseline characteristics of the participants who were treated ($n = 13$) versus untreated ($n = 6$) are described in Table 1. Sleep characteristics before and after 1 week of treatment are reported in Table 2. At baseline, there were no differences in polysomnography parameters between the two groups. CPAP treatment was effective every night in the 13 subjects in the CPAP group (i.e., apnea-hypopnea index < 5 events/h). In contrast, there was no significant change in the severity of OSA in the six subjects treated with sham CPAP.

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Table 1. Baseline Characteristics in 13 Treated and 6 Untreated Subjects

Baseline Characteristics	Treated	Untreated	P Value
Age, yr	56.2 ± 3.2	52.3 ± 1.3	0.27
Male	7 (53.8)	2 (33.3)	0.63
Ethnicity			0.63
African-American	6 (46)	4 (67)	
White	4 (31)	2 (33)	
Hispanic	2 (15)	0 (0)	
Pacific Islander	1 (8)	0 (0)	
BMI, kg/m ²	36.8 ± 2.5	40.1 ± 1.9	0.41
Diabetes diagnosis, yr	2.5 ± 1.2	7.3 ± 2.3	0.09*
HbA1c, %	7.3 ± 0.4	7.0 ± 0.3	0.63
Poorly controlled diabetes [†]	7 (54)	2 (33)	0.63
Oral antidiabetic medications, n			0.42
No medication	6	2	
Metformin alone	3	2	
Combination [‡]	4	2	
Hypertension	4 (31)	3 (50)	0.62
Dyslipidemia	4 (31)	3 (50)	0.62
OSA severity			0.33
Mild to moderate	6 (46)	1 (17)	
Severe	7 (54)	5 (83)	
Sleep duration at home measured by actigraphy, h	6.4 ± 0.3	6.2 ± 0.6	0.69

Definition of abbreviations: BMI = body mass index; HbA1c = hemoglobin A1c; OSA = obstructive sleep apnea.

Data are given as mean ± SEM or n (%).

*P value using Mann-Whitney nonparametric test.

[†]Poorly controlled diabetes defined as HbA1c ≥ 7.0%.

[‡]Includes metformin plus either a sulfonylurea or a thiazolidinedione.

There was no difference in CPAP use over 1 week of treatment in the two groups (active CPAP, 7.92 ± 0.08 h/night; sham CPAP, 7.87 ± 0.11 h/night; *P* = 0.32). Weight did not change from baseline to end of treatment period in either group.

The 24-hour mean plasma glucose decreased significantly more after 1 week of active versus sham CPAP treatment (−13.7 ± 3.6 mg/dl vs. −2.9 ± 1.4 mg/dl; *P* = 0.013). This decrease in mean plasma glucose was associated with a trend for lower 24-hour mean insulin levels (−25.8 ± 16.5 pmol/L vs. 28.4 ± 21.6 pmol/L; *P* = 0.071). Improvement in glucose levels was most prominent during the overnight period, resulting in lower morning fasting glucose levels (Table 2). Individual changes in mean 24-hour plasma glucose and serum insulin levels for all participants are illustrated in Figure 1. Importantly, the beneficial effect of CPAP was of larger magnitude in participants with poor glycemic control at baseline.

Discussion

To the best of our knowledge, this is the first rigorous physiologic proof-of-concept study of CPAP treatment of OSA in T2DM that has positive findings with improvement in glycemic control without an increase in serum insulin levels, suggesting that elimination of OSA decreases insulin resistance.

Our rigorous methodology of 24-hour blood sampling, adherence to standardized meals during 24-hour blood sampling, and ensuring CPAP adherence addresses important limitations faced by several prior studies, such as solely relying on fasting measures of glucose and insulin or HbA1c or being limited by low CPAP adherence. Our findings, however, are in line with a recent randomized controlled trial that reported a significant reduction in HbA1c of 0.4% after 6 months of CPAP therapy in patients with suboptimally controlled T2DM at baseline (mean HbA1c, 7.6%). Of note, in this study, the mean adherence to CPAP was 5.2 hours per night (12). In our study, the degree of improvement in plasma glucose after 1 week of effective CPAP therapy is also equivalent to a drop of approximately 0.4–0.5% of HbA1c, an effect size similar to that achieved by oral pharmacologic agents (13). Moreover, because a drop of 1% in HbA1c levels is associated

Table 2. Sleep/Metabolic Measures at Baseline and after Intervention in 13 Treated and 6 Untreated Subjects

Sleep/Metabolic Measures	Baseline		Change from Baseline		P Value*
	Treated	Untreated	Treated	Untreated	
Polysomnography [†]					
Total sleep time, min	367.2 ± 12.9	386.6 ± 16.1	13.4 ± 11.2	22.5 ± 21.4	0.68
Sleep efficiency, %	76.6 ± 2.7	83.3 ± 1.6	2.4 ± 2.4	2.7 ± 2.5	0.95
Rapid eye movement sleep, min	67.1 ± 8.7	64.5 ± 10.4	25.0 ± 6.6	19.6 ± 7.8	0.63
N1 sleep, min	54.1 ± 7.8	68.1 ± 20.0	−25.5 ± 5.5	9.4 ± 10.3	0.04
N2 sleep, min	226.1 ± 10.3	236.0 ± 9.5	6.4 ± 8.2	−9.6 ± 15.2	0.32
Slow wave sleep, min	19.9 ± 8.1	17.9 ± 10.3	7.6 ± 2.8	3.1 ± 3.6	0.37
Apnea–hypopnea index, per hour of sleep	39.7 ± 8.0	52.3 ± 14.2	−35.9 ± 7.4	0.2 ± 4.6	0.006
3% oxygen desaturation index, per hour of sleep	24.4 ± 6.1	37.4 ± 8.1	−21.7 ± 5.6	1.0 ± 7.5	0.03
Sleep time at <90% oxygen saturation, min	63.9 ± 20.5	90.9 ± 22.4	−58.9 ± 19.6	−13.8 ± 18.4	0.17
Arousal index, per hour of sleep	49.5 ± 7.6	57.5 ± 14.9	−24.9 ± 6.1	−0.5 ± 3.6	0.02
Glucose metabolism from 24-h blood sampling ^{††}					
24-h glucose, mg/dl	152.1 ± 8.8	138.4 ± 6.5	−13.7 ± 3.6	−2.9 ± 1.4	0.01
Overnight glucose, mg/dl	135.7 ± 8.7	110.6 ± 6.3	−12.6 ± 4.2	−1.5 ± 2.5	0.04
Daytime glucose, mg/dl	163.1 ± 10.3	135.2 ± 9.6	−13.6 ± 4.1	−4.9 ± 2.5	0.22

Data are given as mean ± SEM.

*P values by two-sided paired *t* test for the change from baseline between the treated and untreated groups.

[†]There were no statistically significant differences between all baseline variables among the two groups.

^{††}Overnight glucose includes values from 23:00 until 09:00 h. Daytime glucose includes values from 09:00 until 23:00 h.

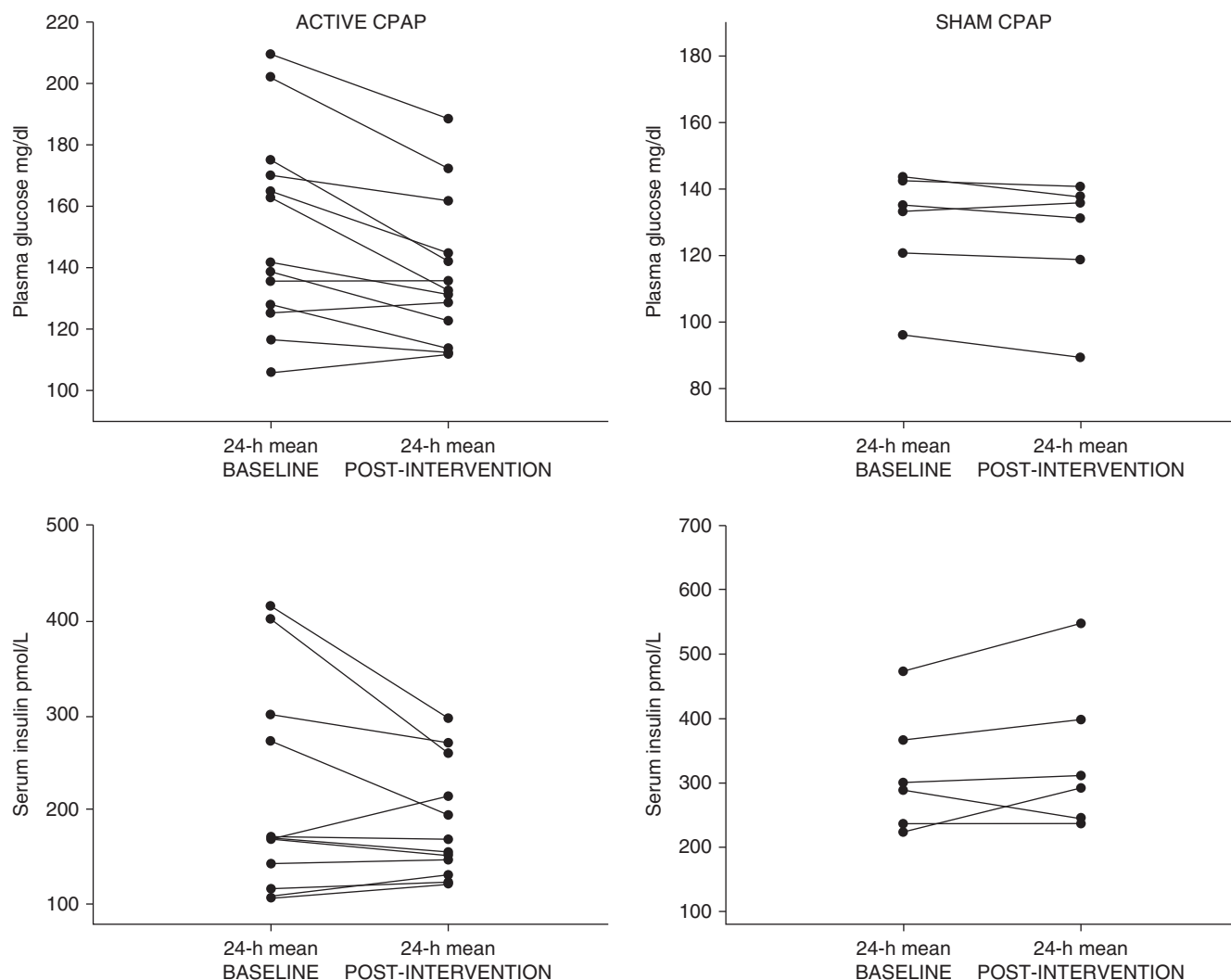


Figure 1. Individual changes in mean 24-hour glucose and serum insulin levels. CPAP = continuous positive airway pressure.

with clinically significant reduction in major macro- and microvascular complications in T2DM, a 0.4% drop in HbA1c achieved by CPAP therapy has clinical relevance in the overall cardiometabolic health of patients with T2DM and comorbid OSA (13).

One limitation of our study is that two subjects assigned to sham CPAP received defective sham devices that delivered therapeutic pressure. However, as polysomnography data were analyzed for every night in the laboratory, there was no ambiguity whatsoever regarding participants receiving active versus inactive treatment. Therefore, we believe a per-treatment analysis for this physiologic proof-of-concept study is appropriate. We performed additional analysis excluding these two participants ($n = 11$ receiving active CPAP vs. $n = 6$ receiving sham CPAP), and the change in 24-hour mean plasma glucose remained larger in the active CPAP group (-12.8 ± 3.5 mg/dl vs. -2.9 ± 4.7 mg/dl; $P = 0.045$).

In conclusion, CPAP treatment of OSA across 7 entire nights results in a clinically significant improvement in glycemic control in T2DM. ■

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Survival after Endobronchial Valve Placement for Emphysema: A 10-Year Follow-up Study

To the Editor:

Bronchoscopic lung volume reduction with endobronchial valves (BLVR) can improve lung function and exercise capacity in appropriately selected patients with emphysema (1–5). Although early data have been encouraging (6), it is not clear whether response to BLVR will translate into sustained survival benefit, as observed after lung volume reduction surgery (LVRS) (7).

Methods

We reviewed the long-term outcome of BLVR in 19 patients with heterogeneous emphysema (Table 1) treated with Emphasys valves, placed to achieve occlusion of a single target lobe, between July 2002 and February 2004 (3, 4, 6). Survival data to November 2015 were compared, using Kaplan-Meier analysis, between those with (n = 5) and those without (n = 14) evidence of atelectasis on thoracic computed tomography scan performed 1 month postprocedure.

Results

In the atelectasis group, two of five patients (40%) were still alive compared with 2 of 14 (14%) of the nonatelectasis group ($P = 0.017$) (Figure 1).

Discussion

These data suggest that successful BLVR may be associated with a substantial, persisting survival benefit similar to that observed after LVRS. The most likely explanation for the occurrence of atelectasis in some, but not other, patients is the absence or presence of collateral ventilation between the target lobe and adjacent lung because of disruption of the interlobar fissures by emphysema. Patients in whom collateral ventilation is thought to be present (either measured directly or assessed using analysis of interlobar fissures on computed tomography scans) are not now recommended for BLVR. A second issue is a technical one around valve placement and airway anatomy. Sometimes it is difficult to achieve a satisfactory seal, and valves may need to have their placement adjusted. Overall, the response rate was similar to that observed in other trials in which patients were not selected on the basis of collateral ventilation (5).

Although it is possible that the difference in survival could be explained by some disparity in the baseline characteristics of the two groups other than collateral ventilation, this seems unlikely. The groups were well matched (Table 1), including for gas transfer, the lung function parameter most strongly associated with survival

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