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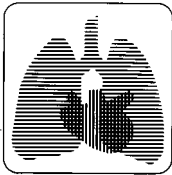
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## reviews

# The Role of Continuous Positive Airway Pressure in the Treatment of Congestive Heart Failure\*

Andrew T. Yan, MD; T. Douglas Bradley, MD; and Peter P. Liu, MD

**Congestive heart failure (CHF) is a serious medical condition frequently associated with sleep-related breathing disorders, which remain underdiagnosed and undertreated. Recent studies have provided important insight into the pathophysiology of sleep apnea syndrome in patients with CHF, with potential therapeutic implications. In addition to abolition of sleep apnea, continuous positive airway pressure (CPAP) treatment can improve cardiac function and relieve symptoms of CHF. Postulated mechanisms include beneficial hemodynamic effects on ventricular remodeling, unloading of fatigued respiratory muscles, and neurohormonal modulation. Although medium-term studies using CPAP to treat sleep-related breathing disorders associated with CHF have been encouraging, more definitive data from ongoing large clinical trials are necessary to clarify its therapeutic role.** (CHEST 2001; 120:1675–1685)

**Key words:** central sleep apnea; Cheyne-Stokes respiration; congestive heart failure; continuous positive airway pressure; obstructive sleep apnea

**Abbreviations:** ACE = angiotensin-converting enzyme; ANP = atrial natriuretic peptide; CHF = congestive heart failure; CI = confidence interval; CPAP = continuous positive airway pressure; CSA = central sleep apnea; CSR = Cheyne-Stokes respiration; OSA = obstructive sleep apnea; LV = left ventricular; LVEF = left ventricular ejection fraction; PCWP = pulmonary capillary wedge pressure

Congestive heart failure (CHF) currently affects 1.5 to 2.0% of the population<sup>1</sup> and is associated with excessive morbidity and mortality. It is the only major cardiovascular disease that is increasing in prevalence and incidence, due to the aging popula-

tion, reduction in acute cardiovascular mortality, and relatively ineffective treatment for CHF. Data from the Framingham Heart Study suggested that the median survival after the onset of CHF was only 1.7 years for men and 3.2 years for women.<sup>2</sup> Despite major advances in therapy, prognosis remains dismal. In the recent Randomized Aldactone Evaluation Study,<sup>3</sup> for example, in which 95% of patients were receiving an angiotensin-converting enzyme (ACE) inhibitor, mortality after 2 years was 46% for the placebo group and 35% for the spironolactone group. CHF has now emerged as the leading cause of hospitalization in patients > 65 years old. In the United States, the annual direct cost of CHF is estimated at \$20 to \$40 billion,<sup>4</sup> thus prompting a search for novel and more effective therapy. One promising approach to this problem is the diagnosis and specific treatment of sleep-related breathing disorders in patients with CHF. This review article summarizes the data on the association between sleep-related breathing disorders and CHF, and on

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the effects of their specific therapy with nasal continuous positive airway pressure (CPAP) on cardiovascular outcomes.

#### EPIDEMIOLOGY OF SLEEP-RELATED BREATHING DISORDERS IN PATIENTS WITH CHF

While substantial evidence indicates that obstructive sleep apnea (OSA) is an independent risk factor in the pathogenesis of myocardial ischemia, and systemic and pulmonary hypertension,<sup>5</sup> the epidemiology of sleep-related breathing disorders in patients with CHF has not been well studied. Recent reports suggest that these breathing disorders are very common in patients with CHF. Indeed, Cheyne-Stokes respiration (CSR), which when present during sleep constitutes a form of central sleep apnea (CSA), was first described in a patient with CHF.<sup>6</sup> Findley et al<sup>7</sup> studied 15 patients with CHF and reported that 40% had CSR with CSA. In patients < 60 years old awaiting heart transplantation, 45% had > 10 episodes of predominantly central apnea per hour.<sup>8</sup> In a 1998 study involving 81 ambulatory, male patients with stable CHF, 40% and 11% were found to have CSA and OSA, respectively.<sup>9</sup> In the largest study to date (and to our knowledge), which included 450 consecutive CHF patients referred to our sleep laboratory, Sin et al<sup>10</sup> found that 62% of patients had sleep apnea defined as an apnea-hypopnea index of > 10 per hour of sleep; 33% of patients had mainly OSA and 29% had mainly CSA. Although these latter figures may reflect a referral bias, it is noteworthy that all the above-cited studies reported a much higher prevalence of sleep-related breathing disorder among patients with CHF than among otherwise healthy subjects, in whom the prevalence is approximately 4 to 9%.<sup>11</sup> Therefore, sleep-related breathing disorders appear to be more common in the CHF population and are probably underdiagnosed.

In the past, CSR-CSA was seen as no more than an enigma whose pathophysiology fascinated generations of physiologists and clinicians. It is only more recently, with the observation that CSR-CSA is associated with increased mortality in patients with CHF, that its clinical significance has become more apparent.<sup>7,12-14</sup> The possibility that CSR-CSA can accelerate the progression of CHF has therefore revived interest in elucidating its pathophysiology. These observations have also heightened interest in examining the potential adverse impact of OSA in patients with CHF. Finally and most importantly, the possibility that abolition of these sleep-related breathing disorders in patients with CHF will lead to improvements in symptoms and survival has been raised.

#### PATHOPHYSIOLOGY OF SLEEP APNEA IN HEART FAILURE

##### OSA

OSA has a number of detrimental physiologic effects on the cardiovascular system that are mediated through several mechanisms. The generation of exaggerated negative intrathoracic pressure against an occluded upper airway during apnea increases systolic transmural pressure and hence left ventricular (LV) afterload, and can reduce stroke volume and cardiac output.<sup>15,16</sup> Augmented venous return to the right ventricle occurs as a result of exaggerated negative intrathoracic pressure. The resulting right ventricular distention promotes leftward shift of the interventricular septum, causing impairment of LV filling and reduction in stroke volume.<sup>17</sup> Hypoxia during apnea can also precipitate cardiac ischemia and arrhythmias, and may even reduce myocardial contractility.<sup>18,19</sup> Recurrent hypoxia and hypercapnea, in concert with apneas and arousals at their terminations, are potent stimuli of the sympathetic nervous system that lead to vasoconstriction, elevations in BP and further increases in LV afterload.<sup>20,21</sup> These adverse effects on the cardiovascular system are likely more pronounced in patients with underlying coronary artery disease or cardiomyopathy than in subjects with normal cardiac function.<sup>22,23</sup>

It has recently been established that OSA is an independent risk factor for chronic hypertension,<sup>24-27</sup> which in turn predisposes to LV failure. Increases in sympathetic nervous system activity and BP at night, secondary to OSA, appear to carry over into the daytime,<sup>28</sup> and probably account, to some extent, for the high prevalence of hypertension in patients with OSA. Some studies<sup>26,27</sup> have shown a dose-response relationship between the frequency of sleep apnea and daytime BP that is independent of known confounding factors, such as age and body mass index. In hypertensive patients with OSA, treatment with nasal CPAP has been reported to reduce overnight urinary norepinephrine levels, sympathetic nervous system activity, and daytime BP.<sup>29</sup> These observations lend further support to a cause-effect relationship between OSA and hypertension. In addition, Hedner et al<sup>30</sup> showed that even normotensive patients with OSA have thicker LV walls than normotensive control subjects. In a long-term, canine model, exposure to OSA over several weeks to months led to the development of daytime hypertension, LV hypertrophy, and a reduction in LV ejection fraction (LVEF).<sup>31,32</sup> These observations suggest that increased LV afterload and sympathetic activation during sleep can, over time, lead to systemic hypertension, LV hypertrophy, and dysfunction. In a 1999 study,<sup>10</sup> approximately one third of

450 patients with CHF secondary to ischemic, hypertensive, or idiopathic dilated cardiomyopathy were found to have OSA. Taken together, these data provide strong evidence that OSA can contribute to the development and progression of LV hypertrophy and failure.

### *CSR With CSA*

CSR-CSA is a form of periodic breathing in which central apneas alternate with ventilatory periods that have a gradually waxing-waning pattern of tidal volumes. Naughton and coworkers<sup>33</sup> demonstrated that in patients with CHF, hyperventilation and the subsequent reduction in PaCO<sub>2</sub> below the apneic threshold play a critical role in the initiation and propagation of CSR-CSA. They also found that compared to CHF patients without CSR-CSA, those with CSR-CSA had significantly lower PaCO<sub>2</sub> while awake and lower mean transcutaneous PCO<sub>2</sub> while asleep. Circulation time, LVEF, and mean nocturnal oxygen saturation did not differ between CHF patients with and without CSR-CSA. Nevertheless, there was a significant correlation between lung-to-chemoreceptor circulation time and the lengths of hyperpnea and CSR-CSA cycle. Thus, the gradual and delayed transmission of changes in PaO<sub>2</sub> and PaCO<sub>2</sub> from the lungs to the carotid bodies because of low cardiac output accounts for the longer hyperpnea and the crescendo-decrescendo pattern of tidal volumes observed in patients with CHF than in patients with CSA but normal cardiac function.<sup>34</sup> Therefore, whereas hyperventilation and reductions in PaCO<sub>2</sub> precipitate central apneas and determine their lengths, low cardiac output and increased circulation time determine the waxing-waning pattern of tidal volumes and lengths of hyperpneas in patients with CSR-CSA.

The cause of hyperventilation remains unclear. Hypoxemia in patients with long-term, stable CHF is usually mild and does not appear to play an important role in causing hyperventilation.<sup>33,35</sup> A more likely explanation for hyperventilation is stimulation of pulmonary vagal irritant receptors by pulmonary congestion. Solin et al<sup>36</sup> showed that pulmonary capillary wedge pressure (PCWP) is higher in CHF patients with CSR-CSA than in those without it; in addition, there was a weak but significant negative relationship between PCWP and PaCO<sub>2</sub>. Tkacova et al<sup>35</sup> also demonstrated that LV end-diastolic volume was almost twice as high in patients with CSR-CSA than in those without it, and was associated with lower PaCO<sub>2</sub>. It is likely that those patients with high end-diastolic volume also had elevated LV filling pressures.

Another possible mechanism for hyperventilation is enhanced ventilatory sensitivity to CO<sub>2</sub>. Javaheri<sup>37</sup> demonstrated that ventilatory responsiveness to CO<sub>2</sub> was greater in CHF patients with CSA-CSR than in those without it. Such an increase in ventilatory drive can contribute to hyperventilation in response to chemical stimuli and arousals from sleep at the termination of apneas. This would, in turn, predispose to hypocapnia-induced central apneas. More recently, Lorzeni-Filho and colleagues<sup>38</sup> confirmed the fundamental role of hypocapnia in the pathogenesis of CSR-CSA by demonstrating that raising PaCO<sub>2</sub> above the apneic threshold, through inhalation of a CO<sub>2</sub>-enriched gas, completely abolished CSR-CSA.

From the clinical standpoint, CSR-CSA has adverse prognostic implications for patients with CHF. Several studies<sup>7,12-14</sup> have consistently shown a higher mortality rate in CHF patients with CSR-CSA, compared to those without CSR-CSA, even after adjustment for other known risk factors. The detrimental effects of CSR-CSA on the cardiovascular system probably arise from factors similar to those described above for OSA, including intermittent hypoxia, frequent arousals from sleep, activation of the sympathetic nervous system, and apnea-related surges in BP and heart rate. However, unlike OSA, negative intrathoracic pressure is not generated during central apneas.

### *Effects of CPAP in Acute Cardiogenic Pulmonary Edema*

CPAP has been used to treat patients with acute cardiogenic pulmonary edema. In a randomized, controlled trial<sup>39</sup> involving 40 patients with acute cardiogenic pulmonary edema, the control group received standard medical therapy and oxygen, while the treatment group received, in addition, CPAP of 10 cm H<sub>2</sub>O via a full face mask. Compared with the control group, the CPAP group had a more rapid and pronounced increase in PaO<sub>2</sub> and decrease in PaCO<sub>2</sub>. There was also a trend toward less treatment failure requiring intubation, using predetermined criteria ( $p = 0.068$ ). In another trial of similar design, Bersten et al<sup>40</sup> studied 39 consecutive patients with severe cardiogenic pulmonary edema. The group randomized to CPAP treatment experienced a significantly greater increase in PaO<sub>2</sub> and decrease in PaCO<sub>2</sub> and respiratory rate. In addition, whereas intubation and ventilation were necessary in 35% of patients randomized to the control group, they were not required in any of the patients who received CPAP ( $p = 0.005$ ). There was, however, no difference in in-hospital-mortality or length of hospital stay. In a larger and longer-term, randomized, con-

trolled study<sup>41</sup> involving 100 patients with cardiogenic pulmonary edema, compared with the control subjects, the CPAP group had a significantly lower alveolar-arterial oxygen tension gradient, higher stroke volume index, and lower rate of intubation and ventilation. At 1-year follow-up, there was no difference in LVEF or mortality between the two groups, likely due to the small sample size. A rigorous systematic review<sup>42</sup> pooled the data from these three randomized trials, and concluded that CPAP was associated with a 26% lower risk of intubation (confidence interval [CI], -13% to -38%) and a trend toward decreased mortality (risk difference, -6.6%; CI, +3% to -16%). Accordingly, acute cardiogenic pulmonary edema is a clear novel indication for treatment with CPAP. CPAP may also be a cost-effective way to prevent recurrent acute pulmonary edema and hospitalizations in patients with end-stage CHF.<sup>43</sup>

#### Effects of CPAP on OSA and CSA

The role of nasal CPAP in the treatment of OSA has been well established.<sup>44</sup> In patients with OSA,

CPAP creates a pneumatic splint, thereby preventing closure of the upper airway during sleep. Numerous studies<sup>44-46</sup> have proved that CPAP improves neurobehavioral function and daytime sleepiness, and may alleviate pulmonary hypertension in patients with OSA. CPAP also relieves OSA in patients with CHF through the same mechanisms. In so doing, it abolishes intermittent apnea-related hypoxia, lowers nocturnal BP and afterload, reduces arousals, and consolidates sleep (Fig 1).<sup>47</sup> On these grounds alone, CPAP is indicated in CHF patients with coexistent symptomatic OSA.

CPAP can also alleviate CSR-CSA in patients with CHF, although its mechanisms are not fully elucidated. When applied over a single night or at a pressure < 10 cm for periods of up to 2 weeks, CPAP has been reported not to alleviate CSR-CSA in most CHF patients.<sup>48,49</sup> However, over periods of 1 to 3 months, randomized, controlled clinical trials have demonstrated marked attenuation of CSR-CSA in association with slight improvement of oxygenation and reductions in the frequency of arousals from sleep.<sup>50,51</sup> Another study<sup>52</sup> showed that central

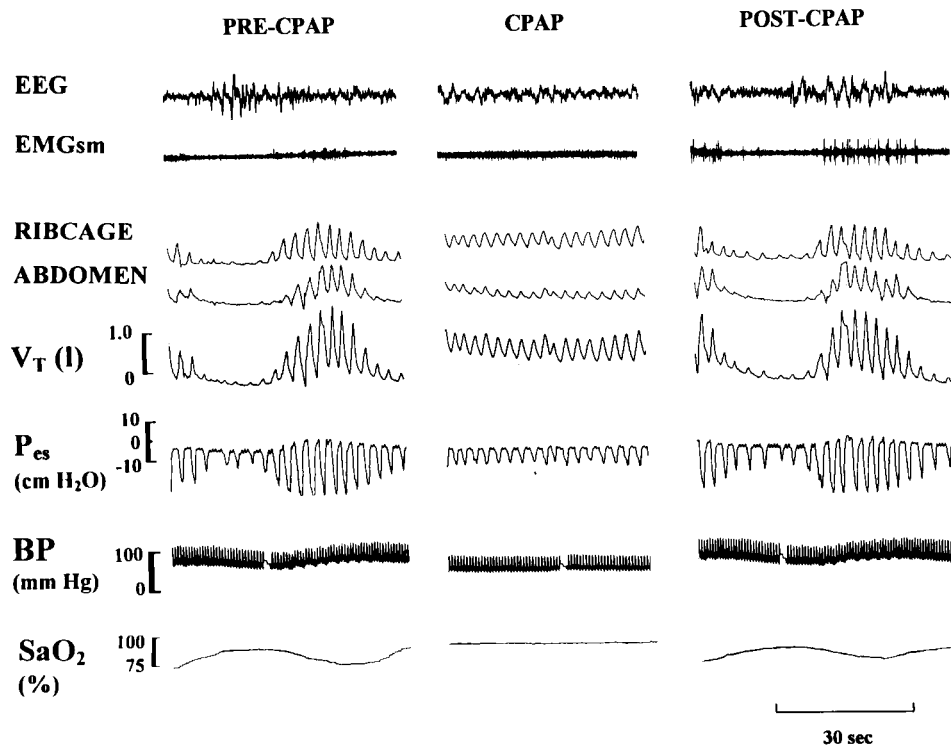


FIGURE 1. Polysomnographic recording<sup>47</sup> during stage 2 sleep before, during, and after CPAP application (PRE-CPAP, CPAP, POST-CPAP, respectively) in a patient with CHF and OSA. The *middle panel* illustrates that by eliminating obstructive apnea, CPAP reduces systolic LV transmural pressure (*ie*, LV afterload) by reducing both negative esophageal pressure (*Pes*) swings and BP. In addition, reductions in pleural pressure amplitude indicate unloading of the inspiratory muscles. Abolition of OSA also improves arterial oxyhemoglobin saturation ( $SaO_2$ ) and eliminates apnea-related arousals. EMGsm = submental electromyogram; VT = tidal volume. Data from Tkacova et al.<sup>47</sup>

apneas and hyperpneas were markedly reduced in frequency by CPAP over 1 month, with a reduction in minute volume of ventilation and a significant increase in PaCO<sub>2</sub> during sleep (Fig 2). These findings suggest that CPAP relieves CSR-CSA by raising PaCO<sub>2</sub> above the apneic threshold. It was hypothesized that CPAP reduced ventilation by redistributing excess lung water to the extrathoracic compartment, thereby reducing stimulation of pulmonary vagal irritant receptors and decreasing ventilatory output. As a result, PaCO<sub>2</sub> would increase. Another potential beneficial effect of CPAP to patients with CSR-CSA relates to lung inflation. By increasing end-expiratory lung volume and thus lung O<sub>2</sub> store, CPAP would dampen apnea-related hypoxic dips and therefore prevent postapneic hyperventilation and hypocapnia. Further research is required to better define the mechanism of action of CPAP in alleviating CSR-CSA in CHF patients.

#### Unloading of Respiratory Muscles

Dyspnea is a prominent and disabling symptom in patients with chronic CHF. Its severity does not appear to be closely related to elevated intrapulmonary vascular pressure or hypoxemia. Although the pathogenesis of dyspnea is likely multifactorial,<sup>53</sup> emerging data indicate that respiratory muscle weakness and dysfunction play an important role. Hammond and coworkers<sup>54</sup> compared handgrip force,

and maximal inspiratory and expiratory pressures in CHF patients with healthy subjects. They found that maximum static respiratory pressures, which were measures of respiratory muscle strength, were disproportionately reduced.<sup>54</sup> This implies that in CHF, respiratory muscles are adversely affected to a greater extent than limb muscles. Another study by McParland et al<sup>55</sup> confirmed this finding; they showed a strong inverse relationship between inspiratory muscle strength and the severity of dyspnea. Moreover, these weakened inspiratory muscles were subject to an increased workload. In a study by Naughton et al,<sup>56</sup> patients with optimally treated CHF had threefold to fourfold greater inspiratory pleural pressure swings than healthy control subjects, probably due to reduced lung compliance caused by pulmonary congestion. These excessive negative inspiratory pleural pressure swings likely play a role in the pathogenesis of dyspnea in patients with CHF. Application of 10 cm H<sub>2</sub>O of CPAP to these patients while awake during regular breathing led to a 40% reduction in the amplitude of pleural pressure swings. This reflected unloading of inspiratory muscles, which was probably due to increased lung compliance secondary to extrathoracic redistribution of lung water. In a randomized, controlled study<sup>57</sup> of patients with CHF and CSR-CSA, nightly application of CPAP over a 3-month period resulted in an improvement of inspiratory but not of expira-

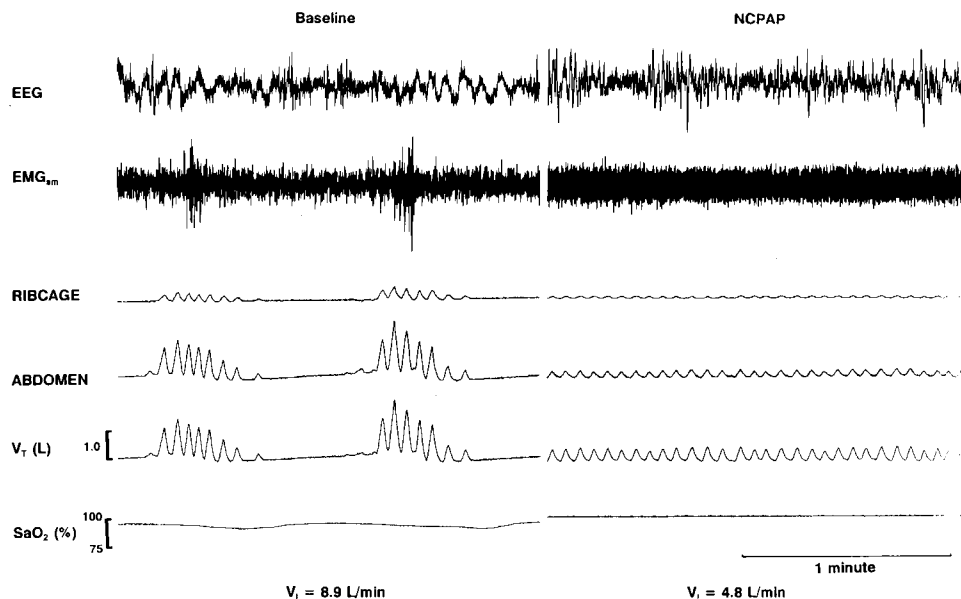


FIGURE 2. Two polysomnographic recordings<sup>52</sup> from the same patient during stage 2 sleep at baseline and at 1-month follow-up receiving 10 cm H<sub>2</sub>O of nasal CPAP. The baseline recording shows typical CSR-CSA with a crescendo-decrescendo pattern of hyperpnea alternating with central apneas. While receiving nasal CPAP, CSR-CSA has resolved and breathing has stabilized in patients in association with a marked reduction in minute ventilation (V<sub>T</sub>) compared to baseline recording. See Figure 1 legend for definitions of abbreviations. Data from Naughton et al.<sup>52</sup>

tory muscle strength, together with alleviation of fatigue and dyspnea. An increase in LVEF was also observed, but this accounted for only 25% of the degree of improvement in inspiratory muscle strength due to CPAP. One possible explanation is that, by unloading the inspiratory muscles, CPAP may have alleviated a state of chronic muscle fatigue. In keeping with this hypothesis, the strength of expiratory muscles, which were not unloaded by CPAP, did not change significantly.

#### *Effects on Preload, Afterload, and Ventricular Function*

ACE inhibitors can alleviate symptoms, reduce hospitalizations, and improve survival in patients with CHF.<sup>58–60</sup> These agents are thought to exert their favorable effects on ventricular remodeling at least partly through reduction in LV afterload. CPAP can also reduce afterload in patients with CHF.<sup>47</sup> Naughton et al<sup>56</sup> showed in awake CHF patients that elevations in intrathoracic pressure induced by CPAP significantly reduced LV afterload by lowering transmural pressure (*ie*, the difference between LV systolic pressure and intrathoracic pressure), but without altering BP.

CPAP can also have beneficial hemodynamic effects in patients with CHF. In the normal heart where cardiac output is largely preload dependent, CPAP decreases cardiac output by reducing LV preload but without reducing afterload. In contrast, because cardiac output in the failing heart is relatively insensitive to changes in preload but very sensitive to reductions in afterload, CPAP-induced reductions in LV transmural pressure can augment cardiac output.<sup>61,62</sup> Pinsky et al<sup>63</sup> first demonstrated that in patients with CHF, intermittent elevations in intrathoracic pressure improved cardiac output. This concept was confirmed and extended by the observation that 5 to 10 cm H<sub>2</sub>O of CPAP caused a dose-related augmentation in cardiac output when applied acutely to patients with stable CHF and elevated PCWP.<sup>64</sup> Baratz and colleagues<sup>65</sup> found CPAP up to 15 cm H<sub>2</sub>O produced significant improvement in cardiac index in 7 of 13 patients admitted to the hospital with acute cardiogenic pulmonary edema.

The above studies were performed in CHF patients while awake. In CHF patients with OSA, CPAP has additional benefits when applied during sleep. First, because OSA causes generation of exaggerated negative intrathoracic pressure, its elimination by CPAP causes a relatively greater increase in intrathoracic pressure and, therefore, a more pronounced reduction in LV afterload than it does in the absence of OSA. Second, because OSA causes

marked increases in BP from wakefulness to stage 2 sleep, abolition of OSA by CPAP markedly lowers nocturnal BP. Thus, the combined effects of increasing intrathoracic pressure and reducing BP through alleviation of OSA by CPAP lead to remarkable reductions in systolic transmural pressure and, thus, LV afterload, even in CHF patients receiving optimal doses of BP-lowering medications.<sup>47</sup> When applied nightly for 4 weeks to eight patients with concomitant OSA and CHF secondary to idiopathic dilated cardiomyopathy, CPAP caused a highly significant improvement of LVEF, measured with the patients awake and not receiving CPAP, from 37 to 49% ( $p < 0.0001$ ).<sup>66</sup> This suggests that the beneficial effects of CPAP at night carry over into the daytime. Withdrawal of CPAP for 1 week resulted in a reduction in LVEF back to the baseline level.

Takasaki et al<sup>67</sup> were the first to report a beneficial impact of nightly CPAP treatment on chronic CHF with CSR-CSA. In conjunction with alleviation of CSR-CSA, they reported a significant increase in LVEF with improvement in cardiac functional class. These findings were confirmed by a larger, randomized, controlled trial<sup>51</sup> involving 29 patients with CHF and CSR-CSA, who were randomized to either a control group or a CPAP group who received nightly CPAP of 10 to 12.5 cm H<sub>2</sub>O, in addition to optimal medical therapy. After 3 months, the CPAP group experienced a reduction in the number of apneas and hypopneas, and a significant improvement of LVEF of 8%. These objective findings were associated with improvements in New York Heart Association functional class and symptom scores on the Chronic Heart Failure Questionnaire. Tkacova et al<sup>68</sup> also demonstrated that improvements in LVEF in the CPAP group were associated with reductions in functional mitral regurgitant fraction. Since functional mitral regurgitation in CHF is due mainly to mitral annular dilatation, its reductions suggested CPAP reduced LV volume. Other studies<sup>52,69</sup> have also reported improvement in LVEF in patients with CSR-CSA after treatment of CPAP for 1 to 3 months. Therefore, not only is CPAP a nonpharmacologic means of improving LV systolic function in patients with CSR-CSA, it may also have a favorable influence on LV remodeling.

#### *Effects on Neurohormonal Activity*

As CHF progresses, the sympathetic nervous system is activated in an attempt to restore circulatory homeostasis, leading to an imbalance in autonomic cardiovascular regulation.<sup>70</sup> While initially this may represent a compensatory mechanism, increasing evidence suggests that sympathetic activation itself plays a role in accelerating deterioration in myocar-

dial function in the long term. Catecholamines, for instance, appear to have direct cardiotoxic effects.<sup>71</sup> In 1984, Cohn et al<sup>72</sup> reported that an elevated plasma norepinephrine level was associated with increased mortality in patients with CHF. More recent clinical trials<sup>73-75</sup> have established that  $\beta$ -blockers improve LVEF and symptoms, and reduce hospitalizations and mortality. Attenuation of the toxic effects of catecholamines and other neurohormones in patients with CHF probably accounts for at least part of this therapeutic benefit.

Abolition of OSA in patients with normal cardiac function lowers catecholamine levels and sympathetic nervous system activity.<sup>29</sup> This effect is presumably due to alleviation of intermittent apnea-related hypoxia and arousals from sleep. However, the effects of CPAP on sympathetic nervous system activity in patients with CHF and OSA have not been elucidated. Nevertheless, the observations that CPAP alleviates OSA and apnea-related hypoxia, reduces the frequency of arousals from sleep, and lowers nocturnal BP in CHF patients all strongly suggest that it also attenuates sympathetic nervous system activity in such patients. Further studies will be required to test this hypothesis.

The increased mortality observed in CHF patients with CSR-CSA, compared to those without this breathing disorder, is thought to be mediated in part by increased sympathetic nervous system activity. This is reflected by elevated plasma and urinary norepinephrine levels, and muscle sympathetic nervous system activity.<sup>69</sup> In a randomized, controlled trial<sup>69</sup> in 18 patients with CHF and CSR-CSA, nightly treatment with CPAP for 1 month led to significant reductions in overnight urinary and daytime plasma norepinephrine concentrations. These effects probably arose from alleviation of CSR-CSA, intermittent dips in  $\text{PaO}_2$  and arousals from sleep. In addition, heart rate decreased and LVEF increased significantly in the CPAP-treated group.

The reduction in cardiac vagal modulation in patients with CHF is manifest by a marked attenuation of high-frequency heart rate variability (*ie*, respiratory sinus arrhythmia), which is a predictor of increased mortality following myocardial infarction as well as in patients with CHF.<sup>76,77</sup> Acute application of CPAP to CHF patients with depressed heart rate variability while they are awake causes a significant increase in high-frequency heart rate variability and a decrease in heart rate.<sup>78</sup> Since sympathetic nervous system activity is not altered by CPAP treatment in CHF patients under these particular conditions, the most likely explanation is an increase in cardiac vagal modulation of heart rate. The mechanism of this effect remains to be determined.

Baroreceptor sensitivity for heart rate is depressed

in patients with OSA.<sup>79</sup> In patients with mild-to-moderate CHF, low baroreceptor sensitivity portends a poor prognosis.<sup>80</sup> In a recent study,<sup>81</sup> abolition of OSA in patients with CHF by CPAP was shown to markedly increase baroreflex sensitivity in conjunction with a reduction in BP. Moreover, following withdrawal of CPAP, baroreflex sensitivity remained elevated above the baseline level. These data indicated that CPAP can acutely increase baroreflex sensitivity in CHF patients with coexistent OSA, and that its effects can persist for some time after CPAP is withdrawn. Since improvements in baroreflex sensitivity could increase high-frequency heart rate variability and contribute to better BP regulation, these findings could have favorable prognostic implications for patients with CHF.

Atrial natriuretic peptide (ANP) is produced and secreted by the atria in response to atrial stretch. As part of the endogenous vasodilator system, it promotes natriuresis and diuresis. Although ANP appears to counteract the overactivation of vasoconstrictor neurohormones and may be protective in patients with CHF,<sup>82</sup> its activation reflects the severity of CHF and is a marker of poor prognosis.<sup>83, 84</sup> In CHF patients with CSR-CSA, 3 months of nightly CPAP treatment was shown to significantly reduce ANP levels measured in the daytime.<sup>68</sup> This was associated with a reduction in mitral regurgitation and an increase in LVEF. Taken together, these observations suggest that ANP levels fall in patients receiving CPAP therapy, owing to a reduction in cardiac filling pressure, wall tension, and volumes.

The above data all indicate that CPAP has the potential to favorably alter neurohormonal activity in patients with CHF. Beneficial effects that have been identified to date include a reduction in sympathetic nervous system activity, an increase in parasympathetic nervous system activity, increases in heart rate variability and baroreflex sensitivity, and a decrease in plasma ANP concentration in various subsets of CHF patients. In combination with the favorable influence of CPAP on cardiac mechanics, these neurohormonal effects underscore the potential for CPAP to improve prognosis in patients with CHF, particularly those with coexistent OSA and CSR-CSA (Table 1).

#### *Effects on Mortality and Cardiac Transplantation Rate*

To date and to our knowledge, only one randomized, controlled trial<sup>85</sup> has addressed the impact of CPAP on hard cardiovascular end points in patients with CHF. In this study, Sin and colleagues<sup>85</sup> examined the effects of nightly CPAP treatment on the primary composite end point of mortality and cardiac

**Table 1—Effects of CPAP Treatment on CHF and Sleep-Disordered Breathing**

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Effects on hemodynamics
Reduced preload and afterload
Increased cardiac output
Increased LVEF
Reduced mitral regurgitation
Alleviation of nocturnal and daytime hypertension
Alleviation of symptoms in chronic heart failure and acute pulmonary edema
Effects on respiratory system
Abolition of sleep apnea
Improvement of nocturnal oxygenation
Improved inspiratory muscle strength
Alleviation of dyspnea and symptoms of sleep apnea
Effects on neurohormonal activity
Reduced sympathetic nervous system activity (decreased awake plasma and overnight urinary norepinephrine concentrations)
Increased baroreflex sensitivity
Increased heart rate variability
Reduced ANP concentration

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transplantation in two groups of CHF patients: 29 patients with CSR-CSA and 37 patients without CSR-CSA. Whereas patients with CSR-CSA randomized to CPAP treatment experienced a significant increase in LVEF 3 months into the trial, patients without CSR-CSA experienced no such benefit. During the first 3 months, patients both with and without CSR-CSA used CPAP an average of 6 h per night. However, two patients in the CSR-CSA group could not be initiated on CPAP. Thereafter, the patients entered an observational period during which they were returned to the care of their referring physicians, and compliance with CPAP and medications was not monitored.

After a median follow-up time of 2.2 years, intention-to-treat analysis of all 66 patients revealed a nonsignificant trend toward reduced mortality and transplant rate in the CPAP-treated group. This became statistically significant with on-treatment analysis, in which two patients unable to tolerate CPAP were excluded (relative risk reduction, 60%;  $p = 0.047$ ). The benefit was greatest in patients with CSR-CSA who complied with treatment, with a significant 81% reduction in the composite end point of mortality and heart transplant, compared to the control group ( $p = 0.0167$ ). In contrast, the patients without CSR-CSA failed to derive any benefit (relative risk reduction, 37%;  $p = 0.449$ ), although the wide CI (0.19 to 2.09) could not exclude clinically important effects.

These findings strongly suggest that CPAP can improve LVEF and survival in CHF patients, especially in those with CSR-CSA. Although the results of this trial are promising, they are not definitive because of the small number of patients studied and

the observational nature of the long-term follow-up. Nevertheless, they emphasize the need for a large-scale, randomized, controlled trial to examine the effects of CPAP on mortality in patients with CHF.

### *Clinical Applications*

CPAP should be considered for therapy of symptomatic or severe OSA in patients with CHF. Here it is indicated on the grounds that it rapidly reverses OSA and, as in OSA without CHF, can be expected to alleviate daytime hypersomnolence and improve alertness. It may in addition lead to remarkable improvements in LV systolic function and cardiac functional status.

Although most studies show that CPAP attenuates CSR-CSA in patients with CHF and improves cardiac functional status, neurohormonal markers, and possibly mortality, a few small and short-term studies<sup>48,49</sup> fail to confirm any beneficial effects of CPAP in patients with CHF. Several reasons may account for these apparently conflicting results. With ACE inhibitors and  $\beta$ -blockers, symptomatic and objective improvement may not be seen until patients have been treated for weeks to months.<sup>4</sup> Because CPAP may act through afterload reduction and favorable neurohormonal modulation, it is possible that the short-term use of CPAP is insufficient to provide any clinical benefit. The lower intensity of CPAP used and poor compliance in the negative studies may also have an impact on the outcome measures. Studies using  $< 7.5$  cm H<sub>2</sub>O generally did not show any beneficial effects. It is therefore crucial to ensure good compliance and use of maximum tolerable pressure for at least a few months, before concluding that treatment is ineffective.

In our center, CPAP is initiated in CHF patients with CSR-CSA with an acclimatization period usually of 2 to 3 days, as in previous trials. Patients are started on a regimen of CPAP at 5 cm H<sub>2</sub>O while awake for a few hours and then overnight. No titration is attempted until 5 cm H<sub>2</sub>O is tolerated overnight. Pressure is then gradually increased by 1 to 2.5 cm H<sub>2</sub>O over the next 1 to 2 days to achieve the target of 10 to 12.5 cm H<sub>2</sub>O. If such pressure cannot be reached during this time, an attempt is made to raise the pressure 1 to 2 months later. We instruct patients to use CPAP for at least 6 h per night. Compliance is generally good with this process of acclimatization.

### CONCLUSION

Although sleep-related breathing disorders are prevalent in the CHF population, they remain underdiagnosed and undertreated. Growing evidence

suggests that there may be a strong pathophysiologic link between CHF and sleep-related breathing disorders. Treatment of OSA by CPAP in patients with CHF is indicated when symptoms of a sleep apnea syndrome exist, just as would be the case in patients without CHF. In this setting, CPAP treatment may provide the additional benefit of improving cardiac function and alleviating CHF symptoms. There are now mounting data to support the use of CPAP in the treatment of acute cardiogenic pulmonary edema. CPAP may also prove to be a valuable adjunctive therapy in chronic CHF with associated CSR-CSA. However, its exact role in the long-term treatment of CSR-CSA in patients with CHF remains to be elucidated.

### Future Directions

While the results of medium-term studies of CPAP are encouraging, insufficient data and unresolved issues have precluded definite clinical recommendations.<sup>86</sup> Although most trials in CHF patients with CSR-CSA have had positive results, it is less clear whether the beneficial effects of CPAP can be extended to patients with CHF but without sleep-disordered breathing. It is also possible that only CHF patients with symptomatic or severe sleep-disordered breathing, as reflected by a high apnea-hypopnea index, derive benefit from CPAP treatment. Because CSR-CSA is more common in male CHF patients, to our knowledge, there have been no studies in which the effects of CPAP on CSR-CSA have been assessed in women. Important gender differences may exist. The role of CPAP in the treatment of diastolic dysfunction remains to be elucidated. More important, most of the studies published are small and relatively short term. The impact on important clinical end points such as mortality has been assessed in only one small-scale study.<sup>85</sup> Clearly, more research is required to better define the potential role of CPAP in the treatment of CHF. Currently, there is a large, long-term, multicenter trial (the Canadian Positive Airway Pressure for Heart Failure trial) addressing the issue of the effects of CPAP on mortality in patients with CHF and CSR-CSA, who are randomized to CPAP or conventional treatment alone. Hopefully, this and other similar trials will guide the use of CPAP treatment for CHF in a rational, evidence-based manner.

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## The Role of Continuous Positive Airway Pressure in the Treatment of Congestive Heart Failure

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