CPAP Should Be Used for Central Sleep Apnea in Congestive Heart Failure Patients

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RATIONALE FOR TREATING CENTRAL SLEEP APNEA IN PATIENTS WITH HEART FAILURE

There are 2 possible rationales for treating Cheyne-Stokes respiration or central sleep apnea (CSA) in patients with congestive heart failure (CHF). First, alleviation of CSA might alleviate symptoms directly related to CSA, such as sleep disruption and excessive daytime sleepiness. Second, treating CSA might improve cardiovascular outcomes, such as cardiovascular function, as well as morbidity and mortality due to CHF.

Regarding the first rationale, there is little evidence that CSA itself gives rise to symptoms of a sleep apnea syndrome. For example, most CHF patients with CSA do not snore and do not complain of excessive daytime sleepiness. Thus, relief of symptoms of CSA is not a strong rationale to treat CSA in patients with CHF. Regarding the second rationale, this is largely based on observations from some, but not all, reports that, in patients with CHF, CSA increases the risk of death and cardiac transplantation independently of known risk factors. This observation suggests the possibility that, in patients with CHF, treating and alleviating coexisting CSA might reduce some of the excess morbidity and mortality attributable to this condition.

Closely linked to this notion is evidence that CSA arises secondary to CHF itself and is, to some extent, a sign of the severity of CHF. For example, although cardiac output does not appear to differ between CHF patients with and without CSA, patients with CSA have higher left ventricular (LV) filling pressures, LV end-diastolic volumes, and sympathetic nervous system activity, as compared with CHF patients without CSA. These are signs of worse cardiovascular function in patients with CSA that should have adverse prognostic implications. In CHF, CSA is associated with chronic hypocapnia. This is related to elevated LV filling pressures and end-diastolic volumes, and pulmonary congestion that may provoke hyperventilation through stimulation of pulmonary vagal irritant receptors, and to increases in central and peripheral chemosensitivity. Hence, treating CSA might improve cardiovascular outcomes either by alleviating CSA per se or by alleviating underlying cardiovascular dysfunction that is associated with CSA.

The prevalence of CSA in patients with stable CHF is approximately 25% to 40%, compared with less than 1% in the general population. This high prevalence in the setting of CHF is probably attributable to derangements in cardiovascular physiology that influence the respiratory system, as described above. Accordingly, because CSA is largely a consequence of CHF, one could anticipate that treatments for CHF that relieved pulmonary edema and/or lowered LV filling pressures might also relieve CSA.

Case series suggest that intensification of pharmacologic therapy for CHF can attenuate CSA. Similarly, in nonrandomized trials, cardiac resynchronization pacemaker therapy was accompanied by alleviation of CSA in association with an improvement of cardiac function. Heart transplantation can also alleviate CSA in patients with CHF. Thus, optimizing CHF therapy can stabilize ventilatory control and attenuate CSA in some patients. These observations suggest that, in addition to optimal contemporary CHF therapy, specific interventions for CSA in patients with CHF would be most effective if the therapy also had direct beneficial effects on cardiovascular function.

RATIONALE FOR USING CONTINUOUS POSITIVE AIRWAY PRESSURE TO TREAT CSA IN CHF

Continuous positive airway pressure (CPAP) has a number of beneficial acute respiratory and cardiovascular effects in patients with CHF. When applied to awake patients with CHF, it increases intrathoracic pressure. This unloads the inspiratory muscles, thereby reducing the work of breathing. It also reduces LV transmural pressure, thereby reducing LV afterload, and reduces LV end-diastolic volume and pressure, thereby reducing preload. This, combined with a reduction in heart rate, reduces overall cardiac workload and increases cardiac pumping efficiency. Randomized trials have shown that when CPAP of 10 cm H2O is applied to patients with acute cardiogenic pulmonary edema, it lowers elevated PCO2, reduces the alveolar-arterial PO2 difference, lowers heart rate, and reduces the rate of intubation, as compared with standard medical therapy. Although not demonstrated di-
The acute cardiac output response to CPAP therapy in awake patients with CHF is dependent on cardiac preload and rhythm. In CHF patients with high LV filling pressure (i.e., ≥12 mm Hg), CPAP of 5 to 10 cm H2O generally augments cardiac output, but in CHF patients with low LV filling pressure (i.e., <15 mm Hg)22,23 or atrial fibrillation,24 CPAP generally reduces cardiac output. However, it is not known whether CPAP has long-term adverse hemodynamic effects when applied nightly to CHF patients with CSA and low filling pressures or atrial fibrillation. As it happens, CHF patients with CSA generally have increased LV filling pressures, as compared with CHF patients without CSA.11 One might anticipate that CPAP applied to such patients would improve hemodynamics. Indeed, this is one of the reasons why CPAP has been used to treat CSA in patients with CHF.

The effects of CPAP on CSA in patients with CHF have been inconsistent in the smaller trials, probably as the result of differences in how the CPAP is applied. In randomized trials in which nocturnal CPAP was applied for 1 night to 2 weeks at low pressure (5 - 7.5 cm H2O), CSA was not alleviated.25,26 In contrast, in trials in which patients were acclimatized to CPAP during a gradual 2- to 7-day titration to higher pressures of 8 to 12.5 cm H2O, the frequency of central apneas and hypopneas fell by 53% to 67% after 2 to 12 weeks.27,28

In small single-center trials lasting 1 to 3 months, CPAP, titrated gradually, alleviated CSA in association with an increase in P<sub>O</sub>2 and improvements in cardiorespiratory function. These included increases in LVEF,29,33,35 and inspiratory muscle strength36 and reductions in functional mitral regurgitation34 and nocturnal and daytime norepinephrine levels,32 as well as daytime plasma atrial natriuretic peptide concentrations.34 These physiologic improvements were associated with significant improvements in symptoms of CHF.32 In 1 trial of CPAP in CHF involving 29 patients with and without CSA (apnea-hypopnea index [AHI] ≥ 15 and <15, respectively), CPAP had no effect on LV ejection fraction (LVEF) or the combined rate of mortality and cardiac transplantation. However, among patients who were compliant with CPAP, the reduction in the combined rate of death and cardiac transplantation during the median 2.2-year follow-up period (p = .059). Among patients who were compliant with CPAP, the reduction in the combined rate of death and cardiac transplantation was significant (p = .017).

Taken together, these studies demonstrated that CPAP improves cardiovascular function in CHF patients with CSA but only when it is titrated slowly to pressures of 8 to 12.5 cm H2O, and is accompanied by reductions in the AHI.4,20,33,35 These findings imply that CPAP improves cardiovascular function over time in CHF patients with CSA by attenuating the adverse cardiovascular effects of CSA. However, because of the small number of participants in those studies, and because β-blockers had not yet come into widespread use for the therapy of CHF, the results of those studies may not be applicable to patients on optimal contemporary pharmacologic CHF therapy. For these reasons, the multicenter Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) Trial sought to determine whether CPAP would improve CSA, morbidity, mortality, and cardiovascular function in CHF patients with CSA on contemporary medical therapy for CHF.37

The CANPAP Trial

The CANPAP trial was a multicenter randomized controlled clinical trial carried out in 10 centers in Canada and 1 in Germany.27 It included 258 patients with CHF (LVEF < 40%) and CSA (AHI ≥ 15/h of sleep, of which > 50% were central), 130 of whom were randomly assigned to a control group and 128 to a CPAP-treated group. These patients were followed for a mean and maximum of 2.2 and 5.3 years, respectively. The first important finding was that compliance with CPAP therapy was very good; 85% of patients assigned to CPAP used it throughout the trial. This is as good or better than adherence to drug therapies in long-term CHF trials.38,39

The intention-to-treat analyses confirmed previous findings that CPAP attenuates CSA (it reduced the AHI by 53%, from 40 to 19 per hour of sleep) but does not affect total sleep time. It also improves nocturnal oxygenation and LVEF and lowers plasma norepinephrine concentrations. Importantly, those effects were sustained with long-term therapy (at least 2 years). In addition, CPAP caused a significant 20-meter increase in 6-minute walking distance, a degree of improvement that is considered clinically significant.38 However, some effects were less pronounced, compared with previous trials. For example, plasma atrial natriuretic peptide concentration did not fall, compared with a significant fall in a previous study.34 The 2.2% rise in LVEF27 was less than the 7.7% increase observed in a single-center randomized trial.33 This difference may be attributable to lower CPAP (8-9 vs 10 cm H2O) and daily CPAP usage (4.3 vs 5.9 hours per day), a higher initial LVEF (24.5% vs 20.0%), or, possibly, the greater proportion of patients who were on β-blockers than in previous studies (77% versus <20%). Because 1 mechanism by which CPAP appears to exert its therapeutic effect is by lowering sympathetic activity, it is possible that β-blockade rendered redundant some of the effects of CPAP. Although the CANPAP trial demonstrated that CPAP attenuates CSA and improves LVEF to a modest extent,27 this increase is similar to that induced by enalapril, which has been shown to reduce mortality in CHF.40-42

Although CPAP attenuated CSA and improved cardiovascular function, there were no significant differences in transplant-free survival (32 vs 32 events, p = .54), rate of hospitalizations, or quality of life, measured by the Chronic Heart Failure Questionnaire, between the 2 groups.27 Survival analysis revealed a divergence of event rates in the first 18 months favoring the control group (p = .02) that reversed after 18 months to favor CPAP (p = .06). This suggests that CPAP had an early adverse effect in some subjects but a late beneficial effect in others. Because of the early divergence of the transplant-free survival curves favoring the control group, lower than anticipated enrollment, and a falling primary-event rate indicating that the original sample-size calculation was insufficient to detect a difference in transplant-free survival between the 2 groups,43 the trial was terminated early.27 Consequently, CANPAP lacked power to conclude with certainty that CPAP does not improve survival in this patient population. A much larger trial would have been required to determine whether the physiologic improvements observed are surrogates for improved survival.44 Nevertheless, the physiologic benefits are probably clinically important, since they are similar to those described for β-blockers for therapy of CHF.

To date, β-adrenergic receptor blockers have proven to be the
most potent pharmacologic agents for improving survival in CHF yet tested. They work mainly by blocking adrenergic activity at peripheral receptors, thereby slowing heart rate and reducing myocardial energy consumption. To put the results of trials of CPAP for CHF patients with CSA into perspective, a brief overview of β-blocker therapy for CHF may be helpful.

The first moderate-sized randomized trial of the selective β1-receptor blocker, metoprolol,45 for treating CHF involved 383 patients. In this trial, metoprolol increased LVEF but did not affect survival, most likely because it was underpowered to do so. Nevertheless, 6 years later, in a much larger trial involving 3991 patients with CHF,26 metoprolol did improve survival. Similarly, in an early randomized trial involving 301 CHF patients,29 those assigned to treatment with carvedilol, a nonselective β1-β2-receptor blocker with α1-receptor blocking and antioxidant properties, experienced an improvement in LVEF and a marginal improvement in 6-minute walking distance but no change in quality of life or mortality rate. Subsequently, in a much larger trial involving 2289 patients with CHF,37 carvedilol caused a significant reduction in mortality. In another trial, involving 3029 patients with CHF,37 it was shown that carvedilol caused a greater reduction in mortality than did metoprolol, suggesting that nonselective β-blockade may be more effective than β1 selective blockade in reducing mortality in CHF. It has also been shown in numerous trials of various β-blockers that an early improvement in LVEF is a good predictor of improved survival.38 These examples illustrate that small trials demonstrating beneficial effects of interventions on cardiovascular function, but without improving mortality, do not preclude the possibility that much larger trials involving the same or similar interventions may demonstrate mortality benefits.

Table 1 displays the physiologic and clinical effects of CPAP in patients with CHF. It shows that CPAP reduces sympathetic activity, during both sleep and wakefulness, in CHF patients with CSA,32,49 but, unlike with the use of β-blockers, this is due to a reduction in central sympathetic outflow rather than to peripheral receptor blockade. Thus, the effects of CPAP are more akin to those of the nonselective β-blocking agent, carvedilol, than to the selective β1 blocking agent, metoprolol. CPAP also slows heart rate, reduces LV wall tension and myocardial O2 consumption,18 and increases nocturnal oxygenation in CHF patients with CSA. In such patients, CPAP also improves LVEF and exercise capacity.27 Interventions for CHF that improve LVEF and exercise capacity in conjunction with lowering of LV afterload, heart rate, and inhibition of sympathetic nervous system activity, but that do not have inotropic properties, have generally improved survival when a large enough sample size has been studied. In particular, an early improvement in LVEF in response to β-blockers is a good predictor of improved survival.37,39,48

### Conclusion

Given the generally beneficial effects of CPAP on CSA and cardiovascular function (especially improved LVEF) in patients with CHF, the lack of documented inotropic or adverse effects with the use of CPAP, and the similarities of the effects of CPAP to those of β-receptor blockers, it is quite likely that a much larger trial of CPAP for CHF patients with CSA would demonstrate a mortality benefit. Even if CPAP does not improve survival, however, these improvements in cardiovascular function do translate into a clinically important improvement in walking distance, which alone would justify a trial of CPAP. CPAP is also well tolerated in CHF patients with CSA. For these reasons, a trial of CPAP should be provided as adjunctive therapy for patients with CHF who continue to have CSA despite being on optimal contemporary medical therapy. However, one must keep in mind that CPAP has only been shown to improve cardiovascular function chronically in CHF patients with CSA when it relieves CSA.4,29,33,35 These observations suggest that alleviation of CSA may be a key factor in improving cardiac function in CHF patients with CSA.

However, if one uses CPAP for this purpose, it must be titrated slowly over several days to weeks to a target pressure of 8 to 12.5 cm H2O.27,37 A follow-up sleep study from 1 to 3 months after initiating CPAP to assess its effect on CSA is therefore an important aspect of clinical management. If at this time the AHI decreases substantially, then the patient could be told to continue the use of CPAP. If, on the other hand, the AHI has decreased only marginally or not at all, then one should probably recommend discontinuing the use of CPAP, since it is unlikely that it will provide any long-term clinical benefits. It is also important to maintain close follow-up once CPAP has been started to maintain good compliance, just as one would when initiating β-blocker therapy for CHF.

### References

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