Suppression of Central Sleep Apnea by Continuous Positive Airway Pressure and Transplant-Free Survival in Heart Failure

A Post Hoc Analysis of the Canadian Continuous Positive Airway Pressure for Patients With Central Sleep Apnea and Heart Failure Trial (CANPAP)

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Background—In the main analysis of the Canadian Continuous Positive Airway Pressure (CPAP) for Patients with Central Sleep Apnea (CSA) and Heart Failure Trial (CANPAP), CPAP had no effect on heart transplant–free survival; however, CPAP only reduced the mean apnea-hypopnea index to 19 events per hour of sleep, which remained above the trial inclusion threshold of 15. This stratified analysis of CANPAP tested the hypothesis that suppression of CSA below this threshold by CPAP would improve left ventricular ejection fraction and heart transplant–free survival.

Methods and Results—Of the 258 heart failure patients with CSA in CANPAP, 110 of the 130 randomized to the control group and 100 of the 128 randomized to CPAP had sleep studies 3 months later. CPAP patients were divided post hoc into those whose apnea-hypopnea index was or was not reduced below 15 at this time (CPAP-CSA suppressed, n=57, and CPAP-CSA unsuppressed, n=43, respectively). Their changes in left ventricular ejection fraction and heart transplant–free survival were compared with those in the control group. Despite similar CPAP pressure and hours of use in the 2 groups, CPAP-CSA–suppressed subjects experienced a greater increase in left ventricular ejection fraction at 3 months ($P=0.001$) and significantly better transplant-free survival (hazard ratio [95% confidence interval] 0.371 [0.142 to 0.967], $P=0.043$) than control subjects, whereas the CPAP-CSA–unsuppressed group did not (for left ventricular ejection fraction, $P=0.984$, and for transplant-free survival, hazard ratio 1.463 [95% confidence interval 0.751 to 2.850], $P=0.260$).

Conclusions—These results suggest that in heart failure patients, CPAP might improve both left ventricular ejection fraction and heart transplant–free survival if CSA is suppressed soon after its initiation. **(*Circulation*. 2007;115:3173-3180.)**

Key Words: apnea, sleep ■ heart failure ■ respiration ■ sleep ■ survival ■ trials

Central sleep apnea (CSA) with Cheyne-Stokes respiration, present in approximately 25% to 40% of patients with heart failure (HF), exposes the failing heart to hypoxia, arousals from sleep, sympathetic nervous system activation, and ventricular arrhythmias.[1–3] Currently debated is whether CSA contributes to mortality independently of other risk factors.[4–6]

The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP) was a randomized, controlled clinical trial involving 258 HF patients with CSA.[7,8] This trial tested the hypothesis that treating CSA with continuous positive airway pressure (CPAP) would improve both survival without heart transplantation (heart transplant–free survival) and cardiovascular function.[7] CPAP attenuated CSA, improved nocturnal oxygen saturation (Sao_2), reduced sympathetic nervous activity, and increased left ventricular ejection fraction (LVEF) and 6-minute walking distance,[8] yet heart transplant–free survival was not altered.

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Previous studies suggest that alleviation of CSA is a key mechanism through which CPAP exerts its beneficial cardio-

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vascular effects in patients with HF. For example, in several single-center trials in which CPAP reduced the apnea-hypopnea index (AHI) of HF patients with CSA by 65% to 75%, to below 15 per hour of sleep, it caused a significant improvement in LVEF.[3,9–11] Reductions in AHI after 1 month of CPAP preceded this increase in LVEF, which did not appear until after 3 months of CPAP.[10] In contrast, in a study in which CPAP did not suppress CSA in HF patients, left ventricular (LV) systolic function did not improve.[12] In a small, single-center trial by Sin and colleagues,[5] CPAP had no effect on LVEF or heart transplant–free survival in HF patients without CSA or obstructive sleep apnea. In contrast, in the same study, application of CPAP to HF patients with CSA increased LVEF in association with a strong trend toward improved heart transplant–free survival ($P=0.056$).

In CANPAP, CPAP caused a 53% fall in the mean AHI, from 40 to 19 per hour of sleep, and therefore did not reduce the average AHI to below the trial inclusion threshold of 15 per hour of sleep.[7,8] This failure of CPAP to more completely reverse CSA may explain its more modest effect on LVEF (increase of 2.2% versus 8% in previous trials)[3,5,10,11] and its failure to alter heart transplant–free survival. We therefore performed a post hoc analysis of the CANPAP database to test the hypothesis that greater suppression of CSA by CPAP to an AHI below the inclusion threshold of 15 per hour of sleep would improve LVEF and heart transplant–free survival.

Methods

Study Design

Details of the study design have been published previously.[7,8] Briefly, CANPAP was a prospective, randomized, open-label trial with blinded evaluation of outcomes that involved 11 centers (see Appendix in the online-only Data Supplement). The research ethics board of each institution approved the protocol. Enrollment followed written informed consent.

Subjects

Candidates for participation in CANPAP included men and women aged 18 to 79 years with New York Heart Association class II to IV HF due to ischemic, hypertensive, or idiopathic dilated cardiomyopathy, stabilized with optimal medical therapy for at least 1 month; LVEF <40% by radionuclide angiography; and CSA. CSA was defined[7] as an AHI ≥15, with >50% of apneas and hypopneas central in nature (see below). Exclusion criteria were pregnancy; myocardial infarction, unstable angina, or cardiac surgery within 3 months of enrollment; and obstructive sleep apnea.

Randomization

Eligible patients were randomized to either a control group who continued optimal medical HF therapy or a treatment group who, in addition, received CPAP. Randomization was performed by computerized schedule in random blocks of 4 and 6 and was stratified by study center. Treatment assignment was communicated to sites by the Data Management Center once it was verified that the patient was eligible. Subjects assigned to CPAP were further randomized in a 2:1:1 ratio to a Respironics REMstar Pro (Respironics, Inc; Murrysville, Pa), ResMed Sullivan VII (ResMed Corp; Poway, Calif), or Tyco Healthcare GoodKnight 420S (Tyco Healthcare; Mansfield, Mass) device, respectively. The use of CPAP devices from 3 different companies was a consequence of the arrangements made for study funding; no significant differences in heart transplant–free survival could be detected among the 3 devices ($P=0.3$).[8]

Baseline Assessment

Patients underwent clinical assessment followed by overnight polysomnography. Sleep stages and arousals, apneas and hypopneas, and mean and minimal arterial oxygen saturation (Sa_{O_2}) were assessed according to uniform methods at all centers.[8,10,13] Respiratory effort was measured by respiratory inductance plethysmography and airflow by nasal pressure.[4,14–17] Central apneas were defined as absent tidal volume for ≥10 seconds without thoracoabdominal motion[10,16] and central hypopneas as a ≥50% reduction in tidal volume from baseline for ≥10 seconds without airflow limitation on nasal pressure.[10,18] Apneas and hypopneas were classified as obstructive if out-of-phase thoracoabdominal motion or airflow limitation was present.[16,18] Resting LVEF was determined by radionuclide angiography.

Initiation of CPAP

CPAP was initiated over 2 to 3 nights in an unmonitored sleep laboratory or hospital bed,[3,10,11] starting at 5 cm H_2O the first night, then increasing by 2 to 3 cm H_2O over the subsequent 1 or 2 nights up to 10 cm H_2O (a level shown to attenuate CSA and improve LVEF)[5,10,11] or until the highest pressure tolerated was reached. Patients were instructed to use CPAP at least 6 hours nightly at home during the trial. If necessary, pressure was raised to 10 cm H_2O or to the highest level tolerated at the 1- or 3-month follow-up visit. At each clinic visit, hours of CPAP use were downloaded from a mask-on time meter.

Assessments of Outcomes

Clinical assessments were performed 1, 3, and 6 months after randomization and every 6 months thereafter. Polysomnography was performed at 3 and 24 months, and LVEF was evaluated at 3, 6, and 24 months after randomization. Subjects were followed up from randomization until death, transplantation, or the end of the study. The primary outcome was the combined rate of all-cause mortality or heart transplantation, with subjects censored after transplantation or, if alive and transplant–free, at the end of follow-up. Time and cause of death or heart transplantation were ascertained from medical records or death certificates and were verified by an end-point adjudication committee.

To test the hypothesis that suppression of CSA by CPAP early in the trial was associated with improved LVEF and heart transplant–free survival, we evaluated only those subjects who underwent polysomnography at 3 months after enrollment. Because an AHI of ≥15 was the cutoff for inclusion in the trial,[7,8] we stratified patients randomized to CPAP into those whose AHI was suppressed by CPAP to <15 at 3 months after randomization (CPAP-CSA–suppressed group) and those whose AHI remained ≥15 at this time (CPAP-CSA–unsuppressed group).

In the CPAP group, the AHI was suppressed to <15 in 57 subjects (57%). However, because the AHI decreased spontaneously to <15 in only 12 subjects (11%) in the control group, the 2 CPAP groups were compared with the entire control group. Secondary outcomes included changes in AHI, mean nocturnal Sa_{O_2}, and LVEF from baseline to 3 months.

Statistical Analysis

Baseline characteristics of patients in the 3 groups were compared by ANOVA with post hoc contrasts by t tests for continuous variables and by χ^2 or Fisher exact test for nominal variables as appropriate. Kaplan-Meier plots were used to visualize heart transplant–free survival. Multivariable Cox proportional hazards analysis was used to compare transplant-free survival in the control group with that in the CPAP-CSA–suppressed and the CPAP-CSA–unsuppressed groups beginning 3 months after randomization at the time of the follow-up polysomnogram. We evaluated for potential confounding by introducing factors that were different between the groups at baseline and recorded factors known to increase the risk of cardiovascular death in HF patients into the models 1 at a time.[4,5,19,20] These were sex, age, and baseline LVEF, New York Heart Association class, AHI, and percent central AHI, as well as the use of

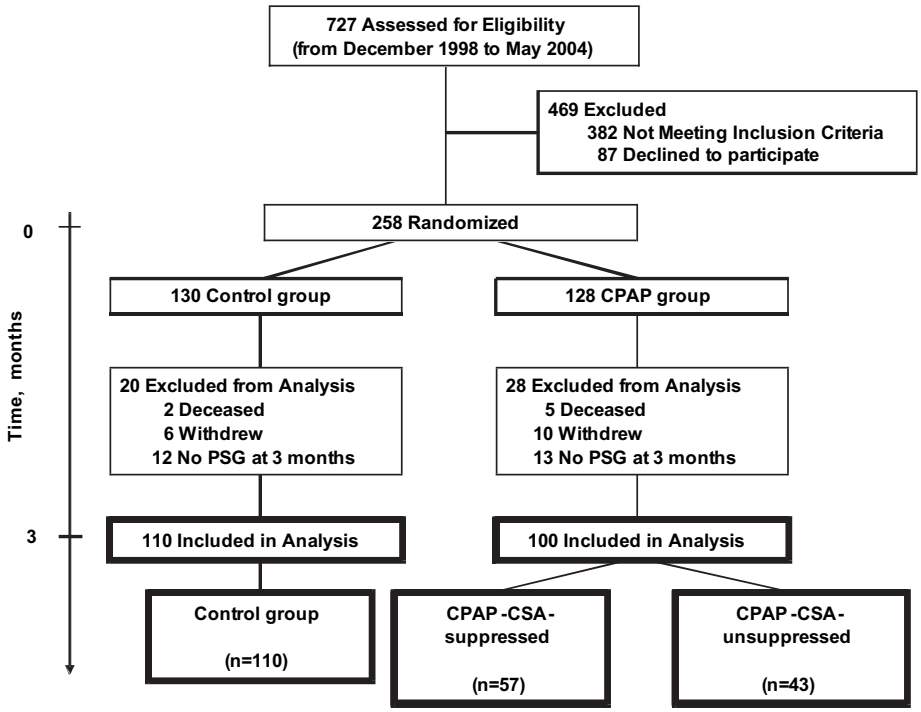


Figure 1. Flow diagram indicating progress of eligible subjects through the study. Bold boxes represent subjects who were included in the analysis of the present report of the CANPAP trial. PSG indicates polysomnography.

β-blockers and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.

We tested the equality of survival between the 3 groups with a likelihood ratio test; this compared Cox models with and without a variable that represented the group. When an overall difference was present, we computed hazard ratios (HRs) comparing each of the CPAP-treated subgroups with the entire control group.

We might also expect that patients having a spontaneous drop in AHI to <15 at 3 months in the control group would have a better outcome; however, in the present study, only 12 subjects in the control group experienced a drop in AHI to <15, and only 1 of these had a primary event. This leads to very low power for examining the effect of a reduction in AHI among control patients. Nevertheless, to evaluate the impact of a spontaneous drop in AHI on LVEF and transplant-free survival, we also compared change in LVEF and transplant-free survival between subjects in the control group whose AHI decreased spontaneously to <15 versus those whose AHI remained ≥15 at 3 months after enrollment.

Two-way repeated-measures ANOVA and Tukey's test were used to compare differences between groups in AHI, mean and minimal nocturnal Sao_2, and LVEF measured at baseline and 3 months after enrollment. Paired *t* tests were used to compare differences within groups. All data analyses were generated by R (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria).[21] All probability values are 2-sided.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Subjects

Of the original 258 patients randomized, 20 in the control group and 28 in the CPAP group did not undergo polysomnography 3 months after randomization for reasons shown in Figure 1. Therefore, the present analysis includes 110 patients in the control group and 100 in the CPAP group. In this latter group, AHI was <15 events per hour 3 months after enrollment in 57 patients, whereas AHI remained ≥15 in 43. Table 1 displays the baseline characteristics of the subjects. The mean AHI of between 34 and 47 events per hour indicates moderate to severe CSA in the 3 groups.

No statistically significant differences existed between the CPAP-CSA–suppressed and control groups in age, sex distribution, race, body mass index, severity and cause of HF, frequency of atrial fibrillation, LVEF, cardiac medications, AHI, or percentage of central apneas and hypopneas (Table 1). Patients in the CPAP-CSA–unsuppressed group were also similar to controls with respect to all baseline characteristics, except they had a higher AHI and a higher percentage of central apneas and hypopneas. Compared with subjects from the CPAP-CSA–suppressed group, those from the CPAP-CSA–unsuppressed group were significantly older, had significantly higher AHI, and had a higher percentage of central apneas and hypopneas. However, no significant difference existed in obstructive AHI between the CPAP-CSA–suppressed and –unsuppressed groups at baseline (3.6 versus 3.3 events/h, $P=0.994$) or at 12 weeks (1.0 versus 2.4 events/h, $P=0.956$). In the CPAP-CSA–suppressed and –unsuppressed groups, no significant difference existed in the proportion of subjects not taking a β-blocker at the time of enrollment who were started on one during the course of the trial (5% and 12%, respectively; $P=0.38$).

Dropouts, Early Deaths, and CPAP Compliance

During the first 3 months after enrollment, 10 and 6 subjects, respectively, within the CPAP and control groups (10% and 5%) dropped out. After the sleep study at 3 months, 4 patients (7%) withdrew from the CPAP-CSA–suppressed group, 6 (14%) from the CPAP-CSA–unsuppressed group, and 14 (13%) from the control group.

TABLE 1. Baseline Characteristics of Subjects

	Control (n=110)	CPAP-CSA Suppressed (n=57)	CPAP-CSA Unsuppressed (n=43)
Age, y	63.6±10.0	60.3±9.1	65.2±9.2*
Male, n (%)	104 (95)	57 (100)	40 (93)
White, n (%)	105 (96)	55 (97)	39 (91)
Body mass index, kg/m^2	29.2±5.6	29.9±5.4	28.6±4.8
New York Heart Association class, n (%)			
II	79 (72)	38 (67)	31 (72)
III or IV	31 (28)	19 (33)	12 (28)
Cause of cardiomyopathy, n (%)			
Ischemic	73 (66)	37 (65)	27 (63)
Idiopathic dilated	33 (30)	18 (32)	15 (35)
Hypertensive	4 (4)	2 (4)	1 (2)
Blood pressure, mm Hg			
Systolic	115±18	113±16	115±22
Diastolic	71±11	72±10	70±11
Heart rate, bpm	71±11	69±11	70±12
Atrial fibrillation, n (%)	20 (18)	15 (26)	11 (25)
LVEF, %	24.2±7.5	25.6±8.1	23.7±7.2
Medications used, n (%)			
ACE inhibitors or angiotensin II receptor blockers	107 (97)	55 (97)	39 (91)
β-Blockers	86 (78)	46 (81)	30 (70)
Loop diuretics	99 (90)	48 (84)	37 (86)
Spironolactone	43 (39)	26 (46)	19 (44)
Digoxin	62 (56)	34 (60)	19 (44)
Total sleep time, min	308±88	320±77	315±72
AHI, n/h sleep	38±16	34±13	47±14†
Central apnea/hypopnea, %	82±19	87±15	91±10‡
Mean Sa_{O_2} during sleep, %	93.0±3.2	93.4±3.6	93.2±3.5

Continuous values are shown as mean±SD. CPAP-CSA–suppressed and CPAP-CSA–unsuppressed groups were defined as having an AHI <15 and ≥15 at 3 months, respectively. ACE indicates angiotensin-converting enzyme.

*Versus the CPAP-CSA–suppressed group (P=0.031).

†Versus the control and CPAP-CSA–suppressed groups (P=0.003 and P<0.001, respectively).

‡Versus the control and CPAP-CSA–suppressed groups (P=0.007 and P<0.001, respectively).

During the first 3 months after enrollment, 5 and 2 subjects from the CPAP and control groups, respectively, died. All 5 deaths in the CPAP group occurred at least 1 month after initiation of CPAP therapy. Their causes of death were progressive heart failure (n=2), myocardial infarction (n=1), and encephalopathy due to cardiac and renal failure (n=1) and to a ruptured abdominal aortic aneurysm (n=1). The 2 deaths in the control group within the first 3 months were attributed to progressive heart failure (n=1) and myocardial infarction (n=1).

No significant difference existed in compliance with CPAP between the CPAP-CSA–suppressed and –unsuppressed groups in that they used CPAP at similar pressures and for similar amounts of time per day during the first 3 months (Table 2). Similar proportions of subjects reached the target pressure of 10 cm H_2O and used CPAP for the minimum target treatment time of 4 hours per day.[7,8]

AHI and LVEF

From baseline to the 3-month follow-up polysomnogram, CPAP caused a greater reduction of the AHI in both the CPAP-CSA–suppressed (mean [95% confidence interval {CI}] −27.5 [−30.8 to −24.2] events per hour of sleep) and the CPAP-CSA–unsuppressed (−12.1 [CI −16.8 to −7.3] events per hour of sleep) groups than in the control group (−2.1 [CI −5.5 to 1.3] events per hour of sleep; Figure 2). The reduction in the AHI was significantly greater in the

TABLE 2. CPAP Pressure and Use

	CPAP-CSA Suppressed (n=57)	CPAP-CSA Unsuppressed (n=43)	P
Pressures applied, cm H_2O			
At initiation	6.9±2.0	6.3±1.9	0.111
At 3 mo	8.9±1.9	8.6±1.8	0.340
At 12 mo	9.7±1.8	9.1±3.2	0.438
No. (%) at ≥10 cm H_2O	33 (58)	17 (44)	0.168
CPAP use, h/d			
At 3 mo	4.6±2.0	4.2±2.5	0.464
At 12 mo	3.6±2.1	3.6±2.7	0.997
No. (%) ≥4 h/d	37 (61)	19 (56)	0.406

Continuous variables are shown as mean±SD.

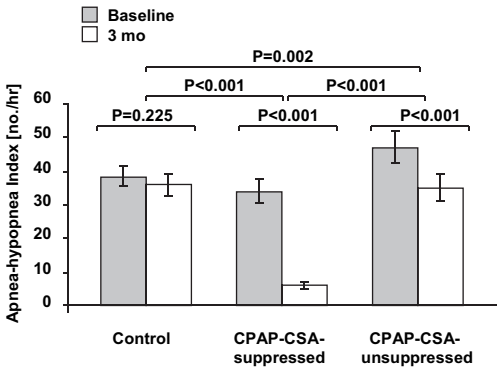


Figure 2. Data shown are means (95% CI). In the control group, no significant change occurred in the number of apneas and hypopneas per hour of sleep (AHI) from baseline to 3 months (from 38 [35 to 41] to 36 [33 to 40] per hour of sleep). In both the CPAP-CSA–suppressed and CPAP-CSA–unsuppressed groups, the AHI was reduced from baseline to 3 months (from 34 [30 to 37] to 6 [5 to 7], $P<0.001$, and from 47 [42 to 52] to 35 [31 to 39] per hour of sleep, respectively; $P<0.001$), and these reductions were significantly greater than in the control group ($P<0.001$ and $P=0.002$, respectively). In addition, the reduction in AHI from baseline to 3 months was greater in the CPAP-CSA–suppressed group than in the CPAP-CSA–unsuppressed group ($P<0.001$). Two-way repeated-measures ANOVA and Tukey's test were used to compare differences between groups. The paired *t* test was used to compare differences within a group.

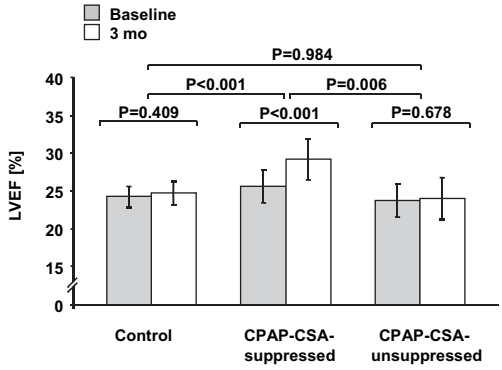


Figure 3. Data shown are means (95% CI). In the CPAP-CSA–unsuppressed group, LVEF did not change significantly from baseline to 3 months (mean change: 0.3% [−1.0% to 1.6%]), and this change did not differ significantly from that in the control group (0.4% [−0.6% to 1.5%]). In contrast, in the CPAP-CSA–suppressed group, LVEF increased significantly from baseline to 3 months (3.6% [2.1% to 5.1%], $P<0.001$), and this increase was significantly greater than in both the control group ($P<0.001$) and the CPAP-CSA–unsuppressed group ($P=0.006$). Two-way repeated-measures ANOVA and Tukey's test were used to compare differences between groups. The paired *t* test was used to compare differences within a group.

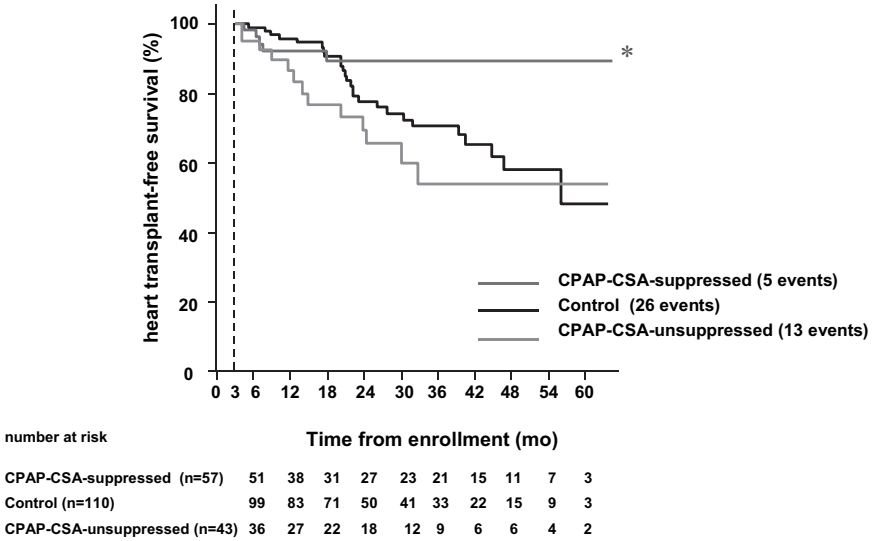
suppressed than in the unsuppressed group. The mean AHI at 3 months was 6 (95% CI 5 to 7) in the CPAP-CSA–suppressed group, 35 (95% CI 31 to 39) in the CPAP-CSA–unsuppressed group, and 36 (95% CI 33 to 40) in the control group. The increase in mean nocturnal Sa_{O_2} was larger in the CPAP-CSA–suppressed group (2.1% [95% CI 1.2 to 3.0]) than in the control group (0.4% [95% CI −0.1 to 0.9], $P<0.001$). Changes in mean nocturnal Sa_{O_2} from baseline to 3 months did not differ significantly between the CPAP-CSA–unsuppressed (1.0% [95% CI 0.6 to 1.4]) and control groups.

LVEF did not change significantly from baseline to 3 months in either the control group or the CSA-unsuppressed group (Figure 3). Change in LVEF in the CSA-unsuppressed group did not differ significantly from that in the control group. In contrast, LVEF increased significantly in the CPAP-CSA–suppressed group, and this increase was greater than in both the control group and the CPAP-CSA–unsuppressed group. The change in LVEF correlated inversely with the change in AHI from baseline to 3 months ($r=-0.229$, $P=0.023$) and with the absolute AHI at 3 months ($r=-0.238$, $P=0.018$). In subjects from the control group whose AHI decreased to <15 at 3 months, no significant change was observed in LVEF. This change was less than the increase in LVEF in the CPAP-CSA–suppressed group but, probably owing to the small number of subjects in the control group (n=12), was not significant (0.3±3.3% versus 3.6±5.6%, $P=0.205$).

Transplant-Free Survival

Primary outcome data were obtained in all subjects, including dropouts. The mean follow-up after the sleep study at 3 months after enrollment was 23 months (range 0 to 61 months).

During follow-up, 26 primary events occurred (21 deaths and 5 heart transplantations; 23%) in the control group, 5 (5 deaths and no heart transplantations; 9%) in the CPAP-CSA–suppressed group, and 13 (9 deaths and 4 heart transplants; 30%) in the CPAP-CSA–unsuppressed group. In the unadjusted model, transplant-free survival was significantly different between the 3 groups ($P=0.016$). Survival was significantly higher in the CPAP-CSA–suppressed group than in the control group (HR [95% CI] 0.371 [0.142 to 0.967]; Figure 4). In contrast, a nonsignificant trend existed toward reduced transplant-free survival in the CPAP-CSA–unsuppressed group compared with the control group (unadjusted HR [95% CI] 1.463 [0.751 to 2.850]). None of the potential confounding variables considered (see Statistical Analysis above) conferred a 10% change in the HR of CPAP-CSA–suppressed and –unsuppressed status, which indicates that no important confounding was present.[22] Nevertheless, because subjects in the CPAP-CSA–suppressed group tended to be younger and to have a lower AHI than subjects from the control group, we derived a model adjusted for age and AHI at baseline. In this model, transplant-free survival was significantly different between the 3 groups ($P=0.011$). Compared with the control group, adjusted transplant-free survival remained significantly greater in the CPAP-CSA–suppressed group (HR 0.345 [95% CI 0.132 to 0.922], $P=0.034$) but tended to be lower in the CPAP-CSA–unsuppressed group (HR 1.632 [95% CI 0.795 to 3.349], $P=0.180$). Neither age nor baseline AHI made any significant independent contribution to transplant-free survival (age: HR 0.993 [95% CI 0.963 to 1.024], $P=0.650$; AHI: HR 0.992 [95% CI 0.972 to 1.012], $P=0.430$). A nonsignificant trend for better transplant-free survival existed in subjects from the control group with a reduction in AHI to <15 than in control subjects whose AHI



number at risk

CPAP-CSA-suppressed (n=57)	51	38	31	27	23	21	15	11	7	3
Control (n=110)	99	83	71	50	41	33	22	15	9	3
CPAP-CSA-unsuppressed (n=43)	36	27	22	18	12	9	6	6	4	2

Figure 4. Kaplan-Meier survival plots demonstrating that compared with the control group, the CPAP-CSA–suppressed group had significantly improved heart transplant–free survival (*unadjusted $P=0.043$), whereas the CPAP-CSA–unsuppressed group did not (unadjusted $P=0.260$).

remained ≥15 after 3 months (HR 0.278 [95% CI 0.038 to 2.00], $P=0.185$).

Discussion

In this stratified analysis of the CANPAP trial, we examined the effects of CPAP on LVEF and transplant-free survival according to the effects of CPAP on CSA 3 months after randomization. The major findings were that in the 57% of patients in whom CPAP reduced the AHI to <15, LVEF and transplant-free survival improved compared with the control group. In contrast, among the 43% of patients in whom CPAP did not reduce the AHI to <15, neither LVEF nor transplant-free survival improved compared with the control group. These findings extend those of a previous smaller randomized trial of CPAP involving HF patients both with CSA and without sleep apnea.[5] In that trial, CPAP had no effect on LVEF 3 months after randomization or on heart transplant–free survival over the median follow-up period of 2.2 years among those without CSA. In contrast, among patients with CSA, CPAP improved LVEF after 3 months and was associated with a trend toward improved transplant-free survival ($P=0.059$).[5]

Uncertainty exists as to whether these effects were due to alleviation of CSA and its adverse actions[3,5,8] or to the direct hemodynamic effects of CPAP, such as reductions in preload and afterload due to increased intrathoracic pressure.[23–26] The present analysis of CANPAP helps to resolve this issue: Compared with the control group, LVEF and transplant-free survival improved in the CPAP patients whose CSA was suppressed but not in those in whom CSA was not suppressed. Indeed, a nonsignificant trend to worse transplant-free survival existed in the CPAP-CSA–unsuppressed group. Because CPAP pressure and hours of use did not differ between the CPAP-CSA–suppressed and –unsuppressed groups, the direct preload- and afterload-reducing effects of CPAP are unlikely to explain improved LVEF and transplant-free survival in the suppressed group. Therefore, suppression of CSA and its adverse effects is more likely to account for the beneficial effects of CPAP on outcomes in the CPAP-CSA–suppressed group.

Interestingly, the survival curves of both the CPAP-CSA–suppressed group in the present secondary analysis of the CANPAP trial (Figure 4) and the CPAP group with CSA in the previous trial[5] began to diverge from the control groups at ≈18 months after randomization. Moreover, in both trials, the overall relative reduction in risk of death and cardiac transplantation was similar in these groups at 64% and 67%, respectively.

In CANPAP, CPAP caused an overall reduction in AHI of 53%, which was less than the 65% to 70% reduction reported in previous single-center trials lasting at least 1 month.[9–11] The reason for this attenuated effect remains uncertain. The 1- to 2-cm H_2O lower mean CPAP achieved in the CANPAP trial compared with the first randomized trial[10] does not appear to explain the variation of CPAP effects on CSA, because the pressures and hours of use did not differ between the CPAP-CSA–suppressed and –unsuppressed groups. No differences existed between the control, CPAP-CSA–suppressed, and CPAP-CSA–unsuppressed groups at baseline in sex, body mass index, race, severity and origin of heart failure, frequency of atrial fibrillation, and use of cardiac medications. Patients from the CPAP-CSA–suppressed group were younger, had less severe CSA, and had a slightly lower proportion of central events than subjects from the CPAP-CSA–unsuppressed group. However, these differences at baseline were modest and, when controlled for in our statistical analyses, did not alter the effect of CPAP on LVEF or transplant-free survival.

Only 5% and 12% of the subjects who were not taking a β-blocker at enrollment were started on one subsequently in the CPAP-CSA–suppressed and CPAP-CSA–unsuppressed groups. These data do not support the possibility that compared with the control group, the better transplant-free survival of the CPAP-CSA–suppressed group was due to greater intensification of medical therapy during the trial.

The present analysis is subject to several limitations. First, it is a post hoc analysis in which stratification of the CPAP-treated patients was based on the results of a polysomnogram performed 3 months after randomization. Because the 2 CPAP-treated groups were not generated randomly, we

cannot rule out the possibility that other unmeasured prognostic factors could explain differences in outcomes between the CPAP-CSA–suppressed and CPAP-CSA–unsuppressed groups compared with the control group. One such factor could be LV filling pressure, because the CPAP-induced increase in intrathoracic pressure generally augments cardiac output acutely when applied to HF patients with elevated filling pressures but reduces it in those with low filling pressures.[23] If patients in the CPAP-CSA–unsuppressed group had low LV filling pressures, hemodynamic impairment by CPAP may have contributed to the ≈50% increased risk (P=0.260) of death or heart transplantation in the CPAP-CSA–unsuppressed group compared with the control group. The lack of statistical significance for this comparison may reflect low study power rather than a lack of difference in transplant-free survival between groups. Second, because suppressed and unsuppressed status could not be ascertained until completion of polysomnography 3 months after randomization, events that occurred during the first 3 months could not be included; more deaths occurred in the patients randomized to CPAP than in the control group (5 versus 3). Third, the CPAP-CSA–suppressed group was younger, had a lower AHI, and had a slightly lower proportion of central events than the CPAP-CSA–unsuppressed group. However, controlling for these factors did not affect the favorable HR for transplant-free survival in the CPAP-CSA–suppressed group. Fourth, because of the lack of a well-validated placebo for CPAP in treating CSA, the CANPAP trial was not placebo-controlled.

In summary, this stratified analysis of the CANPAP trial database suggests that early suppression of CSA by CPAP to an AHI below 15 per hour may improve both LVEF and transplant-free survival. The present data nevertheless do not support the use of CPAP in HF patients with predominantly CSA outside the setting of well-designed randomized trials. However, this possibility could be tested prospectively in 1 of 2 ways. The first approach would have to anticipate and control for the possibility of early harm from CPAP raised by the primary results of the CANPAP trial.[8] We have shown previously that CPAP reduces AHI in HF patients with CSA within 1 month and that this precedes improvement in LVEF.[10,11] In addition, in the CANPAP trial, no deaths or serious adverse effects occurred in HF patients randomized to CPAP within 1 month of its initiation. Therefore, patients with HF and CSA could be randomly assigned to CPAP or a control group and restudied after 1 month. If CPAP suppressed AHI (eg, to <15 events per hour as per the present analysis), then it could be continued; if not, then CPAP could be discontinued and the 2 groups followed up. A second approach would be to determine, in randomized trials, whether other forms of positive airway pressure, which might cause greater suppression of CSA than CPAP, are safe and improve long-term cardiovascular outcomes.[6,27,28]

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CLINICAL PERSPECTIVE

The main hypothesis of the Canadian Continuous Positive Airway Pressure (CPAP) for Patients with Central Sleep Apnea (CSA) and Heart Failure Trial (CANPAP) was that suppression of CSA by CPAP would improve heart transplant–free survival; however, CPAP only reduced the mean apnea-hypopnea index to 19 events per hour of sleep, which remained above the trial entry threshold index of 15 per hour. In the main analysis of CANPAP, CPAP had no effect on heart transplant–free survival; however, whether suppression of the apnea-hypopnea index to <15 per hour would be associated with improved transplant-free survival remained unclear. This stratified analysis of CANPAP tested the hypothesis that suppression of CSA below this threshold by CPAP would improve left ventricular ejection fraction and heart transplant–free survival. Of the 258 heart failure patients with CSA in CANPAP, 110 in the control group and 100 in the CPAP group had sleep studies 3 months later. CPAP patients were divided into those whose apnea-hypopnea index was or was not reduced below 15 at this time (CPAP-CSA–suppressed, n=57, and CPAP-CSA–unsuppressed, n=43, respectively). Their changes in left ventricular ejection fraction and heart transplant–free survival were compared with those in the control group. CPAP-CSA–suppressed subjects experienced a greater increase in left ventricular ejection fraction at 3 months ($P=0.001$) and significantly better transplant-free survival (hazard ratio 0.371 [95% confidence interval 0.142 to 0.967], $P=0.043$) than control subjects, whereas the CPAP-CSA–unsuppressed group did not. These results suggest that in heart failure patients, CPAP might improve both left ventricular ejection fraction and heart transplant–free survival if CSA is suppressed soon after its initiation.