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The Effects of Continuous Positive Airway Pressure on Myocardial Energetics in Patients With Heart Failure and Obstructive Sleep Apnea

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Objectives We sought to examine the short-term and longer term (6-week) effects of continuous positive airway pressure (CPAP) on myocardial energetics.

Background Obstructive sleep apnea (OSA) and heart failure (HF) are both states of increased afterload and metabolic demand. Treatment with CPAP may initially reduce stroke volume but subsequently improves left ventricular function. However, it is not clear whether CPAP therapy favorably affects myocardial energetics and hence improves cardiac efficiency.

Methods Twelve patients with HF were divided into two groups: 7 patients with OSA were treated with CPAP (group I), and 5 patients without OSA served as a control group (group II). Oxidative metabolism was measured using the mono-exponential fit of the myocardial [^{11}C] acetate positron emission tomography time-activity curve (k-mono). Myocardial efficiency was derived using the work metabolic index (WMI = [heart rate × stroke volume index × systolic blood pressure]/k-mono) measured at baseline, during short-term CPAP, and after 6 ± 3 weeks of CPAP.

Results In group I, short-term CPAP tended to reduce SVI ($p = 0.063$) and reduced oxidative metabolism ($p = 0.031$). Work metabolic index did not change. However, longer term CPAP improved left ventricular ejection fraction (38.4 ± 3.3% to 43.4 ± 4.8%, $p = 0.031$), tended to reduce oxidative metabolism (0.047 ± 0.012 to 0.040 ± 0.008 min^{-1}, $p = 0.078$), and improved WMI (7.13 ± 2.82 × 10^6 to 8.17 ± 3.06 × 10^6 mm Hg·ml/m^2, $p = 0.031$). In group II (control), these parameters did not change.

Conclusions In this cohort of patients with HF and OSA, short-term CPAP decreased oxidative metabolism and tended to decrease SVI, but did not alter cardiac efficiency. Longer term CPAP improved cardiac efficiency, indicating an energy-sparing effect. These effects may contribute to the benefits of CPAP therapy. (J Am Coll Cardiol 2007; 49:450–8) © 2007 by the American College of Cardiology Foundation

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Morbidity, mortality, and hospitalization rates for heart failure (HF) remain high despite advances in pharmacologic therapy (1). Sleep-related breathing disorders, including obstructive sleep apnea (OSA), often coexist with HF and may contribute to disease progression (2–4).

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Heart failure is characterized by an energy-depleted state (5). High wall stress from increased afterload increases metabolic demand at the expense of forward kinetic work.

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Increased metabolic demand (myocardial oxygen consumption [MVO_2] and oxidative metabolism) associated with impaired ventricular function indicates a reduced myocardial efficiency that is characteristic of HF (6–8) and correlates with a poor prognosis (8).

Repeated apnea-arousal cycles that characterize OSA lead to altered loading conditions, hypoxia, and sympathetic nervous system activation (2,4,9). These changes during sleep, and the "carryover" daytime effects, may increase metabolic demand in the myocardium, further altering cardiac energetics (2,4,9).

Continuous positive airway pressure (CPAP) therapy has been shown to reduce sympathetic nervous system activation, preload, and afterload in the short-term or longer term setting (2,4). Small studies in OSA and HF patients have demonstrated that 1 to 3 months of CPAP therapy improves left ventricular (LV) systolic function (10–12). However, the mechanisms for the therapeutic effect of CPAP in patients with OSA and HF remain uncertain (2).

[^{11}C] acetate positron emission tomography (PET) provides a non-invasive technique for measuring regional and global myocardial oxidative metabolism (6,13–16), which is closely correlated with tricarboxylic acid cycle flux and MVo_2 (13,14). Combined with an assessment of cardiac function, [^{11}C] acetate PET can be applied as a noninvasive approach to study myocardial energetics and efficiency in vivo (6,15,16).

Therapies that improve LV function at the expense of MVo_2 or oxidative metabolism (thus reducing efficiency) are associated with poorer outcomes (5). In contrast, afterload reduction and beta-blocker therapy, which improve efficiency, are associated with improved patient outcomes (17). Therapy with CPAP appears to improve LV systolic function, but its effects on oxidative metabolism and efficiency in patients with HF and OSA are not known.

The primary aim of this study was to evaluate the daytime carryover effect of longer term (6-week) nocturnal CPAP therapy on cardiac metabolism and efficiency using [^{11}C] acetate PET. The secondary aim was to evaluate the effect of short-term CPAP application on cardiac metabolism and efficiency.

Methods

Study subjects. Study subjects were recruited from the HF clinic of the University of Ottawa Heart Institute. The patient inclusion criteria were: 1) LV systolic dysfunction (left ventricular ejection fraction [LVEF] <40%), 2) symptoms of HF: New York Heart Association functional class II or III, and 3) stable condition (unchanged for >4 weeks).

Exclusion criteria included unstable angina or recent MI (<4 weeks), severe valvular heart disease, permanent pacemaker, and significant restrictive or obstructive lung disease.

The study was approved by the University of Ottawa Heart Institute Human Research Ethics Board. Written informed consent was obtained from all patients.

Experimental protocol. Thirteen HF patients underwent overnight polysomnography to assess for the presence of OSA. Obstructive sleep apnea was diagnosed on nocturnal polysomnography and defined as an apnea/hypopnea index (AHI) >15 (3,18) events/h of sleep (more than 80% of apnea/hypopnea events being obstructive in nature). Patients with the AHI <10 and no indication for CPAP therapy served as a control group.

All patients underwent baseline measurements, including echocardiography and [^{11}C] acetate PET, at rest while awake. Patients with OSA and HF had baseline studies repeated during awake application of short-term CPAP at the pressure determined from the CPAP titration study (discussed in the later text). Echocardiography was repeated 45 min after initiating the therapeutic pressure of CPAP (19) (mean pressure 10.6 ± 1.6 cm H_2O) and followed immediately by [^{11}C] acetate PET.

Subsequently, patients with HF and OSA were treated at home with nightly nocturnal nasal CPAP therapy. Echocardiography and [^{11}C] acetate PET were repeated after 6 ± 3 weeks of nocturnal CPAP therapy (mean pressure 10.6 ± 1.6 cm H_2O).

Patients with HF but without OSA served as the control group and underwent echocardiography and [^{11}C] acetate PET at rest at baseline and after 9 ± 6 weeks (p = NS).

Abbreviations and Acronyms

- **AHI** = apnea/hypopnea index
- **CPAP** = continuous positive airway pressure
- **HF** = heart failure
- **LV** = left ventricle/ventricular
- **LVEF** = left ventricular ejection fraction
- **MVo_2** = myocardial oxygen consumption
- **OSA** = obstructive sleep apnea
- **PET** = positron emission tomography
- **SVI** = stroke volume index
- **WMI** = work metabolic index

Sleep studies. A single overnight polysomnogram was performed using the Alice system (Respironics, Aria LX; Pittsburgh, Pennsylvania). Sleep staging was determined using Rechtschaffen and Kale's criteria (20). An obstructive apnea was defined as cessation of airflow for >10 s with persistent respiratory effort as seen in the ribcage or abdomen signals; hypopnea was defined as a decrease in airflow, ribcage, or abdominal motion by >50% of the baseline signal for >10 s with a ≥4% fall in O_2 saturation. The AHI was the total number of apneas and hypopneas per hour of sleep. Obstructive sleep apnea was defined by AHI >15/h (2,4,18) and >80% of all apnea/hypopnea events had to be obstructive for inclusion.

CPAP titration and therapy. Patients assigned to CPAP had a CPAP titration sleep study to determine the appropriate CPAP pressure >7 days before baseline PET and echocardiography. After all baseline studies were completed, patients were instructed to use the CPAP device (ResMed S7 Elite, ResMed Corp., San Diego, California) every night. Compliance with CPAP was assessed on the day of follow-up assessment using built-in hour meters in the CPAP machines (10). The control patients were not treated with CPAP.

Echocardiography. Ventricular function was assessed by 2-dimensional echocardiography using a Sonos 5500 ultrasound system (Phillips, Andover, Massachusetts) equipped with a 3.2-MHz phased-array transducer. Forward stroke volume (SV) was derived from the velocity-time integral of the pulsed Doppler LV outflow tract velocity signal and the LV outflow tract diameter (21). Stroke volume index (SVI) was derived by dividing SV by the body surface area.

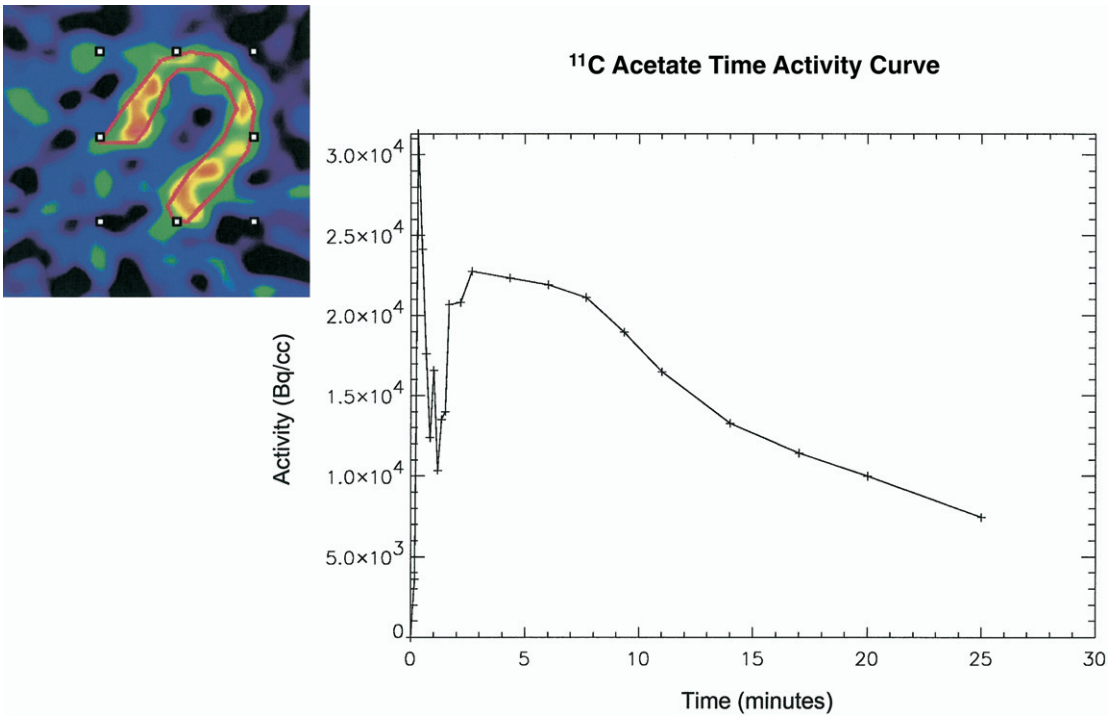

Figure 1 **Example of Myocardial Time-Activity Data From an ^{11}C Acetate Positron Emission Tomography Acquisition**

A monoexponential function fit to the myocardial clearance yields a clearance rate constant; k_{mono} represents the rate of oxidative metabolism and reflects myocardial oxygen consumption.

PET. Immediately following echocardiography, patients were positioned in a quiet and awake state in the Siemens/CTI ART PET scanner (Knoxville, Tennessee) (16). A dynamic PET acquisition was initiated (10 ×10 s; 2 × 30 s; 5 × 100 s; 3 ×180 s; 2 × 300 s), followed by administration of 10 mCi (370 MBq) [^{11}C] acetate intravenously.

[^{11}C] acetate PET data analysis. The reconstructed dynamic PET images were analyzed by applying a region of interest over the whole LV myocardium in 3 to 5 midventricular transaxial planes (16). A mono-exponential function was fit to the myocardial time activity data, and the clearance rate constant (k_{mono}) was determined as described previously (6,22). The mono-exponential fit begins at the point when the blood pool is stable (usually 2 to 4 min after injection) (Fig. 1).

All data were analyzed blind to the clinical and imaging data and to the OSA status.

Assessment of myocardial efficiency. The [^{11}C] acetate clearance data were combined with the stroke work data to derive myocardial efficiency using the LV work metabolic index (WMI), as described previously (6,15,16): $WMI = SVI \times SBP \times HR/k_{mono}$; where SVI is the stroke volume index determined by echocardiography, SBP is systolic blood pressure, HR is heart rate, and k_{mono} is the mono-exponential rate constant for C-11 clearance from the myocardium. This equation is a modification of the minute-work-to-oxygen consumption relationship originally defined as mechanical efficiency (7).

Statistical analysis. Continuous variables are presented as means and standard deviations. Categorical variables are presented as frequencies with percentages. For the analysis of patient characteristic differences, Wilcoxon rank-sum tests were used for continuous measures and Fisher exact tests were used for categorical variables. For intra-group comparisons, Wilcoxon signed-rank tests, nonparametric analog of the paired *t* test, were used to compare differences within groups for continuous variables measured at baseline and after short-term (45 min) and 6 weeks of CPAP. For inter-group comparisons, baseline values and differences in percent changes over time for continuous variables were compared between groups by Wilcoxon rank-sum tests. A p value of <0.05 was considered a statistically significant difference. Statistical calculations were carried out using SAS software (version 9.1.3, SAS Institute, Inc., Cary, North Carolina).

Results

Patient characteristics. Thirteen HF patients were prospectively enrolled in the study between April 2004 and July 2005.

Table 1 Patient Characteristics

	Age (yrs)	Gender	BMI	Etiology	HTN	NYHA Functional Class	LVEF* (%)	Epworth Scale	AHI	Treatment
Group I (with OSA)										
1	57	M	36.0	Ischemic	+	2	36	6	81.1	ARB,BB,DIU
2	79	M	40.7	Nonischemic	+	3	23	3	22.2	ACEI,BB,DIU
3	46	M	42.9	Nonischemic	+	3	23	0	45	ACEI,BB,DIG,DIU
4	68	M	24.3	Ischemic	+	2	33	8	18	ARB,BB,DIU
5	51	M	40.1	Nonischemic	+	2	37	14	52.5	ACEI,BB,DIU
6	55	M	35.8	Nonischemic	–	2	30	4	29	ARB,BB,DIG,DIU
7	70	M	35.5	Ischemic	–	2	29	3	15.5	ACEI,BB,DIU
Mean ± SD	61.0 ± 11.7		36.5 ± 6.1			2.3 ± 0.5	30.7 ± 4.9%	5.4 ± 4.5	37.6 ± 23.6†	
Group II (control)										
1	78	M	27.3	Ischemic	–	3	25	5	0.9	ACEI,BB,DIG,DIU
2	56	M	29.9	Ischemic	+	2	33	4	7.3	ARB,BB,DIG,DIU
3	59	M	26.9	Ischemic	+	2	22	4	0.3	ACEI,BB,DIU
4	56	M	29.7	Ischemic	–	2	32	7	3.2	ACEI,BB
5	59	M	37.9	Nonischemic	+	2	23	4	2.8	ARB,BB
Mean ± SD	61.6 ± 9.3		30.3 ± 4.4			2.2 ± 0.5	27.0 ± 5.1%	4.8 ± 1.3	2.9 ± 2.7	

The Epworth Sleepiness Scale ranges from 0 to 24, with scores of 10 or higher indicating excessive daytime sleepiness. *LVEF by radionuclide angiography, BMI is the weight in kilograms divided by the square of the height in meters; †p = 0.019.

ACEI = angiotensin-converting enzyme inhibitor; AHI = apnea-hypopnea index; ARB = angiotensin receptor blocker; BB = beta-blocker; BMI = body mass index; DIG = digoxin; DIU = diuretic; HTN = hypertension; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OSA = obstructive sleep apnea.

One patient withdrew from the study before the baseline investigations could be completed. Therefore, 12 patients completed the study protocol.

The baseline characteristics of the patients are shown in Table 1. Seven patients were diagnosed as having OSA (group I), and 5 patients without OSA were considered control patients (group II). Baseline characteristics were similar between groups. Three of 7 patients in group I (with OSA) had an ischemic etiology, compared with 4 of 5 patients in group II (control patients) (p = NS). All patients in both groups were receiving a beta-blocker and either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker drug therapy. All patients were clinically stable, with no change in their medication regime during the follow-up period.

Continuous positive airway pressure was administrated at a mean of 10.6 ± 1.6 cm H_2O for 6.2 ± 1.2 h per night to group I (with OSA) during the study period.

Short-term effects of CPAP therapy. Heart rate and blood pressure (BP) were similar at rest and during short-term CPAP administration (Table 2). Short-term CPAP administration tended to reduce SVI (p = 0.063) and reduced LVEF (p = 0.016). Myocardial oxidative metabolism was significantly reduced by short-term CPAP administration (k_{mono}: 0.047 ± 0.012 to 0.041 ± 0.014 min^{-1}, p = 0.031) (Fig. 2). As a result, there was no significant change in the WMI from rest to short-term CPAP administration (7.13 ± 2.82 × 10^6 to 7.40 ± 2.68 × 10^6 mm Hg·ml/m^2, p = NS) (Fig. 2).

Longer-term effects of nocturnal CPAP therapy. There were no significant differences in baseline SVI, LVEF, LV oxidative metabolism, or WMI between the 2 groups.

Heart rate and BP were similar at baseline and after 6 weeks of nocturnal CPAP therapy in both groups (Table 3). There was a slight increase in the body weight in the OSA group, but this was not statistically significant (group I [with OSA]: 103.7 ± 24.9 kg to 106.3 ± 27.7 kg, p = NS; group II (control patients): 90.8 ± 8.8 kg to 90.6 ± 9.4 kg, p = NS]. For the OSA group, there was a wide standard deviation in weight, with no consistent directional change. Also, there was also no clinical deterioration. The slight difference in weight was thus likely due to variation in the measurement.

Longer term (6 weeks) nocturnal CPAP therapy abolished OSA and improved LVEF (p = 0.031) in group I (with OSA). Furthermore, longer term CPAP therapy

Table 2 Effects of Short-Term CPAP Application

	Group I (With OSA) (n = 7)	
Measurements	Rest	Short-Term CPAP
Heart rate, beats/min	59.8 ± 7.0	57.3 ± 7.5
SBP, mm Hg	141.0 ± 19.9	143.1 ± 15.1
SVI, ml/m^2	37.2 ± 8.3	34.3 ± 8.1*
LVEF (%)	38.4 ± 3.3	34.8 ± 5.0†
k_{mono}, min^{-1}	0.047 ± 0.012	0.041 ± 0.014§‡
WMI, mm Hg·ml/m^2	7.13 ± 2.82 × 10^6	7.40 ± 2.68 × 10^6

Values are mean ± SD. *p = 0.063 comparison of rest to short-term CPAP application; †p = 0.016 comparison of rest to short-term CPAP application; ‡p = 0.031 comparison of rest to short-term CPAP application.

CPAP = continuous positive airway pressure; SBP = systolic blood pressure; SVI = stroke volume index; WMI = work metabolic index; other abbreviations as in Table 1

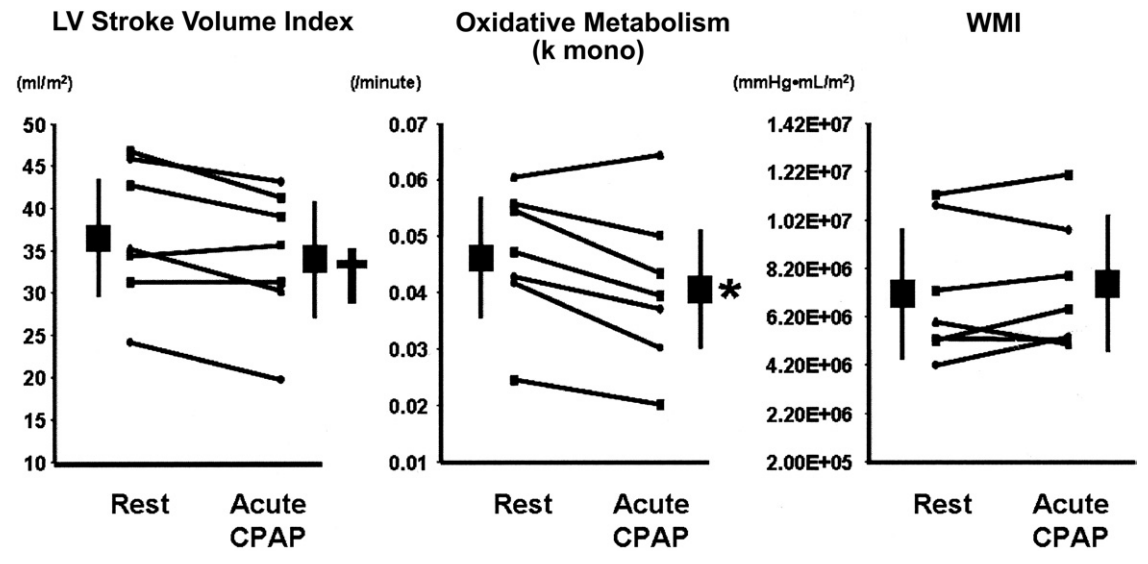

Figure 2 Effects of Short-Term CPAP Application

Stroke volume index, myocardial oxidative metabolism (k_{mono}), and work metabolic index (WMI) at rest and during short-term continuous positive airway pressure (CPAP) administration. *p = 0.031, †p = 0.063 (trend). LV = left ventricular.

tended to decrease daytime LV oxidative metabolism (k_{mono}: 0.047 ± 0.012 to 0.040 ± 0.008 min^{-1}, p = 0.078) while maintaining SVI (p = NS) (Table 3 and Fig. 3). As a result, longer-term CPAP therapy significantly improved the WMI (7.13 ± 2.82 $\times 10^6$ mm Hg·ml/m^2 to 8.17 ± 3.06 $\times$ 10^6 mm Hg·ml/m^2, p = 0.031) (Fig. 3).

In group II (control group), there were no significant changes in SVI, LVEF, LV oxidative metabolism (0.039 ± 0.007/min to 0.036 ± 0.007/min, p = NS), or WMI (8.24 ± 1.90 $\times$ 10^6 to 7.96 ± 2.36 $\times$ 10^6 mm Hg·ml/m^2, p = NS) from baseline to follow-up.

There was a significant improvement in the percent change of WMI in group I (with OSA) after 6 weeks of CPAP therapy compared with group II (control group) (15.9 ± 12.8% vs. −4.1 ± 15.5%, p = 0.044) (Fig. 4).

Discussion

In patients with OSA and HF, short-term CPAP administration decreased oxidative metabolism, tended to decrease SVI and, as a result, did not alter cardiac efficiency. However, longer term nocturnal CPAP led to improved LV systolic function while tending to reduce LV oxidative metabolism, thereby significantly improving cardiac efficiency and demonstrating an energy-sparing effect.

HF therapies. Most pharmacologic agents that are beneficial for HF have at least 2 common characteristics. First, these agents improve cardiac function without increasing MVO_2 (17,23). Heart failure is an energy-depleted state, and the improved survival with beta-blocker and vasodilator therapy relates in part to the energy-sparing effects of these agents (5,23). Inotropic

Table 3 Effects of 6 Weeks of Nocturnal CPAP Therapy

	Group I (With OSA) (n = 7)		Group II (Control) (n = 5)	
Measurements	Baseline	6 Weeks	Baseline	6 Weeks
Heart rate, beats/min	59.8 ± 7.0	58.0 ± 7.8	59.6 ± 12.1	55.3 ± 6.0
SBP, mm Hg	141.0 ± 19.9	141.0 ± 17.8	129.2 ± 24.8	120.9 ± 24.7
Weight, kg	103.7 ± 24.9	106.3 ± 27.7	90.8 ± 8.8	90.6 ± 9.4
SVI, ml/m^2	37.2 ± 8.3	37.6 ± 7.3	42.4 ± 8.8	42.0 ± 8.3
LVEF (%)	38.4 ± 3.3	43.4 ± 4.8*	42.8 ± 6.3	43.5 ± 8.1
k_{mono}, min^{-1}	0.047 ± 0.012	0.040 ± 0.008†	0.039 ± 0.007	0.036 ± 0.008
WMI, mm Hg·ml/m^2	7.13 ± 2.82 $\times$ 10^6	8.17 ± 3.06 $\times$ 10^6*‡	8.24 ± 1.90 $\times$ 10^6	7.96 ± 2.36 $\times$ 10^6

Values are mean ± SD. *p = 0.031 comparison of baseline to 6 weeks within group I; †p = 0.078 comparison of baseline to 6 weeks within group I; ‡p = 0.044 comparison of differences in percent changes over time between group I and group II.
Abbreviations as in Tables 1 and 2.

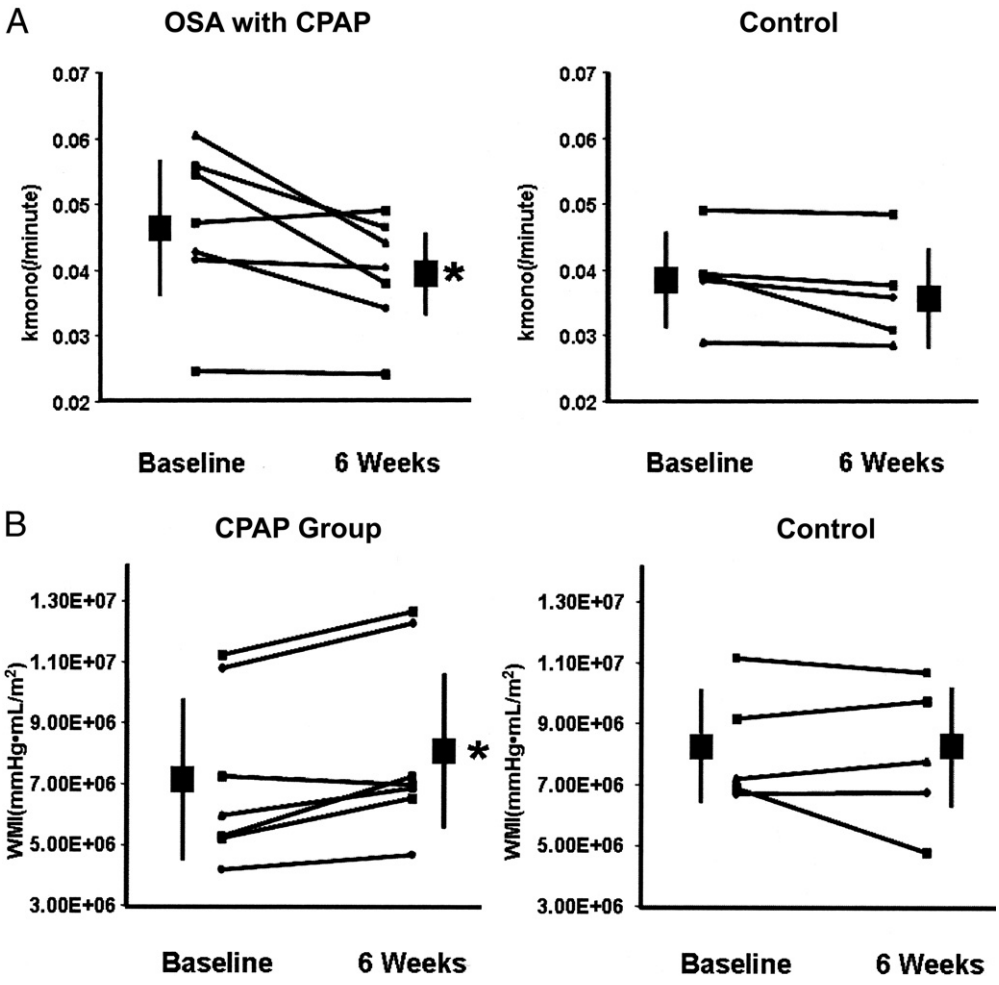

Figure 3 Effects of 6 Weeks of CPAP on Oxidative Metabolism and on Efficiency

(A) k_{mono} at baseline and after 6 weeks of CPAP therapy. *p = 0.078 (trend); **(B)** WMI at baseline and after 6 weeks of CPAP therapy. *p = 0.031. OSA = obstructive sleep apnea; other abbreviations as in Figure 2.

medications, on the other hand, improve performance at the expense of increasing MVO_2. Many of these agents have detrimental effects and increase mortality rates (24,25). The discordance between improved LV performance and increased mortality may result from these agents' detrimental cardiac energetic effects (17,23). Second, most beneficial agents act by blocking neurohormonal activation.

However, less is known about the mechanical therapies for HF, such as CPAP therapy, and whether these therapies also have a beneficial effect on cardiac metabolism and efficiency (and thus cardiac energetics).

Effects of CPAP Therapy. EFFECTS OF SHORT-TERM CPAP ADMINISTRATION. Short-term CPAP administration prevents recurrent hypopnea and associated hypoxia, reduces BP and HR, and reduces sympathetic nervous system activity (19,26). Left ventricular preload and afterload fall through the generation of positive intrathoracic pressure (27). This reduces cardiac output in the normal heart by decreasing venous return and LV filling (2,27). In HF, the response of SV and cardiac output to short-term CPAP administration has been variable (27–30).

In the current study, SVI tended to decrease without change in BP during short-term CPAP administration. This may have related to a reduction in venous return. Alternatively, the acute decrease in SVI may be related to reduced work of ventilation. It is known that hyperventilation models significantly increase cardiac output (31). Use of CPAP may have the opposite effect, reducing demand on the LV. The decrease in SVI would be expected to result in a reduction in metabolic demand. Indeed, short-term CPAP administration also acutely reduced myocardial oxidative metabolism. However, external cardiac efficiency was not altered with short-term CPAP administration, as both SVI and oxidative metabolism were decreased.

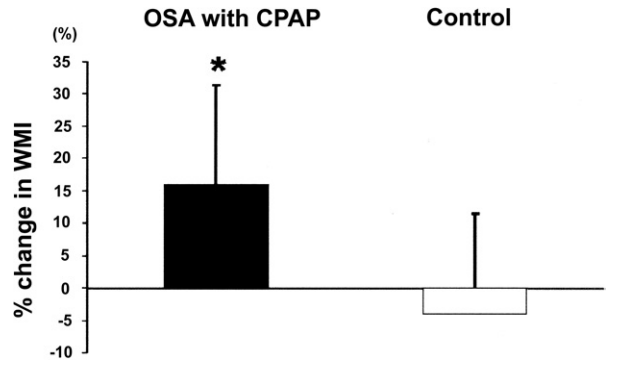

Figure 4 **Percent Change in Myocardial Efficiency**

Percent change of WMI from baseline to 6 weeks after CPAP therapy in group I (with obstructive sleep apnea [OSA]) and in group II (control). *p = 0.044 versus group II (control). Abbreviations as in Figure 2.

LONGER-TERM EFFECTS OF CPAP THERAPY. In patients with OSA and HF, previous studies have demonstrated an improvement in LV systolic function after 1 to 3 months of CPAP therapy (10–12). Recently, a randomized study by Kaneko et al. (10) demonstrated an improvement in LVEF from 25% to 34% in 12 patients receiving 1 month of CPAP therapy (10). The current study is consistent with these previous investigations (10–12) and demonstrated a significant improvement in LVEF after 6 weeks of nocturnal CPAP therapy in patients with OSA and HF.

Potential energy-sparing effects of CPAP. Although the reported hemodynamic responses to CPAP therapy have been variable (27–30), one important consistent effect has been the reduction of LV transmural pressure (27). This, combined with CPAP's effects of eliminating hypoxia and reducing sympathetic activity, has the potential to reduce myocardial energy demand and MVO_2. Because HF is known to be an energy-depleted state (5), CPAP therapy could permit repletion of energy stores and more efficient energy transduction to useful work, which is constantly demanded of the failing heart.

Kaye et al. (28) demonstrated a 20% reduction in MVO_2 after 10 min of CPAP administration, measured via coronary sinus catheterization in patients with HF but without OSA (28). The authors suggested that this reflects an acute beneficial effect of CPAP administration on cardiac energetics. However, a 15% reduction in stroke work was also noted. In this acute setting, reduced MVO_2 with CPAP administration may have simply reflected the reduction in stroke-work and, therefore, no definite benefit on energetics can be inferred. Similar results were observed in the current study, with acute reductions in oxidative metabolism and SVI during short-term CPAP and, as a result, no change in efficiency; the difference was that our patients with HF also had OSA and that we also evaluated longer term CPAP therapy.

It is more difficult to predict the response of myocardial metabolism with longer term CPAP therapy. It is known that 1 to 3 months of CPAP therapy in patients with HF and OSA increases LV function (10–12). If myocardial oxidative metabolism simply parallels SV or stroke work (as observed in our short-term results and by Kaye et al. (28) regarding MVO_2 and stroke-work changes), then myocardial oxidative metabolism may be expected to increase over time, and no improvement in cardiac efficiency may occur. Such a finding would suggest that CPAP therapy was of limited benefit for daytime cardiac energetics, or might even be detrimental to the energy depleted failing heart despite an improvement in LV systolic function (5,23). On the contrary, this was not observed in the current study.

Bradley and Floras (2) have proposed that the favorable effects of CPAP therapy on LV systolic function and sympathetic nervous system activity are similar to beta-blocker therapy. Beta-blocker therapy acutely reduces SV and MVO_2, but chronically improves LV systolic function with reduced MVO_2 and oxidative metabolism. As a result, cardiac efficiency is improved (6,32). The present data show a similar pattern with acute reductions in oxidative metabolism and SVI, but after 6 weeks of nocturnal CPAP therapy, there is reduced myocardial oxidative metabolism with improved cardiac efficiency in patients with OSA and HF. The mechanism for this beneficial effect is not known, but the response does appear similar to beta-blocker effects (2). As proposed for beta-blockade, over time the metabolic benefit of CPAP therapy may allow repletion of energy stores and permit redirection of energy utilization and gene transcription to repair cell injury and restore contractile elements (6,32).

Because the patients in the current study were on beta-blocker therapy, the effect of CPAP is additive to the stable beta-blocker therapy. Previous data from Mansfield et al. (11) showed that longer term CPAP improved LV systolic function in patients with OSA and HF, 79% of whom were already treated with a beta-blocker drug. This study also supports that there is an additive effect of CPAP (11).

Longer term CPAP therapy has also been shown to reduce sympathetic nervous system activity in patients with OSA and HF (33). Such a reduction in sympathetic function may also contribute to the changes in myocardial oxidative metabolism observed in the current study. We did not observe a significant change in HR or BP. However, in the study by Mansfield et al. (11), improvement in LV function was accompanied by a reduction of urinary norepinephrine secretion without significant hemodynamic changes. This suggests that the sympathetic nervous system effects of CPAP may occur independent of changes in HR or BP (possibly because of the concomitant beta-blocker therapy as suggested by the authors). Such sympathetic function changes may directly affect the myocardium, but this notion remains speculative and requires further study.

Study limitations. The sample size of this study is small, but it is similar to previous physiologic studies that have

evaluated CPAP effects in patients with OSA and HF (10,33), as well as other metabolic studies in HF (34). Despite the small population size, beneficial therapeutic effects of CPAP therapy on myocardial energetics were demonstrated. The current study supports the need for larger randomized controlled studies to evaluate the effects and benefits of longer term CPAP therapy. Such a randomized control trial has now been initiated. Results of this study will not be available for 3 to 4 years.

The present study included patients with ischemic and non-ischemic etiologies of HF. The response of myocardial energetics to CPAP therapy may differ depending on the HF etiology. However, a previous study (10) demonstrated a similar improvement in LV function in ischemic and non-ischemic cardiomyopathy with longer term CPAP therapy. Nevertheless, further studies in these specific subpopulations are needed.

The present study included only male subjects, in part reflecting the available population. Although the mechanisms of CPAP effects may be similar, results cannot be directly applied to women. This area requires further study.

Conclusions. On the basis of the results of this pilot study, short-term CPAP administration appears to decrease oxidative metabolism and tends to decrease SVI. As a result, it does not appear to alter myocardial efficiency. Longer term CPAP treatment (6 weeks), on the other hand, may lead to an improvement in LV systolic function and a trend to reduction in oxidative metabolism with a significant improvement in myocardial efficiency. This may indicate an energy-sparing effect of nocturnal CPAP therapy. The cardiac energetic effects may contribute to the clinical benefits observed with CPAP therapy in patients with obstructive sleep apnea and HF. Larger randomized studies are warranted.

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The Effects of Continuous Positive Airway Pressure on Myocardial Energetics in Patients With Heart Failure and Obstructive Sleep Apnea

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