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
We previously showed in randomized trials that the use of CPAP for periods of 1 to 3 months in patients with CHF alleviates CSR-CSA and improves various physiological end points, including LV ejection fraction (LVEF). However, the effects of CPAP on LVEF over similar periods of time in CHF patients without sleep-disordered breathing have not been tested. Furthermore, the long-term effects of CPAP in patients with CHF have not been investigated. Therefore, we studied the effects of CPAP on LVEF in a randomized, controlled clinical trial lasting 3 months in patients both with and without CSR-CSA. We then continued to observe these patients, and we compared the combined rate of all-cause mortality and heart transplantation between patients randomized to receive CPAP and those randomized to a control group.

Methods

Subjects

We recruited CHF patients using the following inclusion criteria: ≤75 years of age; ≥1 clinical episode of CHF; LVEF ≤45%, as measured at rest by equilibrium radionuclide angiography; and New York Heart Association (NYHA) functional class of 2 to 3, despite stable clinical condition while on optimal cardiac medications for ≥1 month before study entry. We excluded patients who had the following conditions: unstable angina, myocardial infarction, or cardiac surgery within 3 months of study entry; primary valvular heart disease; and obstructive sleep apnea, as well as those actively listed for cardiac transplantation.

Sleep Studies

At baseline, sleep studies were performed on all patients who met initial inclusion criteria. Sleep stages were determined by standard criteria.2,3 Oxyhemoglobin saturation was measured with an oximeter. Thoracoabdominal movements were measured by a calibrated respiratory inductance plethysmograph (Respitrace, Ambulatory Monitoring Inc.). Apneas and hypopneas were scored according to established criteria for our laboratory.4,5 The apnea-hypopnea index was defined as the number of apneas and hypopneas per hour of sleep. CSR-CSA was defined as a crescendo-decrescendo pattern of hyperpnea, alternating with central apneas or hypopneas at a rate of ≥15 per hour of sleep in which ≥75% of events were central in nature. An absence of CSR-CSA was defined as an apnea-hypopnea index <15 per hour of sleep.

Protocol

The Human Subjects Review Committee of the University of Toronto approved the study protocol, and all subjects provided written informed consent before entry. LVEF was measured at baseline by equilibrium radionuclide angiography at rest using semiautomated analysis by experienced operators. Eligible patients were stratified according to the presence or absence of CSR-CSA; they were then randomized either to a control group or to a group that received CPAP. Both the control and the CPAP groups continued to receive standard medical therapy for CHF, which consisted of angiotensin-converting enzyme inhibitors, diuretics, digoxin, and β-blockers, as tolerated. Those assigned to CPAP were brought into the sleep laboratory for 2 nights of CPAP titration to a target pressure of 10 to 12.5 cm H₂O or to the maximum pressure tolerated, as previously described.6 At discharge, patients were told to use CPAP for ≥6 hours per night. All patients were brought back for a follow-up clinic visit 1 month later. For those patients receiving CPAP who did not reach the target pressure during CPAP initiation, CPAP was increased to the maximum tolerated pressure at this time.

At 3 months, study personnel, who were blinded to patient treatment assignment, repeated measurements of LVEF during the day. In patients randomized to CPAP, these measurements were made after being off CPAP for ≥4 hours. Referring cardiologists were free to adjust medications at their discretion during the course of the trial. CPAP compliance was assessed using hour meters in the CPAP machines to determine usage during the first 3 months of the study. Adequate compliance with CPAP therapy was defined as ≥3 hours of daily use, averaged over the first 3 months. We used this cutoff because short-term studies have shown that the use of CPAP for this length of time is associated with significant improvements in LVEF and other physiological variables in CHF patients with CSR-CSA.17,22

After completion of the 3-month randomized trial, subjects were returned to the care of their referring physicians. Those on CPAP were advised to continue using it indefinitely. No further follow-up 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).

Outcomes

The primary outcome during the 3-month clinical trial portion of the study was the change in LVEF from baseline to 3 months. The main outcomes during the long-term observational period were death or cardiac transplantation, whichever came first (ie, mortality–cardiac transplantation rate or transplant-free survival). To determine the current status of the study subjects, we telephoned them, their families, or the referring physicians at the time of final contact. In the case of deceased subjects, mortality information, including the date of death, was obtained from their next of kin or referring physician. Cardiac transplantation information was obtained through hospital records at the Toronto General Hospital division of the University Health Network. No patients were lost to follow-up.

Statistical Analysis

Overall results were analyzed; after this, a stratified analysis was performed according to the presence or absence of CSR-CSA. Continuous variables were compared using Student’s t test, and the χ² test was used to compare dichotomous variables. Intention to treat analyses comparing transplant-free survival between CPAP and control groups were made using the Cox proportional hazards model. Data were then subjected to a treatment analysis in which transplant-free survival was compared between the control patients and those randomized to CPAP who complied with CPAP therapy. We used standard equations to construct 95% confidence intervals (CI) around the incidence rate ratios. Kaplan-Meir plots and an interaction term with length of time were used to evaluate the adequacy of the proportional hazards assumption over time, and this assumption was met. Person-time was censored at the time of last follow-up. The following covariates were added to the reference model: age, sex, LVEF, NYHA class, presence or absence of CSR-CSA, and cause of CHF.1,3,18 All of these factors influence CHF prognosis.

Results

Characteristics of the Subjects

A total of 66 patients were enrolled in the study; 29 had CSR-CSA and 37 did not. Two patients with CSR-CSA who were randomized to CPAP treatment were unable to tolerate it from the outset because of discomfort related to the nasal mask. Neither experienced a worsening of CHF during this short period of CPAP exposure. These patients were consid- ered to be CPAP-intolerant noncompliers. The rest of the patients completed the study. No patients were lost to follow-up. Patient characteristics are shown in Table 1. Patients with and without CSR-CSA were comparable in terms of age, NYHA class, total sleep time, medical therapy, and LVEF. However, higher proportions of men and patients with ischemic cardiomyopathy were in the CSR-CSA group than in the non-CSR-CSA group. This is consistent with our previous data showing that male sex and ischemic cardiomyp-
were randomized to the control (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.

Table 2 shows baseline data from CSR-CSA patients who were randomized to receive CPAP treatment, no such improvement was observed.

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%; P = 0.019). In patients without CSR-CSA, neither the CPAP-treated nor the control group experienced any significant improvement in LVEF.

### Table 2. Baseline Characteristics of Randomized Patients With CSR-CSA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group</th>
<th>CPAP Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55.6 ± 11.1</td>
<td>60.4 ± 8.0</td>
<td>0.193</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>100</td>
<td>100</td>
<td>1.000</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy, %</td>
<td>80</td>
<td>86</td>
<td>1.000</td>
</tr>
<tr>
<td>NYHA functional class ≥3, %</td>
<td>33</td>
<td>43</td>
<td>0.452</td>
</tr>
<tr>
<td>AHI, No./hr of sleep</td>
<td>33.4 ± 22.2</td>
<td>46.4 ± 18.9</td>
<td>0.086</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>87</td>
<td>85</td>
<td>0.990</td>
</tr>
<tr>
<td>ACE inhibitors, %</td>
<td>93</td>
<td>77</td>
<td>0.311</td>
</tr>
<tr>
<td>Digoxin, %</td>
<td>73</td>
<td>62</td>
<td>0.689</td>
</tr>
<tr>
<td>β-blockers, %</td>
<td>27</td>
<td>15</td>
<td>0.655</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>19.8 ± 9.0</td>
<td>20.6 ± 11.3</td>
<td>0.825</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean ± SD. AHI indicates apnea-hypopnea index; ACE, angiotensin-converting enzyme.

### Table 3. Baseline Characteristics of Randomized Patients Without CSR-CSA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group</th>
<th>CPAP Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.2 ± 11.7</td>
<td>57.6 ± 10.4</td>
<td>0.221</td>
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<tr>
<td>Male sex, %</td>
<td>80</td>
<td>77</td>
<td>0.800</td>
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<tr>
<td>Ischemic cardiomyopathy, %</td>
<td>55</td>
<td>41</td>
<td>0.611</td>
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<tr>
<td>NYHA functional class ≥3, %</td>
<td>50</td>
<td>35</td>
<td>0.499</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>95</td>
<td>100</td>
<td>0.990</td>
</tr>
<tr>
<td>ACE inhibitors, %</td>
<td>75</td>
<td>94</td>
<td>0.189</td>
</tr>
<tr>
<td>Digoxin, %</td>
<td>80</td>
<td>88</td>
<td>0.667</td>
</tr>
<tr>
<td>β-blockers, %</td>
<td>15</td>
<td>25</td>
<td>0.588</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>23.6 ± 7.9</td>
<td>22.8 ± 10.2</td>
<td>0.809</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean ± SD. AHI indicates apnea-hypopnea index; ACE, angiotensin-converting enzyme.
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.\textsuperscript{3,11} It can also augment cardiac output\textsuperscript{9} and induce a fall in heart rate, both acutely and chronically, in patients with CHF.\textsuperscript{9,17} Among CHF patients with depressed heart rate variability (a marker of poor prognosis), CPAP increases heart rate variability.\textsuperscript{26} 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.\textsuperscript{9,20} These benefits suggest the potential for improved longer-term outcomes.

Subsequent clinical trials have demonstrated that CPAP improves physiological outcomes over periods of 1 to 3 months\textsuperscript{12,17,22} in CHF patients with CSR-CSA. For example, CPAP alleviates CSR-CSA, increases LVEF, and reduces mitral regurgitation and atrial natriuretic peptide levels.\textsuperscript{12,22} It also reduces elevated norepinephrine levels in patients with CSR-CSA.\textsuperscript{17} 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,\textsuperscript{17} LV volume,\textsuperscript{21} pulmonary capillary wedge pressure,\textsuperscript{20} and combined mortality-cardiac transplantation rate\textsuperscript{14–16} 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.\textsuperscript{14–16} 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\textsuperscript{27} and in which patients with higher baseline mortality rates derived a greater survival benefit than those whose baseline mortality rates were lower.\textsuperscript{14}

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 (Figure 3). 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 differential 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.\textsuperscript{28,29} Moreover, with hard outcomes such as mortality and transplantation, the placebo effect is usually insignificant,\textsuperscript{29} making it unlikely to account for the observed transplant-free survival differences between the 2 groups. Also, 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.\textsuperscript{6–8} 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.\textsuperscript{6–8}

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.\textsuperscript{14–16} 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.\textsuperscript{30} Therefore, physicians need to recognize that CSR-CSA is common\textsuperscript{13,25} 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.\textsuperscript{31} 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.

Acknowledgments

Supported by operating grant MA-12422 from the Medical Research Council of Canada. D. Sin is supported by a research fellowship from the Alberta Heritage Foundation for Medical Research. P. Liu is the Heart and Stroke/Polo Chair in Cardiovascular Research.

References


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* Circulation. 2000;102:61-66  
  doi: 10.1161/01.CIR.102.1.61

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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