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Inhibition of Awake Sympathetic Nerve Activity of Heart Failure Patients With Obstructive Sleep Apnea by Nocturnal Continuous Positive Airway Pressure

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OBJECTIVES This study was designed to determine whether reductions in morning systolic blood pressure (BP) elicited by treatment of moderate to severe obstructive sleep apnea (OSA) in heart failure (HF) patients are associated with a reduction in sympathetic vasoconstrictor tone.

BACKGROUND Daytime muscle sympathetic nerve activity (MSNA) is elevated in HF patients with coexisting OSA. In our recent randomized trial in HF, abolition of OSA by continuous positive airway pressure (CPAP) increased left ventricular ejection fraction (LVEF) and lowered morning systolic BP.

METHODS Muscle sympathetic nerve activity, BP, and heart rate (HR) of medically treated HF patients (EF <45%) and OSA (apnea-hypopnea index ≥20/h of sleep) were recorded on the morning after overnight polysomnography, and again one month after patients were randomly allocated nocturnal CPAP treatment or no CPAP (control).

RESULTS In nine control patients, there were no significant changes in the severity of OSA, MSNA, systolic BP, or HR. In contrast, in the 8 CPAP-treated patients, OSA was attenuated, and there were significant reductions in daytime MSNA (from 58 ± 4 bursts/min to 48 ± 5 bursts/min; 84 ± 4 bursts/100 heart beats to 72 ± 5 bursts/100 heart beats; $p < 0.001$ and $p = 0.003$, respectively), systolic BP (from 135 ± 5 mm Hg to 120 ± 6 mm Hg, $p = 0.03$), and HR (from 69 ± 2 min^{-1} to 66 ± 2 min^{-1}; $p = 0.013$).

CONCLUSIONS Treatment of coexisting OSA by CPAP in HF patients lowers daytime MSNA, systolic BP, and HR. Inhibition of increased central sympathetic vasoconstrictor outflow is one mechanism by which nocturnal CPAP reduces awake BP in HF patients with moderate to severe OSA. (J Am Coll Cardiol 2005;45:2008–11) © 2005 by the American College of Cardiology Foundation

Obstructive sleep apnea (OSA), with ≥15 apneic or hypopneic events per hour, is present in 4% to 9% of the adult North American population aged 30 to 60, but its reported prevalence in heart failure (HF) patients with impaired left ventricular (LV) systolic function is substantially higher—between 11% and 37% (1). Heart failure is a condition in which sympathetic activation in the awake state has been linked to premature mortality and sudden death (2). Obstructive sleep apnea-induced apnea, hypoxia, hypercapnia, and arousal trigger surges in central sympathetic vasoconstrictor outflow, peripheral resistance, and blood pressure (BP) during sleep (1). Individuals with normal LV systolic function and OSA exhibit increased muscle sympathetic nerve activity (MSNA) even while awake (3,4). This carryover effect is also evident in HF patients, in whom coexisting OSA is associated with higher daytime MSNA (5).

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In our recent randomized trial involving 24 HF patients (mean LV ejection fraction [LVEF] 27%) with coexisting OSA, 1 month of therapy with nocturnal continuous positive airway pressure (CPAP) caused a increase in daytime LVEF and a significant reduction in morning systolic BP (6). We considered attenuation of daytime sympathetic vasoconstrictor discharge a likely mechanism for this fall in BP. We therefore recruited additional patients to test the hypothesis that abolition of coexisting OSA in HF by CPAP would lower daytime MSNA.

METHODS

Subjects. Following ethics board approval and informed consent, we studied men and women with 1) HF of >6 months duration; 2) LVEF ≤45% (radionuclide angiography); 3) >3 months of stable optimal drug therapy at highest tolerated dose; 4) moderate to severe OSA (≥20 apneas and hypopneas/h of sleep) with >50% of events obstructive (1,7); and 5) sinus rhythm. Exclusion criteria

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Abbreviations and Acronyms

AHI = apnea-hypopnea index
BP = blood pressure
CPAP = continuous positive airway pressure
HF = heart failure
HR = heart rate
LV = left ventricular
LVEF = left ventricular ejection fraction
MSNA = muscle sympathetic nerve activity
OSA = obstructive sleep apnea
SaO_2 = oxyhemoglobin saturation

included: 1) primary valvular heart disease; 2) cardiac pacing; and 3) unstable angina, myocardial infarction, or cardiac surgery within three months (6).

Polysomnography. All subjects underwent a second baseline overnight polysomnographic study, with sleep stages, apneas, hypopneas, and arousals defined and scored as previously described (6,7). Oxyhemoglobin saturation (SaO_2) was monitored by pulse oximetry. The apnea-hypopnea index (AHI) was calculated as the frequency of apneas and hypopneas/h of sleep.

Measurement of HR, BP, and MSNA. The next morning, the electrocardiogram, BP (digital photoplethysmography; Finapres 2300, Ohmeda, Englewood, Colorado) and peroneal MSNA were recorded over 15 min, with subjects awake, resting quietly supine, and breathing without apnea, as confirmed by respiratory inductance plethysmography. Muscle sympathetic nerve activity was expressed as burst frequency (bursts/min) and burst incidence (bursts/100 cardiac cycles) (8,9).

Protocol. Subjects were allocated randomly to either a control group (optimal HF drug therapy) or to a group that, in addition, received CPAP. The night after the baseline sleep study, the latter subjects underwent overnight CPAP titration, during which pressure was adjusted to abolish apneas and hypopneas or to the highest tolerated level. They were then provided a metered CPAP machine to document hours of use and were instructed to apply this for >6 h nightly. After one month the sleep study and the awake study were repeated.

Statistics. All data were acquired and analyzed by investigators blinded to the sequence of studies and treatment. Data are expressed as mean ± SEM. Analyses were performed using SigmaStat 2.03 (SPSS Inc., Chicago, Illinois). Baseline characteristics were compared by two-tailed unpaired *t* tests for continuous variables and the Fisher exact test for nominal variables. Two-way repeated measures analyses of variance, followed by Tukey's test, were used to compare within- and between-group differences in variables obtained one month apart. A p value <0.05 was considered significant.

RESULTS

High-quality MSNA data from both sessions were acquired from 17 subjects, 9 randomized to control and 8 to CPAP (Table 1). Groups were similar for age; body mass index; LVEF; AHI (>80% of respiratory events were obstructive); minimum SaO_2; sleep structure; arousal frequency; and use of digoxin (41%), diuretics (76%), angiotensin-converting enzyme inhibitors (100%), and beta-receptor antagonists (59%).

Neither drug use nor body mass index changed significantly between the baseline and one-month studies. In control patients, there were no significant changes in total or obstructive AHI, or any other polysomnographic variable. In contrast, CPAP, at a pressure of 7.5 ± 0.5 cm H_2O (used 6.0 ± 0.6 h/night), reduced total AHI (from 40.4 ± 7.9 events/h to 8.8 ± 1.5 events/h; $p < 0.001$ within- and $p < 0.01$ between-group interaction), obstructive AHI (from 33.3 ± 4.5 events/h to 4.2 ± 1.0 events/h; $p < 0.001$ within- and $p < 0.005$ between-group interaction), and arousal frequency (from 32.1 ± 8.7/h to 14.3 ± 3.5/h; $p < 0.025$), and increased minimum SaO_2 during sleep (90.8 ± 0.5% vs. 78.4 ± 4.6%; $p < 0.05$).

In the control group, hemodynamic and microneurographic variables were similar on the two study days (Table 2). In CPAP-treated subjects, awake systolic BP fell by 15.4 ± 4.9 mm Hg ($p = 0.015$; $p = 0.04$ for the between-group comparison), as did HR ($p = 0.013$; $p = 0.004$ for between-group comparison). In contrast with control patients, there were significant reductions in MSNA burst frequency in all subjects ($p < 0.001$; $p < 0.009$ for between-group comparison). The MSNA burst incidence also fell ($p = 0.003$) after one month of CPAP treatment (Table 2, Figs. 1 and 2).

DISCUSSION

This is the first randomized trial to examine the impact of treating OSA on MSNA. In those patients with coexisting systolic HF, treating OSA with nocturnal CPAP for one month caused significant reductions in morning MSNA, systolic BP, and HR. Remarkably, these cardiovascular effects of CPAP were observed on a background of medical HF therapy (including angiotensin-converting enzyme in-

Table 1. Subject Characteristics

	Control Group	CPAP Group	p Value
Number of subjects	9	8	
Age, yrs	52.2 ± 4.1	55.0 ± 2.0	0.57
Gender, M:F	7:2	8:0	0.47
BMI, kg/m^2	31.3 ± 1.6	29.9 ± 1.5	0.54
Cause of HF			1.00
ICM, n (%)	5 (55.6)	5 (62.3)	
Non-ICM, n (%)	4 (44.4)	3 (37.5)	
Hypertension, n (%)	5 (55.6)	3 (37.5)	0.64
NYHA functional class			1.00
II, n (%)	4 (44.4)	3 (37.5)	
III, n (%)	5 (55.6)	5 (62.5)	
LVEF, %	28.6 ± 3.0	32.1 ± 3.8	0.48

BMI = body mass index; CPAP = continuous positive airway pressure; HF = heart failure; ICM = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.