Effects of Continuous Positive Airway Pressure on Cardiovascular Outcomes in Heart Failure Patients With and Without Cheyne-Stokes Respiration

Don D. Sin, MD, MPH; Alexander G. Logan, MD; Fabia S. Fitzgerald, RN; Peter P. Liu, MD; T. Douglas Bradley, MD

Background—Continuous positive airway pressure (CPAP) improves cardiac function in patients with congestive heart failure (CHF) who also have Cheyne-Stokes respiration and central sleep apnea (CSR-CSA). However, the effects of CPAP in CHF patients without CSR-CSA have not been tested, and the long-term effects of this treatment on clinical cardiovascular outcomes are unknown.

Methods and Results—We conducted a randomized, controlled trial in which 66 patients with CHF (29 with and 37 without CSR-CSA) were randomized to either a group that received CPAP nightly or to a control group. Change in left ventricular ejection fraction (LVEF) from baseline to 3 months and the combined mortality-cardiac transplantation rate over the median 2.2-year follow-up period were compared between the CPAP-treated and control groups. For the entire group of patients, CPAP had no significant effect on LVEF, but it was associated with a 60% relative risk reduction (95% confidence interval, 2% to 64%) in mortality—cardiac transplantation rate in patients who complied with CPAP therapy. Stratified analysis of patients with and without CSR-CSA revealed that those with CSR-CSA experienced both a significant improvement in LVEF at 3 months and a relative risk reduction of 81% (95% confidence interval, 26% to 95%) in the mortality—cardiac transplantation rate of those who used CPAP. CPAP had no significant effect on either of these outcomes in patients without CSR-CSA.

Conclusions—CPAP improves cardiac function in CHF patients with CSR-CSA but not in those without it. Although not definitive, our findings also suggest that CPAP can reduce the combined mortality—cardiac transplantation rate in those CHF patients with CSR-CSA who comply with therapy. (Circulation. 2000;102:61-66.)

Key Words: heart assist devices ■ sleep apnea, central ■ clinical trials

Despite recent advances in the pharmacological therapy of congestive heart failure (CHF), including angiotensin-converting enzyme inhibitors and β-blockers,1-5 mortality from this disease remains disturbingly high.6 Indeed, recently published data from several centers in the United States indicate that overall death rates from CHF have not changed appreciably over the last several decades.6-8 Therefore, to improve the prognosis of CHF, additional novel approaches to its therapy are required. One promising approach is the use of continuous positive airway pressure (CPAP).

When applied via a nasal mask, CPAP provides a noninvasive mechanical assist to the failing heart by increasing intrathoracic pressure and augmenting stroke volume and cardiac output.9 CPAP also reduces left ventricular (LV) preload and afterload by decreasing LV transmural pressures during diastole and systole.10,11 In doing so, CPAP improves the mechanical efficiency of the failing heart9-11 and helps to reduce mitral regurgitation, possibly through reverse ventricular remodeling.12

CPAP may be a particularly effective therapy for CHF in patients with coexisting Cheyne-Stokes respiration with central sleep apnea (CSR-CSA). Previous studies have shown that CSR-CSA is common in patients with CHF13 and that it is a risk factor for mortality14,15 and heart transplantation.16 This may be due in part to recurrent apnea-related hypoxia and arousals from sleep, which activate the sympathetic nervous system and cause elevations in nocturnal blood pressure.17-19 We previously showed that CPAP alleviates CSR-CSA and reduces sympathetic nervous system activity in such patients.17 CHF patients with CSR-CSA have higher LV filling pressures and volumes than those without it,20,21 and they are more likely to derive hemodynamic benefits from CPAP.9
We previously showed in randomized trials that the use of CPAP for periods of 1 to 3 months in various physiological end points, including cardiovascular function, improves mortality and heart transplantation rate or transplant-free survival. To determine the effects of CPAP on LVEF in similar periods of time in CHF patients without sleep-disordered breathing, we studied the effects of CPAP on LVEF over similar periods of time in patients with chronic heart failure (CHF) who were not tested for this length of time is associated with significant improvements in LVEF and other physiological variables in CHF patients with and without clinical signs of CHF.

Methods

 Subjects

We recruited CHF patients using the following inclusion criteria: ≥75 years of age; ≥1 clinical episode of CHF; LVEF ≤45%, as measured by right ventricular ejection fraction (LVEF%); and New York Heart Association functional class of 2 or 3. We excluded patients who had been tested for this length of time is associated with significant improvements in LVEF and other physiological variables in CHF patients with and without clinical signs of CHF.

Statistical Analysis

Outcomes

The primary outcome during the 3-month clinical trial period of the study was the change in LVEF from baseline to 3 months. The main follow-up period was arranged until the time of final contact by telephone 1.5 years after the last patient was enrolled (median, 2.2 years; maximum, 4.8 years after initial randomization).
opathy are risk factors for CSR-CSA. 25 By definition, the apnea-hypopnea index was higher in patients with than in those without CSR-CSA.

Table 2 shows baseline data from CSR-CSA patients who were randomized to the control (n = 15) and CPAP (n = 14) groups. The 2 groups were similar for all variables shown. Baseline characteristics of the non-CSR-CSA patients randomized to control (n = 20) and CPAP therapy groups (n = 17) were also similar, as illustrated in Table 3.

LVEF

From baseline to 3 months, the increase in LVEF was not significant in either the CPAP-treated (2.5 ± 0.1%; P = 0.12) or the control group (0.5 ± 0.7%; P = 0.71). A stratified analysis revealed that patients with CSR-CSA who were randomized to CPAP and who were tolerant of it used CPAP for 5.6 ± 1.9 hours per night for the first 3 months of the trial period. Among those patients without CSR-CSA who were randomized to CPAP, all were compliers who used it for 6.8 ± 1.8 hours per night during the first 3 months of the trial.

As illustrated in Figure 1, patients with CSR-CSA randomized to CPAP experienced a significant increase in LVEF compared with control subjects (P = 0.019). In patients without CSR-CSA, neither the CPAP-treated nor the control group experienced any significant improvement in LVEF.

Deaths and Cardiac Transplantation

Among patients without CSR-CSA, 10 died and 2 had cardiac transplants (event rate of 32%), whereas in those with CSR-CSA, 12 died and 2 had cardiac transplants (event rate of 48%). Patients with CSR-CSA had a significantly increased mortality—cardiac transplantation rate compared with patients without CSR-CSA, independent of other covariates, including CPAP usage (relative risk, 2.53; 95% CI, 1.08 to 5.94; P = 0.032) (Figure 2).

An intention-to-treat analysis of all 66 patients indicated a trend toward a decreased mortality—cardiac transplantation rate in the CPAP group compared with the control group: 49% of the control group (14 deaths and 3 cardiac transplants) but only 29% of the CPAP group (8 deaths and 1 cardiac transplant) had end-stage events (relative risk reduction, 50%;...
When the 2 CPAP-intolerant patients were excluded, a treatment analysis in the 64 remaining patients revealed a significant reduction for the combined mortality–cardiac transplantation rate in the CPAP group (relative risk reduction, 60%; 95% CI, 2% to 84%; \( P = 0.047 \)), which is expressed as transplant-free survival in Figure 3. Stratified analyses revealed that the relative risk reduction for the combined mortality–cardiac transplantation rate associated with CPAP therapy was much more pronounced in patients with CSR-CSA than in those without it. An intention-to-treat analysis in those with CSR-CSA revealed a strong trend toward a lower mortality–cardiac transplantation rate among those randomized to CPAP compared with the control group (33% event rate in the CPAP group versus 56% in the control group; relative risk reduction, 67%; 95% CI, −4% to 89%; \( P = 0.059 \)). A treatment analysis revealed that patients who complied with CPAP therapy experienced a significant reduction in their mortality–cardiac transplantation rate compared with the control group (25% event rate in CPAP compliers versus 56% in the control group; relative risk reduction, 81%; 95% CI, 26% to 95%; \( P = 0.0167 \)) (Figure 4). The survival curve of CPAP-treated patients separated from the control patients practically from the outset and diverged progressively until the end of the observation period. However, CPAP did not significantly reduce the mortality–cardiac transplantation rate in patients without CSR-CSA (relative risk reduction, 37%; 95% CI, 0.19 to 2.09; \( P = 0.449 \)). Nevertheless, a tendency, similar to that observed in the patients with CSR-CSA, existed for transplant-free survival in the CPAP-treated patients; this curve began to diverge progressively from the control group 20 months after randomization (Figure 5). No adverse effects of CPAP, other than mask discomfort, were reported.

Discussion

This is the first clinical trial in which the effects of CPAP on LVEF and the combined mortality–cardiac transplantation rate have been studied and compared in CHF patients with and without CSR-CSA. Several novel and important observations were made. In patients with CSR-CSA, CPAP caused a significant increase in LVEF during the 3-month trial period that was associated with an 81% relative risk reduction in the long-term mortality–cardiac transplantation rate over a median observation period of 2.2 years among CPAP compliers. In contrast, among CHF patients without CSR-CSA, randomization to CPAP was not associated with any significant improvement in LVEF or transplant-free survival. Finally, we confirmed the findings of previous studies, which demonstrated that CHF patients with CSR-CSA have an increased mortality–cardiac transplantation rate compared with those without CSR-CSA.15,16 These results extend findings from previous studies showing that CPAP has beneficial acute physiological effects on
the cardiovascular system in patients with CHF. CPAP increases intrathoracic pressure, and it reduces LV preload and afterload by decreasing diastolic and systolic transmural pressures. It can also augment cardiac output and induce a fall in heart rate, both acutely and chronically, in patients with CHF. Among CHF patients with depressed heart rate variability (a marker of poor prognosis), CPAP increases heart rate variability. These beneficial cardiovascular effects of CPAP are particularly prominent in patients with elevated pulmonary capillary wedge pressure, who are at greatest risk for CSR-CSA and death. These benefits suggest the potential for improved long-term outcomes.

Subsequent clinical trials have demonstrated that CPAP improves physiological outcomes over periods of 1 to 3 months in CHF patients with CSR-CSA. For example, CPAP alleviates CSR-CSA, increases LVEF, and reduces mitral regurgitation and atrial natriuretic peptide levels. It also reduces elevated norepinephrine levels in patients with CSR-CSA. These results emphasize the potential for CPAP to improve cardiovascular end points in CHF patients, particularly those with CSR-CSA.

In our study, improvements in transplant-free survival in CPAP-treated patients with CSR-CSA were preceded by early improvements in LVEF. In contrast, no improvements in LVEF or transplant-free survival were observed in CPAP-treated patients without CSR-CSA.

Because CHF patients with CSR-CSA have a higher SNA, LV volume, pulmonary capillary wedge pressure, and combined mortality-cardiac transplantation rate than patients without CSR-CSA, they have a greater potential for interventions to improve outcomes. Indeed, in our study, patients with CSR-CSA had a 2.5-fold greater adjusted relative risk for mortality-cardiac transplantation than patients without CSR-CSA. Our data are therefore consistent with those from clinical trials of angiotensin-converting enzyme inhibitors in which early increases in LVEF predicted improved long-term survival and in which patients with higher baseline mortality rates derived a greater survival benefit than those whose baseline mortality rates were lower.

The pattern of transplant-free survival advantage in CPAP-treated patients with CSR-CSA was also of interest. First, this advantage was large for those patients who complied with CPAP therapy. Second, separation of the transplant-free survival curve of the CPAP treated group from the control group occurred early in the trial, corresponding to the early increase in LVEF, and then diverged progressively over the observation period. These findings suggest that CPAP may have a long-lasting beneficial effect in CHF patients with CSR-CSA.

The present trial has a number of limitations with respect to long-term observational data. The number of patients studied was relatively small, so that the results may not be generalizable. Because CPAP compliance was only measured objectively for the 3-month clinical trial period, some patients on CPAP may have discontinued therapy during the remaining observational period. Conversely, some patients originally randomized to control may have subsequently started on CPAP outside the trial. However, these types of problems would have led to an underestimation of the effect size of CPAP. Blinding was also not possible. To minimize the difference between the follow-up and reporting of outcomes, study personnel involved in the data collection were blinded to the treatment assignment of patients. In addition, a placebo was not used because a suitable true placebo for CPAP with no adverse effects probably does not exist. Moreover, with hard outcomes such as mortality and transplantation, the placebo effect is usually insignificant, making it unlikely to account for the observed transplant-free survival differences between the 2 groups. After patients finished the first 3 months of the trial, we did not monitor changes in their pharmacological therapy. It is possible that the medical management of control patients improved, but this would likely diminish, rather than accentuate, the differences between groups.

Our trial design did have certain advantages. Patients were only followed-up in the clinical trial setting for 3 months, after which they were transferred to the care of their referring physicians. This more closely approximates actual clinical practice than does long-term supervision in the setting of a traditional clinical trial. Therefore, the long-term benefits of CPAP therapy observed in patients with CSR-CSA could be more representative of the actual outcomes of this intervention in clinical practice than if patients had been followed in the clinical trial setting throughout the study.

Although in the non-CSR-CSA patients we did not observe a significant transplant-free survival difference between those in the CPAP and control groups, there was a trend in favor of the CPAP group similar to that seen in the CSR-CSA patients. Therefore, we cannot rule out the possibility that with a much larger population, such differences may be found. However, any such effect is likely to be small and may not be evident until treatment has lasted ≥2 years (Figure 4).

In summary, our results agree with those of previous studies in demonstrating that CSR-CSA confers an increased risk for death and cardiac transplantation in patients with CHF. They also confirm that CPAP improves LVEF in CHF patients with CSR-CSA. However, the most important and novel findings of the study were that long-term use of CPAP in patients with CHF is safe and tends to improve transplant-free survival in those with CSR-CSA. In contrast, no such beneficial effects were observed in patients without CSR-CSA. These results indicate that CSR-CSA has specific detrimental effects, and they suggest that this breathing disorder should be a therapeutic target in patients with CHF. Therefore, physicians need to recognize that CSR-CSA is common and include it in the differential diagnosis of conditions that adversely affect prognosis in heart failure. Where CSR-CSA is suspected, an overnight sleep study is required to confirm the diagnosis.

Although our results are promising in regards to the effects of CPAP on transplant-free survival in patients with CSR-CSA, they are not definitive because of the small number of patients studied. They do, however, emphasize the need for a definitive multicenter trial to examine the effect of CPAP on mortality alone in patients with CHF, as articulated in a recent review of sleep-disordered breathing in CHF. Our results indicate that CHF patients with CSR-CSA are probably the
population best suited for such a trial. The Canadian Positive Airway Pressure Trial for Heart Failure (CANPAP), which involves CHF patients with CSR-CSA, constitutes such a trial; it is presently underway.

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