Obstructive Sleep Apnea and Heart Failure
Pathophysiological and Therapeutic Implications

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Obstructive sleep apnea (OSA) exposes the cardiovascular system to intermittent hypoxia, oxidative stress, systemic inflammation, exaggerated negative intrathoracic pressure, sympathetic overactivation, and elevated blood pressure (BP). These can impair myocardial contractility and cause development and progression of heart failure (HF). Epidemiological studies have shown significant independent associations between OSA and HF. On the other hand, recent prospective observational studies reported a significant association between the presence of moderate to severe OSA and increased risk of mortality in patients with HF. In randomized trials, treating OSA with continuous positive airway pressure suppressed sympathetic activity, lowered BP, and improved myocardial systolic function in patients with HF. These data suggest the potential for treatment of OSA to improve clinical outcomes for patients with HF. However, large-scale randomized trials with sufficient statistical power will be needed to ascertain whether treatment of OSA will prevent development of, or reduce morbidity and mortality from HF. (J Am Coll Cardiol 2011;57:119–27) © 2011 by the American College of Cardiology Foundation

Despite therapeutic advances, morbidity and mortality from heart failure (HF) remain high (1). Accordingly, it is important to identify treatable conditions that might contribute to the progression of HF. One such condition may be obstructive sleep apnea (OSA) (2). OSA is caused by repetitive collapse of the pharynx that triggers apneas during sleep. Repetitive apneas expose the cardiovascular system to a cascade of intermittent hypoxia, exaggerated negative intrathoracic pressure, surges in sympathetic nervous system activity (SNA) and blood pressure (BP), and frequent awakenings, all of which may have adverse cardiovascular consequences (3–6).

The purpose of this review is to highlight pathophysiological and therapeutic implications of OSA in patients with HF, and to identify areas of investigation with potential to advance the field. We confine our discussion to HF due to left ventricular (LV) systolic dysfunction.

**Diagnosis of OSA**

Apnea is defined as a >90% reduction in tidal volume lasting ≥10 s, and hypopnea is a reduction in tidal volume of 50% to 90%, lasting ≥0 s accompanied by ≥3% decrease in oxyhemoglobin saturation (SaO2) or terminated by arousal from sleep (7). An OSA disorder is generally defined as the presence of ≥5 episodes of apnea or hypopnea per hour of sleep (i.e., apnea-hypopnea index [AHI]) and when accompanied by either hypersomnolence or at least 2 episodes of choking or gasping during sleep, recurrent awakenings, unrefreshing sleep, daytime fatigue, or impaired concentration or memory, constitutes an OSA syndrome (7). OSA is usually confirmed by overnight polysomnography in a sleep laboratory during which sleep architecture, cardiac rhythm, SaO2, airflow, and thoracoabdominal movements are recorded (7,8). Because of limited availability of polysomnography, portable cardiorespiratory monitoring devices have been developed for in-home screening and diagnosis of OSA. However, many different devices are on the market, several of which have not undergone rigorous validation, particularly in the HF population. Therefore, more research is required to demonstrate their validity in HF patients.

**Pathogenesis of OSA**

Patients with OSA generally have a narrow pharynx related to fat accumulation in the neck that compromises the pharyngeal lumen, to micrognathia, or to tonsillar hypertrophy. At sleep onset, loss of pharyngeal dilator muscle tone causes complete or partial pharyngeal collapse causing obstructive apneas and hypopneas, respectively (9).

Although OSA probably contributes to the development or progression of HF, HF might also contribute to causation of OSA. According to this view, fluid accumulation in the legs...
while upright during the day could shift into the neck when recumbent during sleep. Such fluid displacement might cause distension of the neck veins and/or edema of the peripharyngeal soft tissue that increases peripharyngeal tissue pressure, predisposing to pharyngeal obstruction.

To explore this possibility, several studies employed lower body positive pressure via anti-shock trousers inflated to 40 mm Hg to mimic overnight rostral fluid movement in healthy nonobese men. Lower body positive pressure displaced approximately 300 to 350 ml of fluid from both legs, increased neck circumference, pharyngeal airflow resistance, and collapsibility, and reduced pharyngeal caliber (10–12). In 23 otherwise healthy nonobese men, Redolfi et al. (13) demonstrated that the greater the amount of fluid displaced spontaneously from the legs overnight, the greater the overnight increase in neck circumference and the AHI (R = −0.773, p < 0.001). Yumino et al. (14) made similar observations in men with HF and predominantly OSA. Overnight reduction in leg fluid was, in turn, directly proportional to sitting time during the day and degree of leg edema, and inversely proportional to physical fitness. These observations strongly suggest that in HF, overnight rostral fluid displacement from the legs contributes to the severity of OSA by causing fluid accumulation in the neck that narrows the pharynx and increases its collapsibility during sleep. The volume of fluid displacement is related to sedentary living and leg edema. Nevertheless, whether OSA precedes or arises secondary to HF, once present, it is likely to provoke adverse cardiovascular effects.

Night-to-night variations in rostral fluid displacement may help to explain some of the internight variability in the AHI that has been described in OSA patients without HF (15). Therefore, alterations in volume status in HF patients might also be accompanied by alterations in the AHI. However, there are few data on night-to-night variability of AHI in patients with HF.

Both OSA and central sleep apnea (CSA) are common in patients with HF and can coexist in the same patient (16,17). Yumino et al. (14) showed in HF patients that with progressively greater amounts of nocturnal rostral fluid displacement, there was a gradation from an AHI <15, to OSA with an AHI ≥15, to CSA with AHI ≥15. These findings help to explain why OSA and CSA can coexist in HF patients, and why the predominant type can change over time (16,18): apnea type and severity may vary according to alterations in fluid volume status and cardiac function. For example, data from the CANPAP (CANadian continuous Positive Airway Pressure for patients with heart failure and central sleep apnea) trial demonstrated a spontaneous conversion from predominantly CSA to predominantly OSA in 18% of subjects in the control arm in association with an improvement in left ventricular ejection fraction (LVEF) (19). If the improvement in LVEF was accompanied by decreased fluid retention and overnight rostral fluid shift, this might be 1 mechanism through which this conversion occurred.

Cardiovascular Effects of OSA

Effects of sleep. Normally, metabolic rate, SNA, BP, and heart rate (HR) decrease (20), and cardiac vagal activity increases during non-rapid eye movement (REM) sleep (21). Although intermittent surges in SNA, BP, and HR occur in REM sleep, in general, the average BP and HR remain below waking levels (20). Thus, sleep is characterized by cardiovascular quiescence. However, this is disrupted by OSA with potentially adverse consequences. In addition, patients with HF sleep approximately 1.3 h less than subjects without HF, and may not enjoy fully the restorative effects of sleep (22,23).

Mechanical effects. During obstructive apneas, negative inspiratory intrathoracic pressure generated against the occluded pharynx increases LV transmural pressure, and hence afterload (Fig. 1) (24). It also increases venous return, augmenting right ventricular (RV) pre-load, whereas OSA-induced hypoxic pulmonary vasoconstriction increases RV afterload (25). Consequent RV distension and leftward septal displacement during diastole impairs LV filling (26). This combination of increased LV afterload and diminished preload reduces stroke volume and cardiac output more in HF patients than in healthy subjects (27,28). Whereas stroke volume recovers abruptly to baseline in healthy subjects at apnea termination, recovery is delayed in patients with HF (24).

Increased LV transmural pressure also increases myocardial oxygen demand while simultaneously reducing coronary blood flow during which apnea-related hypoxia reduces oxygen delivery (2,24,29). This can precipitate myocardial ischemia and impair cardiac contractility and diastolic relaxation (30,31). Over time, such stresses may contribute to development or progression of cardiac remodeling, hypertrophy, and failure.

Autonomic effects. Intermittent hypoxia and CO₂ retention stimulate central and peripheral chemoreceptors that augment SNA (32) (Fig. 2). Apnea also enhances SNA by eliminating reflex inhibition of SNA arising from pulmonary stretch receptors (33). Reductions in stroke volume and BP during obstructive apneas unload carotid sinus baroreceptors and reflexively augment SNA. This is exaggerated in patients with HF (29). Arousal from sleep at apnea termination also augments SNA and reduces cardiac vagal activity.
that precipitate post-apneic surges in BP and HR (34). These adverse autonomic effects of OSA may persist into wakefulness (35–37).

Spaak and colleagues (38) demonstrated that among patients with HF, the presence of OSA was associated with higher muscle SNA than in those without OSA. These observations in conjunction with those of Usui et al. (39), that treating OSA with continuous positive airway pressure (CPAP) in HF patients reduced muscle SNA in association with BP lowering, indicated that OSA contributes to BP elevations partly via sympathetic excitation. Elevated SNA is associated with increased mortality risk in patients with HF (40), probably by causing cardiac beta-adrenoreceptor desensitization, myocyte injury and necrosis, and hypertension (41). Reduced cardiac vagal activity that increases HR but reduces high frequency HR variability may also contribute to an increased risk for cardiac arrhythmias and mortality (42). Therefore, OSA may contribute to worse prognosis in HF at least partly through autonomic dysregulation.

**Oxidative, inflammatory, and vascular endothelial effects.** Intermittent hypoxia and post-apneic reoxygenation induce oxidative stress, generate reactive oxygen species, and provoke inflammation. Reactive oxygen species diminishes nitric oxide levels and hence, impairs endothelially mediated vasodilation that could contribute to development of hypertension (43). Patients with OSA have low plasma nitrite concentrations and attenuated endothelium-dependent vasodilation that can improve with CPAP (44).

Reactive oxygen species can also activate nuclear transcriptional factors, including nuclear factor-kappa B (NF-κB), which stimulates production of inflammatory mediators such as tumor necrosis factor-α, interleukin [IL]-6, IL-8, and C-reactive protein, as well as adhesion molecules such as intracellular and vascular cell adhesion molecules, E selectin, and CD15 (45). Such effects could facilitate endothelial damage and atherogenesis. In mice, exposure to intermittent hypoxia and a high cholesterol diet provokes lipid peroxidation and induces aortic atherosclerosis, although neither stimulus alone has this effect (46). Therefore, the combination of OSA with hypercholesterolemia may be atherogenic. Compared with control subjects, patients with OSA display greater signs of early atherosclerosis, including increased carotid intima-media thickness, and a higher prevalence of silent brain infarcts (47–49). Non-randomized studies reported that treatment of OSA by CPAP lowered levels of several inflammatory mediators (50,51), and a randomized trial demonstrated that treatment of OSA by CPAP reduced carotid intima-media thickness, supporting a cause–effect relationship between OSA and atherosclerosis (52). Therefore, promotion of coronary atherosclerosis, the commonest cause of HF, is another means by which OSA could contribute to the development of HF.
Arrhythmogenic effects. Intermittent hypoxia can cause HR to decrease, increase, or remain constant depending on whether parasympathetic or sympathetic activity dominates, or whether their influences are relatively equal, respectively (53). In dogs, pacing of the right atrium increases the autonomic activity of the right pulmonary arterial ganglionated plexi during apnea, and induces atrial fibrillation (AF) (54). Stimulation of such ganglionated plexi during obstructive apneas may therefore be one means by which OSA can induce AF. Myocardial stretch caused by the mechanical effects of OSA may also precipitate atrial and ventricular arrhythmias (55). Myocardial ischemia and activation of cardiac inflammatory pathways can also predispose to atrial and ventricular arrhythmias (56,57).

Although epidemiological studies have not demonstrated an increased prevalence of bradyarrhythmias in OSA (58), apnea-induced hypoxia can provoke atrioventricular block and asystole that is reversible by atropine or treatment of OSA (59–61). These observations demonstrate a role for OSA in their causation.

Compared with subjects without OSA, those with severe OSA are more likely to have AF, nonsustained ventricular tachycardia, ventricular bigeminy, and trigeminy (58). Several studies showed that OSA predicts new-onset AF (62,63) or its recurrence following cardioversion to sinus rhythm (64). On the other hand, 2 studies in patients with and without HF demonstrated strong relationships between AF and CSA, but not OSA (65,66). Such discrepancies may be explained by differences in patient populations and classification of respiratory events. Two observational studies reported that treatment of OSA by tracheostomy was accompanied by a reduction in the frequency of tachyarrhythmias (67), and that the recurrence rate of AF 1 year after cardioversion was significantly lower in patients with CPAP-treated OSA than those with untreated OSA (64). In a randomized trial, treatment of OSA by CPAP in patients with HF reduced the frequency of nocturnal ventricular ectopy (68). In HF patients with cardioverter-defibrillators, device discharges occurred more frequently in patients with than those without sleep apnea, particularly during sleep time, suggesting a link between OSA and nocturnal malignant arrhythmias (4,69,70).

**Epidemiology and Clinical Features of OSA**

Data from the Sleep Heart Health Study showed that OSA with an AHI ≥11 was independently associated with 2.38 relative odds of having HF (4). Hypertension is likely an intermediate step between OSA and HF (3). Indeed, hypertensive subjects whose BP does not fall normally at
night (i.e., nondippers) have greater risk for LV hypertrophy and failure than those whose BP falls normally at night (i.e., dippers) (71). Since OSA causes nondipping of BP at night, it may contribute to this increased risk (72). Other factors, described above, may also contribute to the development of HF.

Several polysomnographic studies in HF patients reported prevalences of OSA (12% to 53%) higher than in the general population (Fig. 3) (17,73–75). Risk factors for OSA in patients with HF include older age, male sex, and greater body mass index (BMI) (17). Arzt et al. (22) reported that compared with the general population, in whom AHI increases as a function of BMI, HF patients have lower BMI for any given AHI, with a much weaker correlation between AHI and BMI. Consequently, factors other than obesity, such as nocturnal rostral fluid displacement, must play a greater role in the pathogenesis of OSA in the HF than in the general population.

In patients with HF, OSA is more common in men than in women (17), and most are habitual snorers (76). However, compared with the general population, HF patients with OSA complain of hypersomnolence less often, and have lower Epworth Sleepiness Scale scores at any given AHI (22). In contrast to the general population, there is no significant relationship between the Epworth score and increasing AHI. Furthermore, for any given AHI, patients with HF have a longer sleep-onset latency, and less sleep than the general population despite being less sleepy (22).

Marin et al. (5) reported, in subjects without HF, that those with untreated, severe OSA (AHI ≥30) had a 2.9 times higher fatal cardiovascular event rate than controls (AHI <5). Punjabi et al. (77) reported similar results. Wang et al. (78) reported that among 37 patients with untreated moderate to severe OSA, the mortality rate was higher than in 113 patients with mild or no OSA (p = 0.029) after controlling for confounding factors (Fig. 4). In another study, patients with HF were divided into those...
with ischemic (n = 79) and nonischemic (n = 114) cardiomyopathy, and were subdivided into those with and without SA of whom approximately 50% had mainly OSA. In the ischemic group, mortality was significantly higher in those with, than in those without SA (p = 0.043), due mainly to a higher sudden death rate (70). Mortality rate appeared to increase with an AHI >15. In contrast, in the nonischemic group, SA was not associated with increased mortality. These data imply that patients with ischemic HF are more susceptible to the adverse effects of apnea-related hypoxia, elevated SNA, and/or cardiac arrhythmias, possibly related to worsening of myocardial ischemia, than those with nonischemic HF. In contrast, Roebuck et al. (79) did not find increased mortality associated with OSA in patients with HF. However, since they did not analyze separately those with treated and untreated OSA, conclusions are difficult to draw.

**Treatment of OSA in Patients With HF**

**Effects of HF therapy on OSA.** There are no studies in which the effects of therapy of HF on OSA have been tested. However, Kraiczi et al. (80) compared the efficacy of atenolol, enalapril, losartan, and hydrochlorothiazide, frequently used HF medications, on BP among hypertensive OSA patients without HF. AHI was not influenced by any of those drugs. Since fluid retention from HF may contribute to the pathogenesis of OSA, Bucca et al. (81) tested the effects of furosemide and spironolactone among 15 patients with diastolic HF and OSA in an uncontrolled trial. Following therapy, pharyngeal caliber increased in association with reduced systolic BP and HR, resulting in reduced LV afterload (86). This cardiac unloading is accompanied by improved myocardial oxidative metabolism (87).

In a 1-month randomized trial involving HF patients with severe OSA, but normal Epworth Sleepiness scores (<10), fixed-pressure CPAP increased LVEF by 9% in association with reduced systolic BP and HR (88). CPAP also reduced sympathetic vasoconstrictor activity (39), indicating that this was a mechanism by which BP was lowered. CPAP also increased high-frequency HR variability and baroreflex sensitivity, indicating an increase in parasympathetic modulation of HR (89,90). Egea et al. (91) also reported that in 50 HF patients with normal Epworth scores not available; RCT randomized-controlled trial; SBP diastolic blood pressure; ESS Epworth sleepiness scale; CPAP = continuous positive airway pressure; AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure; DBP = diastolic blood pressure; LVEF = left ventricular ejection fraction; NA = data not available; RCT = randomized-controlled trial; SBP = systolic blood pressure.

### Table 1 Clinical Trials Assessing Effects of CPAP on Cardiac Function in HF Patients With OSA

<table>
<thead>
<tr>
<th>First Author (Ref. #) Year</th>
<th>Study Design</th>
<th>n</th>
<th>Duration (Months)</th>
<th>AHI</th>
<th>LVEF (%)</th>
<th>ESS</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaneko et al. (88) 2003</td>
<td>RCT</td>
<td>12</td>
<td>1.0</td>
<td>45.2</td>
<td>28.5</td>
<td>5.7</td>
<td>−0.5</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6/−2</td>
</tr>
<tr>
<td></td>
<td>CPAP</td>
<td></td>
<td></td>
<td>37.1</td>
<td>25.0</td>
<td>6.8</td>
<td>−28.8*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−10*/−3</td>
</tr>
<tr>
<td>Mansfield et al. (92) 2004</td>
<td>RCT</td>
<td>21</td>
<td>3.0</td>
<td>26.6</td>
<td>33.6</td>
<td>8.8</td>
<td>−8.4</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−6</td>
</tr>
<tr>
<td></td>
<td>CPAP</td>
<td></td>
<td></td>
<td>25.0</td>
<td>37.6</td>
<td>9.5</td>
<td>−21.1*</td>
</tr>
<tr>
<td>Smith et al. (93) 2007</td>
<td>RCT-double crossover</td>
<td>23</td>
<td>1.5</td>
<td>36.0</td>
<td>29.0</td>
<td>10.0</td>
<td>NA</td>
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<tr>
<td></td>
<td>Sham CPAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>ACPAP</td>
<td></td>
<td></td>
<td>35.0</td>
<td>27.2</td>
<td>6.9</td>
<td>−7.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−1.6/1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>44.0</td>
<td>28.8</td>
<td>8.6</td>
<td>−32.9</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>−0.0/0.4</td>
</tr>
</tbody>
</table>

*p < 0.01 for comparison between groups. †p < 0.05 for comparison between groups. ‡This study included patients with both obstructive and central sleep apnea. Therefore, all data shown here were for patients with OSA only, except for AHI.

ACPAP = auto-titrating continuous positive airway pressure; AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure; DBP = diastolic blood pressure; LVEF = left ventricular ejection fraction; NA = data not available; RCT = randomized-controlled trial; SBP = systolic blood pressure; HF = heart failure; LVEF = left ventricular ejection fraction; NA = data not available; RCT = randomized-controlled trial; SBP = systolic blood pressure.
scores, CPAP improved LVEF after 3 months. However, CPAP did not improve Epworth scores, quality of life (QOL), New York Heart Association functional class, or 6-min walking distance. In a 3-month randomized trial involving 40 patients with less severe HF and OSA but an elevated Epworth score (>10), Mansfield et al. (92) reported that CPAP reduced urinary norepinephrine concentration, and improved LVEF and QOL, but not BP. In another randomized trial, Smith et al. (93) found no improvement in LVEF in HF patients with OSA while on CPAP. In contrast to the previously mentioned trials, they used autotitrating CPAP, and did not confirm that it eliminated OSA on a sleep study at the end of the trial.

These observations lead to several conclusions (Table 1). First, fixed-pressure CPAP consistently increased LVEF and decreased SNA (39,68,88,92). Second, larger CPAP-related increases in LVEF and reductions in BP occurred in trials involving patients with lower LVEF and higher AHIs (88,91–93). Third, CPAP improved Epworth scores and QOL in patients with Epworth scores >10 (92), but failed to do so in patients with Epworth scores <10 (91). Finally, autotitrating CPAP failed to improve LVEF (93). Thus, differences in trial design, methodologies, patient characteristics, and the type of CPAP employed may explain some of the discrepancies in their results.

Two nonrandomized observational studies addressed the effects of treating OSA on morbidity and mortality in HF patients (Table 2). In the first, there was a trend to lower mortality in the 14 who accepted CPAP than in the 37 who did not (p = 0.07) over 2.9 years (78). In the second, involving 88 HF patients with OSA, hospitalization-free survival was significantly greater in the 65 CPAP-treated patients than in the 23 untreated patients over 2.1 years (94). Although promising, these results are not conclusive due to the nonrandomized nature of the studies and their small sample sizes.

The evidence in the preceding text suggests that, just as in the non-HF population, the main indication for treating OSA in HF patients is hypersonolence, where treating OSA reduces sleepiness and improves QOL (92). However, most HF patients with OSA are not hypersonolent (22). In such patients, indications for treating OSA have not been clearly defined. Adequately powered randomized trials will be required to assess whether treating OSA in nonsleepy HF patients improves cardiovascular outcomes.

Conclusions

OSA has adverse cardiovascular effects and is associated with reduced survival in patients with HF. Although small-scale randomized trials demonstrate that treating OSA in HF patients improves cardiovascular and autonomic function, and in patients with hypersonolence, reduces sleepiness, such trials have not established whether treating OSA reduces morbidity and mortality. Consequently, further research is required to establish basic mechanisms by which OSA contributes to cardiac dysfunction, and large-scale randomized trials are needed to determine whether treating OSA in nonsleepy HF patients reduces morbidity and mortality. In the broader context, it would also be valuable to examine alternatives to CPAP for treating OSA in patients with HF. For example, intensified diuresis or applying the principles of chronopharmacology to block adverse nocturnal cardiovascular effects of OSA might be explored. Accordingly, opportunities abound to advance knowledge in this field and to improve the outlook for the many patients with HF who also suffer from OSA.

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REFERENCES


Table 2 Observational Studies Assessing Efficacy of CPAP on Morbidity and Mortality in HF Patients With OSA

<table>
<thead>
<tr>
<th>First Author (Ref. #) Year</th>
<th>n</th>
<th>Mean/Maximum Follow-Up yrs</th>
<th>Age (yrs)</th>
<th>BMI (kg/m²)</th>
<th>Male (%)</th>
<th>AHI</th>
<th>LVEF (%)</th>
<th>ICM (%)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al. (78) 2007</td>
<td>88</td>
<td>37 2/7.3</td>
<td>58.5</td>
<td>30.1</td>
<td>87</td>
<td>32.8</td>
<td>25.9</td>
<td>41</td>
<td>Trend for reduced mortality in treated group (p = 0.07)</td>
</tr>
<tr>
<td>Kasai et al. (94) 2008</td>
<td>88</td>
<td>65 2.1/4.8</td>
<td>59.8</td>
<td>24.9</td>
<td>83</td>
<td>38.1</td>
<td>35.0</td>
<td>30</td>
<td>Lower death and hospitalization risk in treated group (p = 0.03)</td>
</tr>
</tbody>
</table>

*p < 0.05 for comparison between groups.

BMI = body mass index; ICM = ischemic cardiomyopathy; OSA = obstructive sleep apnea; other abbreviations as in Table 1.


Key Words: heart failure • pathophysiology • prognosis • sleep apnea.