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# Influence of Obstructive Sleep Apnea on Mortality in Patients With Heart Failure

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**Objectives** This study sought to determine, in patients with heart failure (HF), whether untreated moderate to severe obstructive sleep apnea (OSA) is associated with a higher mortality rate than in patients with mild to no sleep apnea (M-NSA).

**Background** Obstructive sleep apnea is common in patients with HF and exposes the heart and circulation to adverse mechanical and autonomic effects. However, its effect on mortality rates of patients with HF has not been reported.

**Methods** In a prospective study involving 164 HF patients with left ventricular ejection fractions (LVEFs) ≤45%, we performed polysomnography and compared death rates between those with M-NSA (apnea-hypopnea index [AHI] <15/h of sleep) and those with untreated OSA (AHI ≥15/h of sleep).

**Results** During a mean (± SD) of 2.9 ± 2.2 and a maximum of 7.3 years of follow-up, the death rate was significantly greater in the 37 untreated OSA patients than in the 113 M-NSA patients after controlling for confounding factors (8.7 vs. 4.2 deaths per 100 patient-years, p = 0.029). Although there were no deaths among the 14 patients whose OSA was treated by continuous positive airway pressure (CPAP), the mortality rate was not significantly different from the untreated OSA patients (p = 0.070).

**Conclusions** In patients with HF, untreated OSA is associated with an increased risk of death independently of confounding factors. (J Am Coll Cardiol 2007;49:1625–31) © 2007 by the American College of Cardiology Foundation

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Central and obstructive sleep apnea (OSA) are common in patients with heart failure (HF), in whom they may worsen prognosis by increasing sympathetic nervous system activity (SNA), raising blood pressure and triggering myocardial ischemia and arrhythmias (1–6). Several studies have reported on mortality associated with central sleep apnea in patients with HF (7–11). However, only 1 study examined the potential influence of OSA on mortality in HF patients (11). Although that study reported no influence of OSA on the combined rate of death and heart transplantation, it was inconclusive for several reasons. First, most patients were on a heart transplant list at the time of enrollment, so that the timing of transplantation was a matter of chance based on organ availability. Second, in the survival analysis of HF patients with OSA, no distinction was made between patients whose OSA was treated versus those in whom it was not treated by continuous positive airway pressure (CPAP). Thus, neither the potential influence of untreated OSA nor of treating OSA on survival was examined.

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Obstructive apneas expose the cardiovascular system to intermittent hypoxia and sympathetic activation (12), and in addition, generate exaggerated negative intrathoracic pressure, which increases left ventricular wall tension and lowers stroke volume (13,14). Such stresses could contribute to

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**Abbreviations and Acronyms**

**AHI** = apnea-hypopnea index
**BMI** = body mass index
**CPAP** = continuous positive airway pressure
**HF** = heart failure
**HR** = hazard ratio
**LVEF** = left ventricular ejection fraction
**M-NSA** = mild to no sleep apnea
**NYHA** = New York Heart Association
**OSA** = obstructive sleep apnea
**$Sa_{O_2}$** = arterial oxygen saturation
**SNA** = sympathetic nervous system activity

morbidity and mortality in HF. Furthermore, cross-sectional data from the Sleep Heart Health Study showed that the presence of OSA was associated with increased odds of having HF, independently of known risk factors (15). Epidemiologic studies involving patients with HF have reported prevalences of OSA of 12% to 53% (4,5,16). These data suggest that OSA is common in patients with HF, and emphasize the importance of determining its prognostic significance.

If OSA contributes to mortality in HF, then its treatment might improve prognosis. Randomized trials show that alleviation of OSA by CPAP in patients with HF lowers SNA, blood pressure, and heart rate; increases left ventricular ejection fraction (LVEF); and reduces nocturnal ventricular ectopy (17–20). However, thus far, no study has examined the effect of CPAP on mortality in HF patients with OSA. In a recent nonrandomized observational study in patients without HF, Marin et al. (21) reported that men with severe untreated OSA had higher fatal and nonfatal cardiovascular event rates than men without OSA. Conversely, fatal and nonfatal cardiovascular event rates in patients whose severe OSA was treated by CPAP did not differ from subjects without OSA. Using an observational design similar to that of Marin et al. (21), our primary objective was to determine, in patients with HF, whether untreated moderate to severe OSA is associated with a higher mortality rate than in patients with mild to no sleep apnea (M-NSA). A secondary objective was to assess whether the mortality rate is lower in patients whose OSA is treated by CPAP.

## Methods

**Study design.** In this prospective, observational epidemiologic study, all patients with HF newly referred to the Heart Failure Clinic of the Mount Sinai Hospital in Toronto between September 1, 1997, and December 1, 2004, underwent overnight polysomnography. They were followed up until January 1, 2005, at which point their vital status was determined. The protocol was approved by the local ethics review board, and all subjects provided written informed consent before entry.

**Subjects.** Candidates for inclusion were patients with: 1) chronic HF caused by ischemic or nonischemic dilated cardiomyopathy for at least 6 months; 2) left ventricular systolic dysfunction defined as a LVEF of ≤45% at rest by radionuclide angiography or echocardiography performed within 3 months before the diagnostic sleep study; 3) dyspnea (New York Heart Association [NYHA] functional class 2 to 4); and 4) stable clinical status on stable optimal medical therapy for at least 1 month before entry. Exclusion criteria were: 1) unstable angina, myocardial infarction, or cardiac surgery within the previous 3 months; 2) pregnancy; and 3) prior history of sleep apnea.

**Polysomnography.** Polysomnography was performed in all subjects using standard polysomnographic techniques (17). Sleep stages and arousals were scored according to standard criteria (22,23). Respiratory efforts and tidal volume were measured by respiratory inductance plethysmography (Respitrace, Ambulatory Monitoring, Inc., White Plains, New York) (24). Arterial oxygen saturation ($Sa_{O_2}$) was monitored by oximetry. Obstructive apneas and hypopneas were scored according to established criteria (4,17). Patients were divided into categories according to the frequency of apneas and hypopneas per hour of sleep (i.e., apnea-hypopnea index [AHI]): M-NSA, AHI <15/h of sleep; moderate to severe OSA (AHI ≥15/h of sleep, of which ≥50% were obstructive); and central sleep apnea (AHI ≥15/h of sleep, of which >50% were central). Patients with predominantly central sleep apnea were excluded from further analysis. The AHI cutoff of 15/h was chosen to conform to that used in previous studies in which mortality risk was associated with OSA in patients without HF (25), and the effects of CPAP on mortality in HF patients with central sleep apnea were tested (9,26).

Patients found to have OSA, and their cardiologists, were informed of their diagnosis. Subsequently, patients referred to the sleep clinic for management of their OSA were offered CPAP. Patients who accepted CPAP therapy had a second overnight polysomnogram during which CPAP was titrated to abolish OSA, or to the highest tolerated pressure. Per our usual clinical practice, these patients were evaluated in our sleep disorders clinic 3 months later, and yearly thereafter. Treated OSA was defined as initiation of CPAP therapy, followed by documentation in the sleep disorders clinic that the patient continued to use CPAP at that time. All patients who were using CPAP at that time also reported using it at their yearly clinic visits. Patients were considered to have untreated OSA if they did not start CPAP, or if they started CPAP but stopped using it before the 3-month follow-up clinic assessment (21).

**Outcome.** The outcome was the cumulative rate of death from the date of the diagnostic sleep study until January 1, 2005. For purposes of outcome analysis, patients with OSA were stratified into treated and untreated OSA groups. The status of all subjects at this time was first ascertained by a telephone call to them, their families, or their referring physicians. Dates and causes of death were obtained from the subjects' medical records, or where such records were unavailable, from their families or referring physicians.

**Statistical analysis.** Baseline characteristics of patients in the 3 groups were compared by analysis of variance. Post

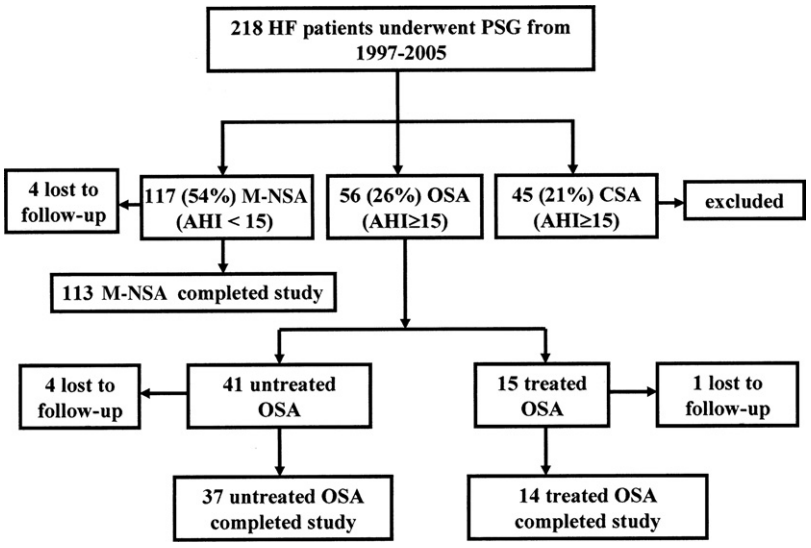


**Figure 1** **Progress of the Cohort Through the Study**

AHI = apnea-hypopnea index; CSA = central sleep apnea; HF = heart failure; M-NSA = mild to no sleep apnea; OSA = obstructive sleep apnea; PSG = polysomnography.

hoc contrasts to assess differences between the untreated OSA and M-NSA groups and between the treated and untreated OSA groups were by 2-sided *t* tests for continuous variables, and by chi-square for nominal variables, except where expected counts were <5, in which case, a Fisher exact test was used.

To determine whether OSA increased the risk of death independently of other risk factors, survival was compared between patients with M-NSA and those with untreated OSA in a multivariable Cox proportional hazards model over the course of the study. Because a 3-month follow-up clinic visit was not required to classify subjects as having M-NSA, or for those with OSA not prescribed CPAP as being untreated, this survival analysis started from the baseline assessment. Confounding variables were those that conferred at least a 10% change in the hazard ratio (HR) for OSA when added to the model (27). Independent variables were introduced into the model one at a time and included LVEF, NYHA functional class, age, gender, body mass index (BMI), medications, and a history of hypertension, diabetes, atrial fibrillation, and ischemic and nonischemic cardiomyopathy.

For the comparison of survival between patients with treated and untreated OSA, Kaplan-Meier survival analysis and the Prentice-Wilcoxon modification of the log-rank test (28) were carried out. Because a 3-month clinic visit was required to determine whether an OSA patient was treated, subjects who died before the scheduled 3-month clinic visit were excluded from this survival analysis. A p value of <0.05 was considered statistically significant. Data are given as mean ± SD unless stated otherwise. All analyses were done using SPSS 12.0.1 (SPSS Inc., Chicago, Illinois).

## Results

**Subjects.** We enrolled 218 patients with HF, of whom 45 (21%) were found to have predominantly central sleep apnea, and were excluded from further analysis; M-NSA was found in 117 (54%) patients and OSA in 56 (26%). Patients were followed up prospectively for a mean of 2.9 ± 2.2 years (range 1 month to 7.3 years), during which 9 (6%) were lost to follow-up. Complete follow-up data were obtained in 164 (95%) patients, of whom 113 had M-NSA, 37 had untreated OSA, and 14 had treated OSA (Fig. 1). Of the 37 patients with untreated OSA, 28 never started CPAP (mainly because of lack of hypersomnolence) (16), and 9 underwent a CPAP titration but discontinued it before their first follow-up clinic visit 3 months later.

**Untreated OSA. PATIENT CHARACTERISTICS.** Baseline characteristics of the patients with M-NSA and those with untreated OSA are shown in Table 1. For all comparisons of nominal variables between the untreated OSA group and the M-NSA group, chi-square tests were used. As expected, the proportion of men was significantly higher in the patients with untreated OSA than in those with M-NSA. However, neither age, BMI, LVEF, NYHA functional class, nor the proportion with a history of ischemic heart disease, hypertension, or diabetes differed between the 2 groups. Epworth Sleepiness Scale scores were within normal limits and were similar in the 2 groups as well (16,17). Medications and cardioverter-defibrillator use were also similar except that a higher proportion of untreated OSA patients was on diuretics.

The mean AHI of patients with untreated OSA was 33/h of sleep, indicating moderate to severe OSA (Table 2). They had

**Table 1 Baseline Characteristics of the Patients**

| | M-NSA | Untreated OSA | Treated OSA |
|---|---|---|---|
| n | 113 | 37 | 14 |
| Age, yrs | 53.5 ± 13.8 | 58.5 ± 12.0 | 53.2 ± 9.4 |
| Gender, male/female | 74:39 | 32:5* | 14:0* |
| Body mass index, kg/m$^2$ | 29.0 ± 5.4 | 30.1 ± 5.2 | 32.3 ± 4.5* |
| Left ventricular ejection fraction, % | 25.5 ± 10.3 | 25.9 ± 8.7 | 23.9 ± 8.8 |
| NYHA functional class | 2.4 ± 0.7 | 2.3 ± 0.5 | 2.3 ± 0.6 |
| Ischemic cardiomyopathy, % | 35.4 | 40.5 | 35.7 |
| Nonischemic cardiomyopathy, % | 64.6 | 59.5 | 64.3 |
| History of hypertension, % | 34.5 | 43.2 | 64.3 |
| History of diabetes, % | 22.1 | 29.7 | 35.7 |
| History of hyperlipidemia, % | 31 | 35.1 | 64.3* |
| Epworth Sleepiness Scale | 7.3 ± 3.9 | 7.6 ± 3.8 | 7.4 ± 2.9 |
| Medications | | | |
| Diuretics, % | 72.6 | 91.9 | 71.4 |
| Beta-blockers, % | 81.4 | 83.8 | 78.6 |
| ACE inhibitors, % | 46.9 | 54.8 | 53.8 |
| ACE inhibitors or AT2 antagonists, % | 93.8 | 89.2 | 100 |
| Digoxin, % | 42.5 | 48.6 | 35.7 |
| Statins, % | 29.3 | 30 | 38.5 |
| ICD, % | 4.4 | 0 | 7.1 |

Continuous data are expressed as mean ± SD. *$p < 0.05$ compared with M-NSA.
ACE = angiotensin-converting enzyme; AT2 = angiotensin-2 receptor; ICD = implantable cardioverter-defibrillator; M-NSA = mild to no sleep apnea; NYHA = New York Heart Association; OSA = moderate to severe obstructive sleep apnea.

more frequent arousals from sleep, as well as significantly lower minimum nocturnal $Sa_{O_2}$ than the M-NSA group. However, the mean $Sa_{O_2}$ did not differ between the 2 groups.

**MORTALITY.** In the untreated OSA group, 9 (24%) died (5 sudden death, 1 myocardial infarction, 3 progressive HF), representing a mortality rate of 8.7 per 100 person-years, whereas in the M-NSA group, 14 (12%) died (5 sudden death, 3 myocardial infarction, 6 progressive HF), indicating a mortality rate of 4.2 per 100 person-years (Fig. 2). Three deaths in the untreated OSA group occurred in those who underwent a CPAP titration study, but who either did not receive CPAP at home, or quit using it before 3 months. These occurred 625, 724, and 814 days after enrollment. Only 3 deaths occurred within 3 months of enrollment: 1 occurred after 32 days in an M-NSA patient, and 2 occurred after 47 and 90 days in untreated OSA patients who never received CPAP. Thus, because we were able to ascertain M-NSA versus untreated OSA status at 3 months in all subjects, we were able to analyze mortality data from the time of enrollment.

The unadjusted HR showed a trend for increased mortality in the untreated OSA versus the M-NSA groups that

**Table 2 Baseline Polysomnographic Data**

| | M-NSA | Untreated OSA | Treated OSA |
|---|---|---|---|
| Total sleep time, min | 307.1 ± 77.6 | 291.7 ± 93.0 | 319.7 ± 64.0 |
| Sleep latency, min | 22.4 ± 22.5 | 22.4 ± 30.4 | 17.8 ± 24.6 |
| Sleep efficiency, % | 73.7 ± 16.4 | 69.9 ± 19.8 | 75.0 ± 10.4 |
| Apnea-hypopnea index, n/h sleep | 6.9 ± 3.9 | 32.8 ± 14.3* | 38.8 ± 15.9† |
| Obstructive events, % | N/A | 84.2 ± 14.0 | 86.2 ± 14.1 |
| Movement arousals, n/h sleep | 17.8 ± 13.7 | 31.7 ± 11.7* | 36.3 ± 14.2† |
| Mean $Sa_{O_2}$, % | 95.1 ± 2.1 | 94.6 ± 2.8 | 93.9 ± 3.9 |
| Minimum $Sa_{O_2}$, % | 87.4 ± 7.5 | 84.2 ± 9.7 | 80.4 ± 12.4† |

*$p < 0.05$ compared with M-NSA. †$p < 0.05$ compared with untreated OSA.
$Sa_{O_2}$ = oxyhemoglobin saturation; other abbreviations as in Table 1.

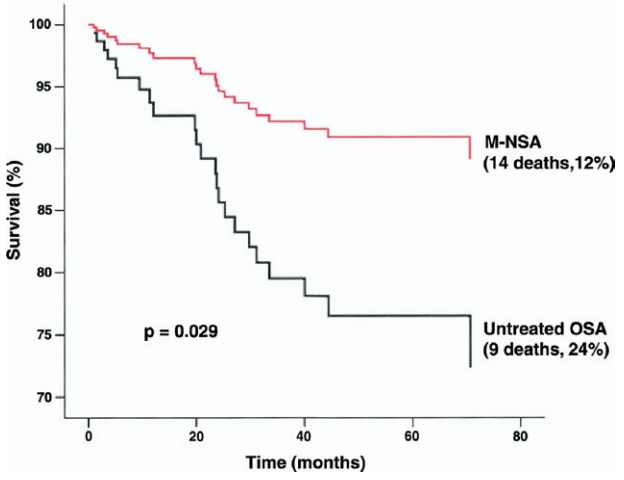


**Figure 2 Multivariable Cox Proportional Hazards Survival Plots for Patients With M-NSA Versus Untreated OSA**

Multivariable Cox proportional hazards plots showing worse survival of heart failure patients with untreated obstructive sleep apnea (OSA) than in those with mild to no sleep apnea (M-NSA) (hazard ratio = 2.81, p = 0.029) after adjusting for significant confounders (left ventricular ejection fraction, New York Heart Association functional class, and age per Table 3). The adjusted survival curves are shown at the average values of these confounders.

**Table 3** Multivariate Hazards Ratios for Mortality Rate

| Variables | Hazard Ratio | p Value | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Untreated OSA | 2.81 | 0.029 | 1.11 | 7.10 |
| LVEF | 0.93 | 0.006 | 0.88 | 0.98 |
| NYHA functional class | 2.30 | 0.037 | 1.04 | 5.08 |
| Age | 1.05 | 0.005 | 1.02 | 1.09 |

LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

was of borderline significance (HR = 2.024, p = 0.099). However, after adjusting for the significant confounders (LVEF, NYHA functional class, and age) in the multivariable Cox proportional hazards model, the HR associated with untreated OSA was significant (HR = 2.81, p = 0.029) (Table 3). The addition of other variables listed in the statistical analysis section above did not lead to any substantive changes to the HR, and are therefore not included in the final model.

**Treated OSA. PATIENT CHARACTERISTICS.** Fourteen patients had treated OSA. For comparisons of nominal variables between the untreated and treated OSA groups, chi-square tests were used for ischemic and nonischemic cardiomyopathy, history of hypertension, history of hyperlipidemia, and digoxin, whereas Fisher exact tests were used for comparisons of gender distribution, history of diabetes, use of diuretics, beta-blockers, and angiotensin-converting enzyme inhibitors.

There were no significant differences in baseline demographic characteristics between the untreated and treated OSA groups (Table 1). Epworth Sleepiness Scale scores were within normal limits and were similar in these 2 groups. Medication and cardioverter-defibrillator use was also similar. Patients with treated OSA had significantly higher AHIs than patients with untreated OSA, but there were no significant differences in other polysomnographic variables, including frequency of arousals and the mean and minimum nocturnal $Sa_{O_2}$ between the 2 groups (Table 2).

**MORTALITY.** There were no deaths in the 14 treated OSA patients, and therefore the Cox proportional hazards model could not be used to adjust for other variables or to estimate and test significance of the HR. Instead, the Kaplan-Meier analysis and the Prentice-Wilcoxon modification of the log-rank test were used. Two patients in the untreated OSA group who were never prescribed CPAP but who died before 3 months after the baseline assessment were excluded from this analysis. There were no patients who died within 3 months of starting CPAP. Among the 35 remaining patients in the untreated OSA group, 7 died after 3 months (mortality rate of 7.2 per 100 person-years) versus 0 deaths among the 14 treated OSA patients. This trend for reduced mortality in the treated OSA group, however, was not statistically significant (p = 0.07).

## Discussion

Only 1 previous study examined the influence of OSA on mortality rate in patients with HF (11). However, that study included only 22 HF patients with OSA and 23 without sleep apnea. The results of that study were inconclusive mainly because no distinction was made between patients whose OSA was treated versus those in whom it was not treated by CPAP. Therefore, the most important finding of our study was that in a much larger unselected population of 164 patients with HF, those with untreated OSA had a significantly higher mortality rate than those with M-NSA over mean and maximum follow-up times of 2.9 and 7.3 years, respectively. This difference remained significant even after controlling for those confounding variables (i.e., age, LVEF, and NYHA functional class) that altered independently the HR relating OSA to mortality (HR = 2.81, p = 0.029) (27). Thus, in patients with HF, untreated OSA was an independent risk factor for death.

We found that 26% of patients with HF recruited consecutively from an HF clinic, irrespective of symptoms of sleep apnea, had moderate to severe OSA, defined as an AHI ≥15/h. Thus, OSA is common in patients with HF (4). There are many adverse effects of OSA that could contribute to the increased mortality rate we observed in HF patients with untreated OSA. Generation of negative intrathoracic pressure during obstructive events causes both an increase in left ventricular afterload and a decrease in left ventricular preload, accompanied by reductions in stroke volume (14). Apnea-related hypoxia also can reduce cardiac output by impairing myocardial contractility (29) and increasing pulmonary artery pressure (1). The combination of repetitive apneas, hypoxia, and arousals from sleep stimulate reflex increases in central SNA, which are greater in patients with than in those without HF (30). The resultant surges in blood pressure further increase afterload and myocardial $O_2$ demand. In the face of reduced $O_2$ supply, this increase in $O_2$ demand can provoke myocardial ischemia and arrhythmias, and may increase the risk of sudden death during sleep (6,31). Moreover, this increase in SNA is sustained into wakefulness (13). These effects summate with those of HF to cause greater SNA than either condition alone (32). Long-term exposure to elevated SNA can cause cardiac myocyte necrosis and apoptosis, beta-adrenoceptor desensitization, arrhythmias, and an increase in mortality rate (9,32,33). In addition, OSA is associated with vascular endothelial dysfunction (34), elevated C-reactive protein, inflammatory mediators, cytokines, and markers of oxidative stress (35–37), all of which could promote progression of HF and reduce survival.

The second interesting finding of our study was that mortality tended to be lower, although not significantly so, among the 14 HF patients whose OSA was treated with CPAP for at least 3 months than in the untreated OSA group over a mean follow-up period of 2.9 years (0 deaths vs. 7.2 deaths per 100 person-years, respectively, p = 0.070).

Treated and untreated patients were comparable in terms of cardiovascular conditions and risk factors including age, gender distribution, BMI, LVEF, NYHA functional class, and diabetes. Medication use was similar in the 2 groups. Treated and untreated OSA patients were also comparable for sleep-stage distribution, frequency of arousals, and mean and minimum $Sa_{O_2}$, whereas treated OSA patients had a higher AHI, indicating more severe OSA. Thus, if OSA is a risk factor for mortality in HF patients, those in the CPAP-treated group, who had more severe OSA than those in the untreated OSA patients, should have had higher mortality, rather than the trend to lower mortality that we observed. Therefore, our data suggest that in patients with HF, treatment of OSA by CPAP has the potential to improve survival. On the other hand, it could be that patients with HF who accepted CPAP were more health conscious or compliant with other treatments, and this might have had a beneficial effect on their survival.

These results follow logically from the results of previous randomized clinical trials of CPAP in HF patients with OSA; CPAP reverses OSA acutely, eliminates apnea-related hypoxia, dampens negative intrathoracic pressure swings, and lowers blood pressure (13). Randomized clinical trials showed that treatment of OSA by CPAP in patients with HF reduces ventricular ectopy during sleep; lowers blood pressure, heart rate and SNA during both sleep and wakefulness; and improves LVEF (17–20).

However, our observations regarding the effect of CPAP on survival are subject to several limitations. First, although there was a trend to lower mortality in the CPAP-treated group than in the untreated OSA group, this difference was not statistically significant. Second, CPAP was not allocated randomly to patients. Third, we did not monitor hours of CPAP use, but rather simply recorded whether patients were using it or not at follow-up visits. Thus we could not be certain of CPAP compliance or whether CPAP-treated patients continued to use it throughout the study period. Finally, because of the small number of subjects and deaths involved in this analysis and the absence of any deaths in the treated OSA group, we were unable to control for potentially confounding factors by use of multivariable Cox proportional hazards analysis. Many patients with OSA in our study were not started on CPAP, most likely because they were not self-referred for sleep assessment and lacked subjective sleepiness, which is the usual indication for CPAP. Lack of sleepiness is compatible with their low Epworth Sleepiness Scale scores that were well within the nonsleepy range (mean 7.6) (Table 1), and consistent with previous reports (5,16,17,37,38). Among the 9 who started CPAP but discontinued it before the 3-month follow-up clinic visit, most stopped because they were not sleepy beforehand, and as a consequence, either had no reduction in daytime sleepiness or had difficulties tolerating the CPAP mask.

These observations are consistent with previous reports indicating that lack of daytime sleepiness and lower AHI are associated with poor CPAP compliance (39). They also suggest that the lack of daytime sleepiness among HF patients with OSA could pose an obstacle to good CPAP compliance in the clinical setting. We previously showed excellent CPAP compliance among nonsleepy HF patients with OSA in the setting of randomized trials (17,18,20). However, these trials involved more intensive follow-up, which in itself has been shown to improve CPAP compliance, than the present clinic-based observational study (39). Similar to the present findings, Roebuck et al. (11) reported, in another observational study of CHF patients, that only 26% of patients with OSA were initiated on CPAP, and only one-half of those continued to use it for more than 6 months. These observations suggest that maintenance of good CPAP compliance in HF patients with OSA who do not complain of hypersomnolence can be achieved, but that it may require more intensive initiation and follow-up than in the present study.

Our results are also compatible with those of Marin et al. (21), who performed a long-term nonrandomized observational study similar to ours, but only included men. That study had several of the same limitations as ours. The CPAP was offered to patients with OSA in a nonrandom fashion. Patients who did not accept it were considered untreated, whereas those who accepted CPAP and continued to use it were considered treated. Like us, they reported that patients with untreated OSA but without HF had a higher cardiovascular mortality rate than those without OSA after controlling for confounding factors. Although no direct comparison of mortality rate between treated and untreated OSA patients was made, the mortality rate in men with treated OSA did not differ from those without OSA.

Our findings also complement those of Marin et al. (21) in several ways. First, in our study, patients both with and without OSA did not come from a sleep clinic population, but were drawn from an unselected HF population. They were included regardless of the presence or absence of a complaint of excessive daytime sleepiness, and in fact, most did not complain of sleepiness. In contrast, Marin et al. (21) studied patients referred to a sleep disorders clinic because of a suspicion of sleep apnea, most of whom complained of sleepiness. Data from the present study suggest that even in the absence of subjective sleepiness, untreated OSA has an adverse impact on prognosis in patients with HF. Second, because we studied a different patient population who had HF and included both men and women, our results suggest that untreated OSA has generally adverse effects on survival in diverse populations. Third, we compared survival directly in treated and untreated HF patients with OSA, and observed a nonsignificant trend to greater survival in those who were treated.

## Conclusions

Data from this prospective observational study with up to 7.3 years of follow-up suggest that in patients with HF, OSA confers an increased risk of death independently of

known risk factors. Although they also suggest a tendency for treatment of OSA by CPAP in patients with HF to improve survival beyond that achieved with optimal pharmacological therapy, our data cannot be considered definitive in this latter respect because this tendency was not statistically significant, and because of the limitations of our study design as previously discussed. These observations do, however, provide a strong rationale for conducting a large-scale, randomized trial to determine whether treating OSA in patients with HF improves survival.

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