

## ORIGINAL ARTICLE

# Continuous Positive Airway Pressure for Central Sleep Apnea and Heart Failure

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## ABSTRACT

**BACKGROUND**

The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure trial tested the hypothesis that continuous positive airway pressure (CPAP) would improve the survival rate without heart transplantation of patients who have central sleep apnea and heart failure.

**METHODS**

After medical therapy was optimized, 258 patients who had heart failure (mean age [±SD], 63±10 years; ejection fraction, 24.5±7.7 percent) and central sleep apnea (number of episodes of apnea and hypopnea per hour of sleep, 40±16) were randomly assigned to receive CPAP (128 patients) or no CPAP (130 patients) and were followed for a mean of two years. During follow-up, sleep studies were conducted and measurements of the ejection fraction, exercise capacity, quality of life, and neurohormones were obtained.

**RESULTS**

Three months after undergoing randomization, the CPAP group, as compared with the control group, had greater reductions in the frequency of episodes of apnea and hypopnea (−21±16 vs. −2±18 per hour,  $P<0.001$ ) and in norepinephrine levels (−1.03±1.84 vs. 0.02±0.99 nmol per liter,  $P=0.009$ ), and greater increases in the mean nocturnal oxygen saturation (1.6±2.8 percent vs. 0.4±2.5 percent,  $P<0.001$ ), ejection fraction (2.2±5.4 percent vs. 0.4±5.3 percent,  $P=0.02$ ), and the distance walked in six minutes (20.0±55 vs. −0.8±64.8 m,  $P=0.016$ ). There were no differences between the control group and the CPAP group in the number of hospitalizations, quality of life, or atrial natriuretic peptide levels. An early divergence in survival rates without heart transplantation favored the control group, but after 18 months the divergence favored the CPAP group, yet the overall event rates (death and heart transplantation) did not differ (32 vs. 32 events, respectively;  $P=0.54$ ).

**CONCLUSIONS**

Although CPAP attenuated central sleep apnea, improved nocturnal oxygenation, increased the ejection fraction, lowered norepinephrine levels, and increased the distance walked in six minutes, it did not affect survival. Our data do not support the use of CPAP to extend life in patients who have central sleep apnea and heart failure.

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**C**ENTRAL SLEEP APNEA, WHICH IS PRESENT in approximately 25 to 40 percent of patients with chronic heart failure,<sup>1-3</sup> results from cyclic hyperventilation and falls in the partial pressure of arterial carbon dioxide below the apnea threshold.<sup>4</sup> The condition affects cardiovascular function adversely by causing tissue hypoxia, arousals from sleep, and activation of the sympathetic nervous system, and it independently increases the risk of death.<sup>1,5,6</sup>

In short-term, single-center randomized trials lasting one to three months involving small numbers of patients who had central sleep apnea and chronic heart failure, continuous positive airway pressure (CPAP) attenuated the central sleep apnea, increased the left ventricular ejection fraction (LVEF), reduced daytime levels of atrial natriuretic peptide and plasma norepinephrine, and improved the patients' quality of life.<sup>4,7,8</sup> In one trial, among patients receiving CPAP, there was a trend toward fewer deaths and heart transplantations.<sup>5</sup> However, that trial involved only 29 patients and was conducted before there was wide use of beta-blockers to treat heart failure.

We therefore undertook a multicenter trial to test the hypothesis that long-term treatment of central sleep apnea with the use of CPAP in patients who have heart failure and are receiving optimal medical therapy reduces the combined rates of death and heart transplantation.<sup>9</sup> During the trial, we also evaluated the effect of CPAP on the LVEF, quality of life, submaximal exercise, number of hospitalizations, and levels of plasma norepinephrine and atrial natriuretic peptide.

## METHODS

### STUDY DESIGN

The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) trial was a randomized, open-label trial in which outcomes were evaluated at 11 centers<sup>9</sup> by investigators blinded to the treatment assignments. It was supported by a grant from the Canadian Institutes of Health Research (CIHR) University Industry Program (UI-14909) in partnership with Respicronics, ResMed, and Tyco Healthcare. The sponsors had no role in the conception or design of the study; the collection, analysis, or interpretation of the data; or the drafting or revision of the manuscript. The research ethics board of each institution approved the protocol.<sup>8</sup> Enrollment oc-

curred after patients provided written informed consent.

### PATIENTS

Candidates for participation in the trial included men and women 18 to 79 years of age who had New York Heart Association (NYHA) functional class II through IV heart failure due to ischemic, hypertensive, or idiopathic dilated cardiomyopathy and whose condition had been stabilized by means of optimal medical therapy for at least one month; an LVEF of less than 40 percent on radionuclide angiography; and central sleep apnea, defined as 15 or more episodes of apnea and hypopnea per hour of sleep, more than 50 percent of which were determined to be central rather than obstructive. The exclusion criteria were pregnancy, myocardial infarction, unstable angina or cardiac surgery within the previous three months, and obstructive sleep apnea.

### BASELINE ASSESSMENT

Eligible patients underwent clinical assessment followed by overnight polysomnography. Sleep stages and arousals, episodes of apnea and hypopnea, and the mean and lowest arterial oxygen saturation levels were assessed according to uniform methods at all centers.<sup>4,10,11</sup> Respiratory efforts were measured with the use of respiratory inductance plethysmography, and airflow by nasal pressure.<sup>2,3,6,12-15</sup> Central sleep apnea was defined as the absence of tidal volume for 10 or more seconds without thoraco-abdominal motion,<sup>3,4</sup> and central hypopnea as a reduction of 50 percent or more in tidal volume from baseline for 10 or more seconds without airflow limitation, as detected with the measurement of nasal pressure.<sup>4,12</sup> Apnea and hypopnea were classified as obstructive if there was out-of-phase motion of the rib cage and abdomen, or if airflow limitation was present.<sup>3,12</sup> The apnea-hypopnea index was defined as the number of episodes of apnea and hypopnea per hour of sleep. The diagnosis of central sleep apnea required an apnea-hypopnea index of 15 or more events per hour, with more than 50 percent of the events determined to be central rather than obstructive.<sup>2,3</sup>

Resting LVEF on radionuclide angiography, the distance walked in six minutes,<sup>16</sup> and the quality of life (assessed with the use of patients' responses to the Chronic Heart Failure Questionnaire, which assesses patients' functioning with regard to dyspnea, fatigue, emotional functioning, and disease mastery

according to a seven-point scale, with lower scores indicating worse condition)<sup>4,17</sup> were then determined. At three centers, the levels of atrial natriuretic peptide and plasma norepinephrine were measured between 9 a.m. and 11 a.m.

#### RANDOMIZATION

Eligible patients were randomly assigned to the control group, who continued to receive optimal medical therapy for chronic heart failure,<sup>18</sup> or to the treatment group, who received CPAP in addition to the medical therapy. Randomization was performed by a computer-generated schedule in random blocks of four and six and was stratified according to study center and brand of CPAP device. Treatment assignment was communicated to the study centers by the data management center after verification that the patient met all the eligibility criteria. Patients assigned to CPAP underwent further randomization in a 2:1:1 ratio to one of the devices (Respironics Remstar Pro, ResMed Sullivan VII, or Tyco Healthcare GoodKnight 420S, respectively). The use of CPAP devices from three different companies was a consequence of the arrangements made for study funding.

#### INITIATION OF CPAP

CPAP was initiated over two to three nights, which the patients spent in an unmonitored sleep laboratory or a hospital bed,<sup>4,7,8</sup> starting at a pressure of 5 cm of water the first night, then increasing by 2 to 3 cm of water over the next one or two nights until reaching a pressure of 10 cm of water (a level shown to attenuate central sleep apnea)<sup>4,5,7</sup> or the highest pressure tolerated. Patients were instructed to use CPAP for at least six hours nightly at home during the trial. If necessary, the pressure was raised to 10 cm of water or the highest level tolerated at the follow-up visits at the end of month 1 or month 3. At each follow-up visit, the number of hours during which CPAP was used was downloaded from a meter that measured the amount of time the mask was used.

#### ASSESSMENT OF OUTCOMES

Clinical assessments were performed at one, three, and six months after randomization, and every six months thereafter. Polysomnography was performed at 3 and 24 months. LVEF, the distance walked in six minutes, and quality of life were assessed at 3, 6, and 24 months. At three centers, levels of plasma norepinephrine and atrial natri-

uretic peptide were obtained at 3, 6, and 24 months. Patients were followed from randomization until death, heart transplantation, or the end of the study. The time and cause of death or time of heart transplantation were ascertained from medical records or death certificates and were verified by an endpoint adjudication committee.

To confirm previous evidence that CPAP attenuates central sleep apnea and improves cardiovascular function after three months, we calculated the changes from baseline in the apnea-hypopnea index, mean and minimum nocturnal oxygen saturation, LVEF, and levels of plasma norepinephrine and atrial natriuretic peptide at three months and throughout the remainder of the trial.<sup>4,7,8</sup> The primary outcome was the combined rate of death from all causes and heart transplantation (the data were censored as of the date of transplantation). Secondary outcomes included death alone and transplantation-free survival, with censoring of data on patients who dropped out, the number of hospital admissions confirmed on the basis of medical records, and changes from baseline in the distance walked in six minutes and in the quality of life.

#### SAMPLE SIZE

The size of the sample for the primary outcome was calculated with the use of the log-rank test, assuming an annual event rate of 24 percent in the control group,<sup>5,6,9,15</sup> with a relative hazard ratio for CPAP of 0.65. At a two-sided alpha level of 0.05, with 80 percent power, we estimated that 204 patients per group would be required.<sup>19</sup>

#### STATISTICAL ANALYSIS

Kaplan-Meier estimates were used to visualize survival without heart transplantation. Cox proportional-hazards analysis was used to compare transplantation-free survival between groups. The primary statistical analysis was according to the intention-to-treat principle. A secondary analysis of this outcome, with data on those who dropped out censored as of the dropout date, was also performed. Generalized linear models for binomial and Poisson distributed outcomes were used to assess changes in the overall event rate over time.<sup>20</sup>

Further analyses with the use of Cox proportional-hazards models examined the effects of interactions between the treatment assignment and compliance with the treatment, age, NYHA class, LVEF, cause of heart failure, medications, and body-mass index on the primary outcome. The number

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Control Group (N=130)	CPAP Group (N=128)
Age — yr	63.5±9.8	63.2±9.1
Male sex — no. (%)	123 (95)	125 (98)
White race — no. (%)	123 (95)	121 (95)
Body-mass index†	29.3±6.5	28.8±5.5
NYHA class — no. (%)		
II	86 (66)	86 (67)
III or IV	44 (34)	42 (33)
Type of cardiomyopathy — no. (%)		
Ischemic	88 (68)	83 (65)
Idiopathic dilated	38 (29)	42 (33)
Hypertensive	4 (3)	3 (2)
Left ventricular ejection fraction — %	24.2±7.6	24.8±7.9
Medication — no. (%)		
ACE inhibitors	106 (82)	99 (77)
AR blockers	23 (18)	24 (19)
Beta-blockers	99 (76)	98 (77)
Loop diuretics	116 (89)	110 (86)
Spironolactone	46 (35)	43 (34)
Digoxin	74 (57)	66 (52)
Nitrates	28 (22)	31 (24)
Sleep time — min		
Total sleep	304±84	308±82
Stage 1 sleep	56±43	58±38
Stage 2 sleep	178±62	177±65
Stage 3 and 4 sleep	32±38	31±32
REM sleep	40±25	43±27
Arousals from sleep — no./hr of sleep	28±23	29±23
Apnea–hypopnea index — no./hr of sleep	40±17	40±15
Central apnea and hypopnea — %	87±14	91±12
Mean SaO <sub>2</sub> during sleep — %	93.1±3.1	93.2±3.7
Lowest SaO <sub>2</sub> during sleep — %	81.7±6.5	82.1±8.2
Distance walked in six minutes — m	418±130	399±121
CHFQ score‡		
Dyspnea	4.2±1.3	4.0±1.2
Fatigue	3.9±1.3	3.9±1.5
Emotional functioning	4.7±1.3	4.7±1.2
Disease mastery	5.1±1.3	4.9±1.4
Plasma norepinephrine — nmol/liter	2.3±1.1§	3.0±2.0¶
Atrial natriuretic peptide — pg/ml	208±118	195±116**

\* Values are means ±SD, unless otherwise indicated. There were no significant differences in the baseline values between the control group and the CPAP group. Race was determined by the investigators. CPAP denotes continuous positive airway pressure, ACE angiotensin-converting enzyme, AR angiotensin II receptor, REM rapid-eye movement, SaO<sub>2</sub> arterial oxyhemoglobin saturation, and CHFQ Chronic Heart Failure Questionnaire.

† Body-mass index is defined as the weight in kilograms divided by the square of the height in meters.

‡ The Chronic Heart Failure Questionnaire assesses patients' functioning with regard to dyspnea, fatigue, emotional functioning, and disease mastery according to a seven-point scale, with lower scores indicating worse condition.

§ Data were available for 39 control patients.

¶ Data were available for 36 patients.

|| Data were available for 40 control patients.

\*\* Data were available for 37 patients.

of hospital admissions in the two groups were compared with the use of the Wilcoxon rank-sum test. For the analysis of repeated measurements of the secondary outcomes collected over time, we used a model of longitudinal data, and the measurements were compared between groups with the use of linear mixed-effects models, wherein we examined interactions between time and treatment over the duration of the trial. We also analyzed secondary outcomes a priori after three months, which was the point in the study for which we had the most complete follow-up data. All data analyses were performed with S-Plus 6.2 software (Insightful). All P values are two-sided. Continuous data are expressed as means ±SD, unless otherwise indicated.

After the first 200 patients had been followed for a minimum of six months, the data and safety monitoring committee performed a prespecified interim analysis. It recommended termination of the study because of an early divergence of the transplantation-free survival curves favoring the control group, enrollment at only 50 percent of the predicted rate, and a falling rate of death and heart transplantation that precluded the ability to detect a difference in the primary outcome between the two groups with the originally predicted sample size. On the basis of this recommendation, the executive committee stopped the trial on May 21, 2004.

RESULTS

PATIENTS

Of 727 patients who were screened between December 1998 and May 2004, 345 met the eligibility criteria, of whom 258 agreed to participate and underwent randomization: 130 patients were assigned to the control group and 128 to the CPAP group. Table 1 shows the similarity in baseline characteristics of the two groups. Ninety-six percent of the patients were men, consistent with the epidemiology of heart failure in patients of a similar age<sup>21</sup> and with the predominance of men among those with heart failure who have central sleep apnea.<sup>3,4,6,15,22,23</sup>

The mean apnea–hypopnea index of 40 per hour indicates severe central sleep apnea. Although some misclassification of hypopnea is possible, the overwhelming predominance of episodes of central apnea and hypopnea makes overlap with mainly obstructive sleep apnea unlikely (Table 1).

**COMPLIANCE AND DROPOUT RATE**

During the course of the trial, 20 patients in each group (15.5 percent) dropped out, refusing further evaluation. In the CPAP group, the average number of hours of daily use of CPAP varied between 4.3 hours during the first three months to 3.6 hours at one year and beyond. The CPAP averaged 8 to 9 cm of water at three months and beyond.

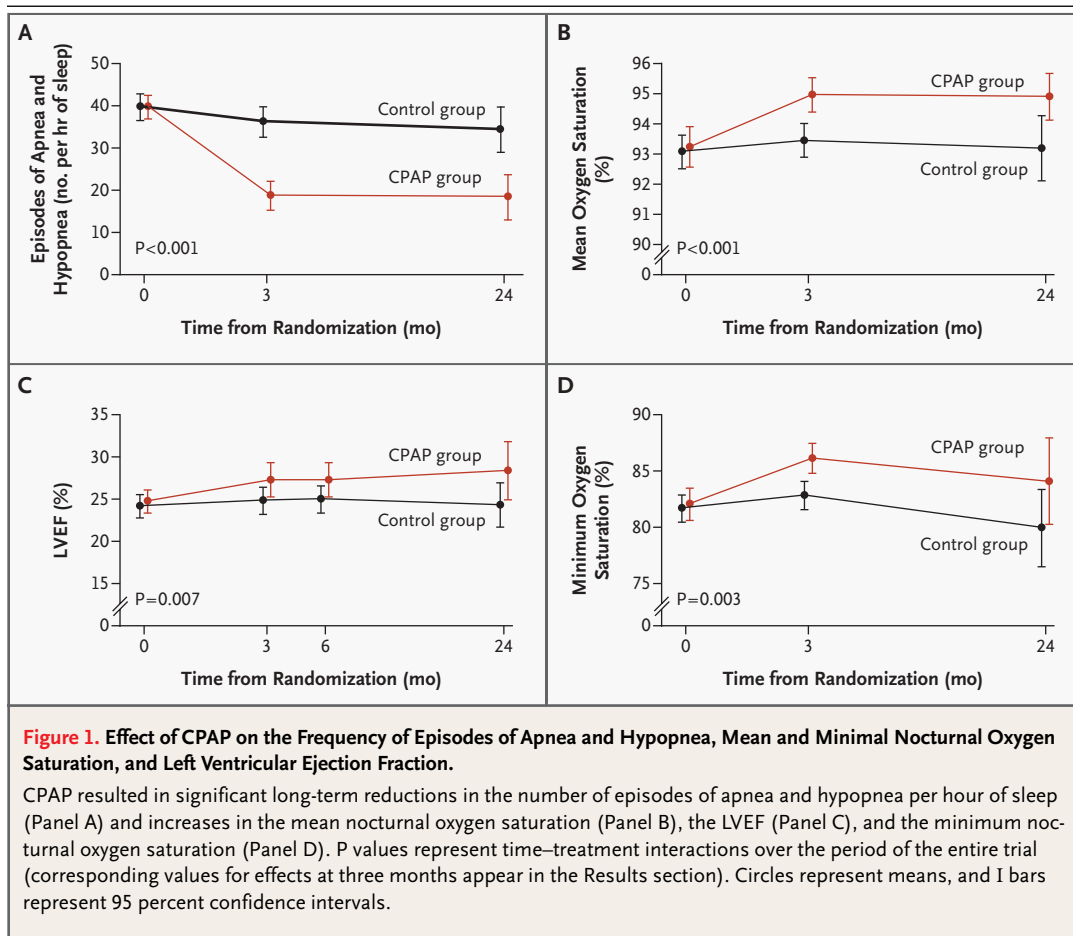
**EFFECT OF CPAP ON CENTRAL SLEEP APNEA AND CARDIOVASCULAR FUNCTION**

At three months, the patients assigned to CPAP had a greater (50 percent) reduction in the apnea-hypopnea index than those in the control group ( $-21 \pm 16$  vs.  $-2 \pm 18$  per hr,  $P < 0.001$ ) (Fig. 1) and greater increases in mean oxygen saturation ( $1.6 \pm 2.8$  percent vs.  $0.4 \pm 2.5$  percent,  $P < 0.001$ ) and minimum oxygen saturation ( $4.7 \pm 7.3$  percent vs.  $0.9 \pm 6.0$  percent,  $P < 0.001$ ) (Fig. 1). These changes were sustained throughout the trial. There were no changes in sleep time, distribution of sleep stages,

or frequency of arousal in either group ( $P > 0.19$  for each variable). At three months, CPAP caused a greater increase in LVEF ( $2.2 \pm 5.4$  percent vs.  $0.4 \pm 5.3$  percent,  $P = 0.02$ ) (Fig. 1) and a greater reduction in levels of plasma norepinephrine ( $-1.03 \pm 1.84$  vs.  $0.02 \pm 0.99$  nmol per liter,  $P = 0.009$ ) than did no intervention. These benefits were sustained for up to two years. CPAP had no significant effect on levels of atrial natriuretic peptide ( $P = 0.64$ ).

**PRIMARY OUTCOME**

Collection of follow-up data on patients for the primary end point stopped on May 21, 2004, when the trial was terminated by the executive committee. Primary outcome data were obtained for all patients, including dropouts. The mean follow-up interval was 2 years (range, 0 to 64 months). The rate of the primary event decreased from 20 to 4 per 100 person-years between 1998–1999 and 2004 ( $P = 0.003$ ) (Fig. 2). This falling event rate was associated with a changing pattern of drug therapy.



During the same period, more patients were receiving beta-blockers (a change from 58 percent to 86 percent,  $P < 0.001$ ) and spironolactone (a change from 14 percent to 41 percent,  $P = 0.001$ ) and fewer patients were receiving digoxin (a change from 72 percent to 36 percent,  $P = 0.002$ ) at the time of enrollment. The use of beta-blockers and spironolactone also increased between the time of baseline assessment and the time of the last follow-up visit for the two groups (beta-blockers, from 77 percent to 83 percent,  $P < 0.001$ ; and spironolactone, from 34 percent to 51 percent,  $P = 0.04$ ), but between the groups, the changes did not differ significantly ( $P > 0.18$  for each drug).

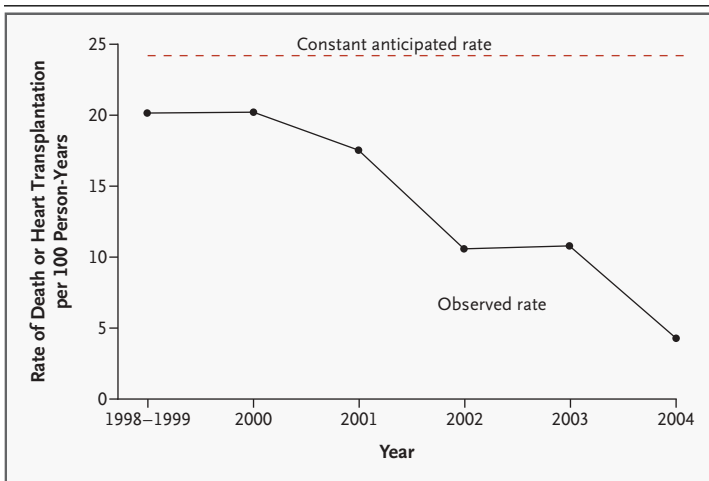
During follow-up, there were 28 deaths and four heart transplantations in the control group and 27 deaths and five heart transplantations in the CPAP group. Most of the deaths were due to cardiovascular causes (Table 2). In the proportional-hazards model, there was no difference in transplantation-free survival between the control group and the CPAP group (hazard ratio for heart transplantation, 1.16; 95 percent confidence interval, 0.71 to 1.90;  $P = 0.54$ ) (Fig. 3). However, the hazards appeared to be nonproportional during the follow-up period (chi-square=10.9,  $P = 0.001$ ). There was a divergence of event rates in the first 18 months favoring the control group (hazard ratio for an event, 1.5;  $P = 0.02$ ) that was reversed after 18 months to favor CPAP (hazard ratio for an event, 0.66;  $P = 0.06$ ).

The level of CPAP and the hours of use were not related to the rate of the primary event. There was no significant interaction between treatment assignment and the seven variables included in the statistical analysis. A post hoc analysis did not detect any significant difference in the primary event rate among the three CPAP devices ( $P = 0.31$ ).

**SECONDARY OUTCOMES**

Death rates alone did not differ significantly between the two groups of patients (hazard ratio for death, 1.1; 95 percent confidence interval, 0.65 to 1.88;  $P = 0.714$ ). With the use of a time-dependent covariate to indicate dropout, the analysis of survival among the patients who did drop out was found to be worse than among those who did not (hazard ratio for death, 3.8;  $P < 0.001$ ), with 10 events among the 20 dropouts from the CPAP group and 9 events among the 20 dropouts from the control group. Neither overall transplantation-free survival (hazard ratio for death, 1.04; 95 percent confidence interval, 0.78 to 1.4;  $P = 0.778$ ) nor survival during the first 18 months (hazard ratio for death, 1.4;  $P = 0.10$ ) differed significantly between patients in the control group and those in the CPAP group who remained in the trial.

The number of hospitalizations did not differ significantly between the control group and the CPAP group (hospitalizations per patient per year,  $0.56 \pm 0.56$  vs.  $0.61 \pm 0.72$ ;  $P = 0.45$ ). The distance



**Figure 2. The Primary Event Rate (Death or Heart Transplantation per 100 Person-Years) for the Two Groups Combined.**  
The primary event rate fell from 83 percent to 17 percent of the predicted rate over the course of the trial.

Cause	Control Group	CPAP Group
	no. (%)	no. (%)
<b>Cardiovascular</b>		
Progressive heart failure	8 (29)	10 (37)
Sudden death	7 (25)	9 (33)
Vascular, noncardiac	3 (11)	1 (4)
Related to medical procedure	1 (4)	2 (7)
Myocardial infarction	1 (4)	1 (4)
Cancer	2 (7)	1 (4)
Other	4 (14)	2 (7)
Unknown	2 (7)	1 (4)
<b>Total</b>	<b>28</b>	<b>27</b>

\* Cardiovascular causes accounted for 78 percent of the deaths. There were no significant differences in the causes of death between the control group and the CPAP group or in cardiovascular causes of death (73 percent vs. 85 percent in the control group and the CPAP group, respectively;  $P = 0.33$ ).

walked in six minutes increased more in the CPAP group than in the control group at three months (20.0±55 vs. -0.8±64.8 m, P=0.016), but not over the whole study period; the average difference was 11.1 m (95 percent confidence interval, -5.3 to 27.5), favoring the CPAP group (P=0.18). Changes in patients' scores on the Chronic Heart Failure Questionnaire did not differ significantly between the two groups.

DISCUSSION

The CANPAP trial tested the effects of CPAP on morbidity and mortality among patients with central sleep apnea and chronic heart failure. The trial addressed two important issues: First, it confirmed the findings of previous small, short-term trials that CPAP attenuates central sleep apnea, improves nocturnal oxygenation and left ventricular systolic function, and lowers plasma norepinephrine levels,<sup>4,5,7</sup> and it showed that these effects are sustained with long-term therapy. Second, the trial failed to demonstrate any beneficial influence of CPAP on transplantation-free survival, number of hospitalizations, or quality of life. Therefore, although CPAP improved several physiological outcomes, this improvement did not translate into longer transplantation-free survival. CPAP did result in an increase of 20 m in the distance walked in six minutes during the first three months of follow-up, but this improvement was not sustained.

CPAP has been shown to improve cardiovascular function in patients with heart failure who have central sleep apnea only when the treatment reduces the apnea-hypopnea index.<sup>4,5,7,8,22</sup> Because CPAP does not attenuate central sleep apnea in patients with heart failure when the treatment is titrated over one night,<sup>22-24</sup> we mandated a gradual upward-titration protocol.<sup>4,7,8</sup> This resulted in a significant reduction in the apnea-hypopnea index, which was accompanied by an increase in nocturnal oxygen saturation that persisted for at least two years. Nonetheless, the reduction of 50 percent in the apnea-hypopnea index was less than had been achieved in previous trials with the use of similar upward titration and CPAP pressures,<sup>4</sup> factors that may have contributed to the lack of a beneficial effect on clinical outcomes.

Improvement in daytime LVEF may be due to several factors, including a reduction in cardiac sympathetic drive,<sup>7,25,26</sup> left ventricular unloading resulting from an increase in intrathoracic pres-

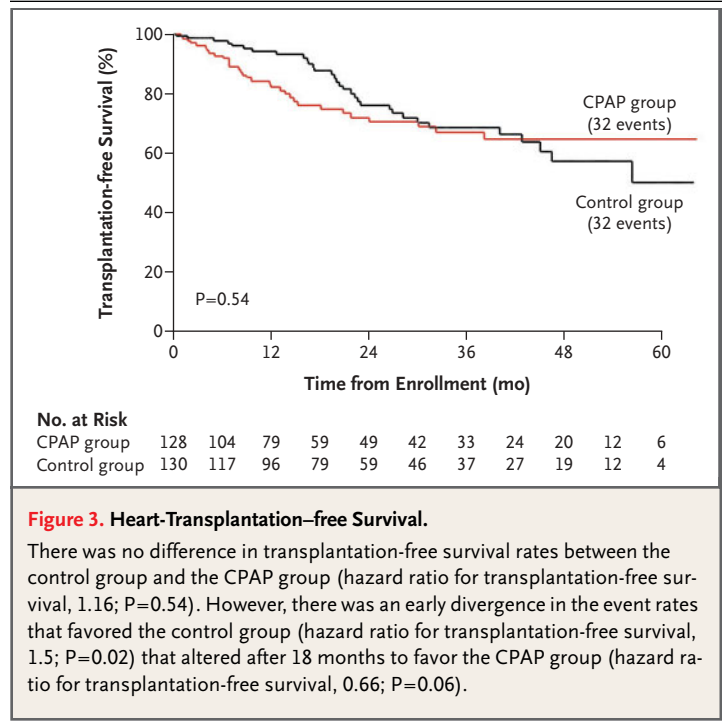


Figure 3. Heart-Transplantation-free Survival.

There was no difference in transplantation-free survival rates between the control group and the CPAP group (hazard ratio for transplantation-free survival, 1.16; P=0.54). However, there was an early divergence in the event rates that favored the control group (hazard ratio for transplantation-free survival, 1.5; P=0.02) that altered after 18 months to favor the CPAP group (hazard ratio for transplantation-free survival, 0.66; P=0.06).

sure,<sup>27</sup> and reduced myocardial ischemia due to improvement in oxygen saturation.<sup>28,29</sup> However, the increase of 2.2 percent in the LVEF was less than the increase of 7.7 percent observed in our first randomized trial.<sup>4</sup> We attribute this difference to the higher initial LVEF (24.5 percent vs. 20.0 percent) and the greater proportion of patients receiving beta-blockers in the present trial (77 percent vs. <20 percent). Owing to the overlap in the effects of beta-blockade and CPAP on ventricular function,<sup>30</sup> the potential for further improvement in the LVEF when CPAP is added may be limited. The high rate of use of beta-blockers may also have reduced the potential for a beneficial effect on clinical outcomes.

The early divergence of event rates that initially favored the control group but favored the CPAP group after 18 months was not anticipated (Fig. 3). It suggests that CPAP had an early adverse effect in some patients. Two possible reasons may be the effect of the dropouts and improvements in background medical therapy. The early difference in transplantation-free survival between the control group and the CPAP group is diminished if it is calculated by excluding the patients who dropped out (among whom event rates were higher than among those who did not drop out). Background medical therapy is of importance, because the acute effect of CPAP in heart failure is a function of left ventric-

ular preload: when filling pressures are high, the cardiac output increases, and when pressures are low, it decreases.<sup>31</sup> We cannot exclude the possibility that upward titration of CPAP reduced cardiac output in some patients with low filling pressures, owing to more vigorous diuresis or other medical interventions. If so, a slower CPAP titration might have avoided some adverse events.

In summary, CPAP attenuated central sleep apnea and improved nocturnal oxygenation, left ventricular function, sympathetic nervous activity, and (at least initially) submaximal exercise performance. However, the CANPAP trial did not demonstrate a beneficial effect of CPAP on morbidity or mortality in these patients with central sleep apnea and heart failure. Because of a declining primary event rate, which was possibly due in part to concurrent improvements in drug therapy,<sup>32,33</sup> it would have required a trial three times the size of ours to determine whether the physiological improvements observed were surrogates for clinically important outcomes.<sup>19</sup> Although the CANPAP trial ultimately lacked the power to conclude with certainty that CPAP is ineffective in this patient popu-

lation, our data do not support its routine use to extend life in patients with central sleep apnea and heart failure. However, this recommendation may not be applicable to patients with heart failure who have obstructive sleep apnea, the pathophysiology of which, arising from pharyngeal occlusion, differs from that of central sleep apnea.<sup>1-3,34-38</sup>

Supported by a grant from the Canadian Institutes of Health Research (CIHR) through its University–Industry Program (UIP). In accordance with the policy of the UIP, one third of the funding was provided by the CIHR and two thirds was provided by the industry partners. Four industry partners each agreed to provide 25 percent of the industry contribution, including donation of its brand of CPAP device. One industry partner (Healthdyne) was acquired by another (Respironics), which provided 50 percent of the industry contribution. Supported also by a Senior Scientist Award from the Canadian Institutes of Health Research (to Dr. Bradley); a National Scientist Award from the Fonds de la Recherche en Santé du Québec (to Dr. Sériès); and by a Canada Research Chair in Integrative Cardiovascular Biology and a Career Investigator Award from the Heart and Stroke Foundation of Ontario (to Dr. Floras).

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#### APPENDIX

The following investigators and study administrators participated in the CANPAP trial: *Executive Committee*: T.D. Bradley (chair), A.G. Logan, and J.S. Floras. *Advisory Committee*: N. Anthonisen and E.R. Smith. *Data and Safety Monitoring Committee*: M. Bourassa (chair), D. Stewart, and L. Magee. *End Point Adjudication Committee*: J.S. Floras (chair), I. Belenkie, and J. Howlett. *CANPAP Sites and Investigators*: Canada — University of Calgary, Calgary, Alta.: I. Belenkie and W. Whitelaw; University of Alberta, Edmonton: M. Heule; Dalhousie University, Halifax, N.S.: D. Morrison and J. Howlett; University of Western Ontario, London: K.A. Ferguson; McGill University, Montreal: R.J. Kimoff and M. Smilovitch; Laval University, Quebec City, Que.: F. Sériès and M.H. Leblanc; University of Toronto, Toronto: Site A — Toronto General Hospital of the University Health Network: T.D. Bradley, A.G. Logan, J.S. Floras, H. Ross, D. Delgado, and R.S.T. Leung; Site B — St. Michael's Hospital: P.J. Hanly; University of British Columbia, Vancouver: J. Fleetham, K. Gin, and J. Wilson; University of Manitoba, Winnipeg: S. Corne and E. Azevedo; Germany — University of Regensburg, Regensburg: M. Pfeifer, S. Montalvan-Dobmayr, and T. Schichtl. *CANPAP trial managers*: F.S. Fitzgerald, N. Catherine, and G. Hopkins. *Data management center*: Prosserman Centre for Health Research, Samuel Lunenfeld Research Institute of the Mount Sinai Hospital, University of Toronto, Toronto (D. Ng, data manager). *Trial statisticians*: G. Tomlinson and R.K. Parkes.

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