Effect of Continuous Positive Airway Pressure on Sleep Structure in Heart Failure Patients with Central Sleep Apnea

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Study Objectives: At termination of obstructive apneas, arousal is a protective mechanism that facilitates restoration of upper airway patency and airflow. Treating obstructive sleep apnea (OSA) by continuous positive airway pressure (CPAP) reduces arousal frequency indicating that such arousals are caused by OSA. In heart failure (HF) patients with central sleep apnea (CSA), however, arousals frequently occur several breaths after apnea termination, and there is uncertainty as to whether arousals from sleep are a consequence of CSA. If so, they should diminish in frequency when CSA is attenuated. We therefore sought to determine whether attenuation of CSA by CPAP reduces arousal frequency.

Design: Randomized controlled clinical trial.

Patients and Setting: We examined data from 205 HF patients with CSA (apnea-hypopnea index [AHI] ≥ 15, > 50% were central) randomized to CPAP or control who had polysomnograms performed at baseline and 3 months later.

Measurements and Results: In the control group, there was no change in AHI or frequency of arousals. In the CPAP-treated group, the AHI decreased significantly (from [mean ± SD] 38.9 ± 15.0 to 17.6 ± 16.3, $P < 0.001$) but neither the frequency of arousals nor sleep structure changed significantly.

Conclusion: These data suggest that attenuation of CSA by CPAP does not reduce arousal frequency in HF patients. We conclude that arousals were not mainly a consequence of CSA, and may not have been acting as a defense mechanism to terminate apneas in the same way they do in OSA.

Keywords: Arousal, sleep structure, central sleep apnea, sleep physiology

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SLEEP STRUCTURE IS INVARIABLY DISRUPTED BY AROUSALS FROM SLEEP IN PATIENTS WITH SLEEP APNEA.[1,2] IN OBSTRUCTIVE SLEEP APNEA (OSA), arousals from sleep that typically terminate apneas, trigger activation of the pharyngeal dilator muscles and facilitate resumption of airflow. Indeed, several studies report that 75% to 80% of obstructive events are terminated by arousals.[3,4] Accordingly, in OSA, arousals are considered to be an important defense mechanism for reestablishing airway patency, thus preventing asphyxia. On the other hand, this protective mechanism inevitably disrupts sleep. When OSA is alleviated by continuous positive airway pressure (CPAP), the frequency of arousals is immediately reduced in association with consolidation of sleep and an increase in the proportion of both slow wave and REM sleep.[5-8] One can therefore conclude that OSA causes arousal from sleep, and that this, in turn, reduces the amounts of slow wave and REM sleep.

In patients with heart failure (HF) and coexisting Cheyne-Stokes respiration with central sleep apnea (CSA), arousals often follow central apneas and hypopneas.[2,9,10] However, in contrast to OSA, these arousals often occur several breaths after apnea termination, suggesting that in such cases, they are not an important defense mechanism that contribute to resumption of airflow. Arousals, whether occurring during the apnea-hyperpnea cycle or not, provoke abrupt increases in ventilation and decreases in PCO_2. If PCO_2 falls below the threshold for apnea, central apnea ensues.[11,12] Among patients with CSA, either with or without HF, abrupt increases in ventilation, and falls in PCO_2, mainly provoked by arousals, precede more than 90% of episodes of Cheyne-Stokes respiration and repetitive central apneas.[11,12] Moreover, in previous studies, it has been shown that CPAP only partially suppresses CSA such that the frequency of apneas and hypopneas/h of sleep (apnea-hypopnea index or AHI) only falls by approximately 30% to 70% in patients with HF.[13-21] Perhaps this was because it did not eliminate one stimulus to the Cheyne-Stokes respiratory cycle: arousal-mediated hyperpneas. Therefore, arousals may contribute to causation of CSA.

If arousals are mainly a consequence of CSA in patients with HF, they should diminish if CSA is attenuated by treatment. If, on the other hand, arousals are a cause of, or are incidental to CSA, then suppression of CSA in HF patients may have little or no effect on arousal frequency or sleep structure. There is controversy on this point: some articles reported that CPAP and other interventions that suppress CSA either reduced arousal frequency or increased the amounts of slow wave and REM sleep,[13-15] whereas others did not.[16-21] However, all of these studies were small ($n \leq 24$), or of short duration (1 day to 1 month), and simply reported arousal frequency and sleep structure, but without discussing the significance of whether or not they improved. Our objective, therefore, was to determine in a much larger, longer-term randomized trial, whether attenuation of CSA by CPAP in patients with HF reduces the frequency of arousals from sleep or improves sleep structure. To this end, we analyzed the arousal frequency and sleep structure at baseline and follow-up of patients enrolled in a randomized clinical trial

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of CPAP to treat CSA in patients with HF (Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure trial [CANPAP]).

METHODS

Study Design

Details of the study design have been published previously.[22] Briefly, CANPAP was a prospective randomized, open-label trial with blinded evaluation of outcomes, involving HF patients with CSA in 11 centers (see Appendix). It tested the effects of CPAP on CSA and cardiovascular outcomes. The Research Ethics Board of each institution approved the protocol. Enrollment followed written informed consent.

Subjects

Candidates for participation in CANPAP were men and women aged 18 to 79 years with New York Heart Association (NYHA) Class II to IV HF due to ischemic, hypertensive, or idiopathic dilated cardiomyopathy, stabilized on optimal medical therapy ≥ 1 month; left ventricular ejection fraction (LVEF) < 40% by radionuclide angiography; and CSA, defined 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 continuing 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.

Baseline Assessment

Patients underwent clinical assessment followed by overnight polysomnography. All polysomnographic studies were performed and scored according to uniform techniques and standards at all centers. Sleep stages were scored in 30-sec epochs according to standard criteria,[23] while arousals were scored according to the American Sleep Disorders Association guidelines, and the frequency of arousals/h of sleep was expressed as the arousal index (ArI).[24] Leg movements lasting 0.5-5 sec separated by intervals of 4-90 sec and occurring in a series of ≥ 4 consecutive movements were scored as periodic leg movements (PLM) according to the standard criteria.[25] Periodic leg movements were not scored if their onset occurred after the onset of arousals or occured at the resolution of apnea or hypopnea. The periodic leg movement index (PLMI) was defined as the number of PLMs per hour of sleep. Respiratory movements were measured by respiratory inductance plethysmography, and airflow by nasal pressure.[22,26] Central apneas were defined as absent tidal volume for ≥ 10 sec without thoracoabdominal motion and central hypopneas as a ≥ 50% reduction in tidal volume from baseline for ≥ 10 sec with in-phase thoracoabdominal motion and without airflow limitation on nasal pressure.[21] Apneas and hypopneas were classified as obstructive if out-of-phase thoracoabdominal motion or airflow limitation was present. The diagnosis of CSA required an AHI ≥ 15 with > 50% of the events central in nature.

Initiation of CPAP

CPAP was initiated over 2 to 3 nights in an unmonitored sleep laboratory or hospital bed, 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 until 10 cm H_2O (a level shown to attenuate CSA and improve LVEF)[21,22] or until the highest pressure tolerated was reached. Patients were instructed to use CPAP ≥ 6 h 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 following randomization, and every 6 months thereafter. Polysomnography was performed at 3 and 24 months, and LVEF at 3, 6, and 24 months post-randomization. Subjects were followed from randomization until death or heart transplant or the end of the study. The primary outcome, the combined rate of all-cause mortality or heart transplantation, has been reported.[22,27]

To assess the effect of attenuation of CSA by CPAP on arousal frequency and sleep structure, we evaluated those subjects who underwent sleep studies 3 months after enrollment. Since we aimed to assess the effect of CPAP on CSA and sleep structure, we analyzed polysomnographic data from all subjects in the control group, but only subjects using CPAP on the night of the 3-month follow-up sleep study in the CPAP group. The primary analysis focused on sleep structure at the 3-month follow-up assessment because far more data were available at this time than at 2 years (205 subjects at 3 months versus 71 subjects at 2 years). However, we also examined sleep structure at the 2-year follow-up in those patients who completed this assessment.

Statistical Analysis

Although polysomnographic technicians were aware of whether subjects were on CPAP or not at the time of the follow-up sleep studies, these studies were scored by personnel unaware of the treatment allocation. All other tests were both acquired and analyzed without knowledge of treatment allocation. Data are expressed as mean ± SD unless stated otherwise. Analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, Illinois). With respect to baseline data, for continuous variables, unpaired *t*-tests were used to evaluate between-group differences if the data were normally distributed. Non-normally distributed data were compared by Mann-Whitney test. For nominal and ordinal variables, chi-square or Fisher exact test were used as appropriate. With respect to follow-up data, analysis of covariance was used to compare the changes of continuous outcomes from baseline between the 2 groups. P-values of < 0.05 were considered statistically significant.

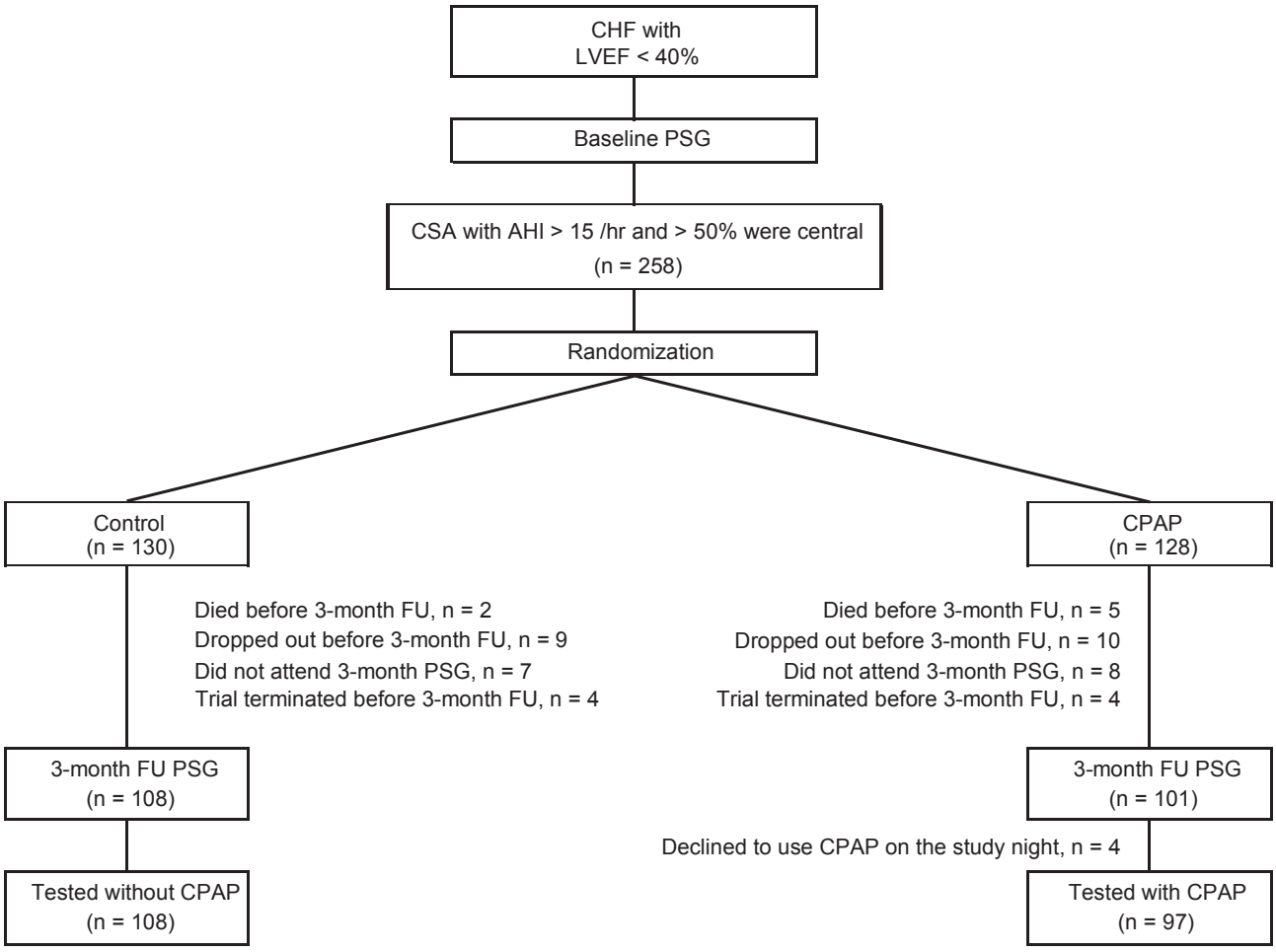

Figure 1—Flow Diagram Indicating Progress of Eligible Subjects Through the Study

RESULTS

Subjects

Figure 1 illustrates the flow of subjects through the study. Of 258 patients who were enrolled, 130 were randomized to the control group and 128 to the CPAP group. Three months after randomization, 108 patients in the control group, and 101 in the CPAP group underwent follow-up sleep studies. However, in the latter group, 4 patients randomized to CPAP were no longer using it at this time, and therefore were studied without CPAP. Therefore, 108 and 97 patients in the control and CPAP groups, respectively, underwent sleep studies according to protocol at the 3-month follow-up. The reasons for not undergoing a sleep study at the 3-month follow-up are shown in Figure 1.

Patient baseline characteristics are summarized in Table 1. There were no significant differences in age, sex distribution, body mass index, cause of HF, NYHA class, LVEF, prevalence of atrial fibrillation/flutter, blood pressure, severity of CSA, or medication use between the 2 groups. The baseline characteristics of the 53 patients who did not have a follow-up sleep study at 3 months did not differ from those who did, except for a higher prevalence of NYHA class III-IV in the former group (46% vs. 30%, P = 0.03).

Effects of CPAP on CSA and Sleep Structure

As displayed in Table 2, none of the baseline polysomnographic variables differed significantly between the 2 groups ($P \geq 0.08$ for all variables), and there was no correlation between the ArI and PLMI ($R = -0.04$, $P = 0.61$). Patients randomized to CPAP used it at an average pressure of 8.8 ± 1.8 cm H_2O for 4.6 ± 2.1 h/day. After 3 months, the CPAP group experienced a significant reduction in total AHI (by 55%), and in central and obstructive AHIs that was greater than in the control group ($P < 0.001$ for all variables), who had no significant reduction in the AHI. Since we did not use a desaturation criterion for hypopnea, the fall in the AHI on CPAP also indicates attenuation of periodic breathing without desaturation. The mean and lowest SaO_2 also increased more in the CPAP group than in the control group ($P < 0.001$ for both). The increases in mean and lowest SaO_2 were significant within the CPAP group ($P < 0.001$ for both). Within the control group, there were also slight but significant increases in mean and lowest SaO_2 ($P = 0.04$ for both).

With respect to sleep structure, there were no significant changes in the ArI, total sleep time, sleep efficiency, sleep onset latency, PLMI, or the percentage of any of the sleep stages in the CPAP group compared to the control group ($P \geq 0.14$ for all variables). To determine if suppression of CSA affected arousal

Table 1—Characteristics of the Subjects at Baseline

	Control group (n = 108)	CPAP treated group (n = 97)	P-value
Age, y	63.5 ± 10.0	62.2 ± 9.3	0.25
Sex (M : F)	102 : 6	94 : 3	0.39
BMI, kg/m^2	29.2 ± 5.6	29.4 ± 5.2	0.73
Cause of dilated cardiomyopathy, no (%)			
Ischemic	73 (68)	62 (64)	0.79
Idiopathic	31 (29)	32 (33)	0.79
Hypertensive	4 (4)	3 (3)	0.79
NYHA class, no (%)			
II	78 (72)	66 (68)	0.51
III-IV	30 (28)	31 (32)	0.51
LVEF, %	24.1 ± 7.6	24.7 ± 7.7	0.53
Atrial fibrillation/flutter, no (%)	20 (19)	24 (25)	0.28
Blood pressure, mm Hg			
Systolic	115 ± 18	115 ± 19	0.77
Diastolic	71 ± 11	71 ± 11	0.72
Severity of CSA			
Total AHI, no/h	37.8 ± 15.1	38.9 ± 15.0	0.59
Central AHI, no/h	33.0 ± 15.0	35.4 ± 15.1	0.26
Mean SaO_2, %	93.1 ± 3.3	93.2 ± 3.6	0.70
Lowest SaO_2, %	81.9 ± 6.3	81.4 ± 8.1	0.82
Medication use, no (%)			
ACEIs and/or ARBs	105 (97)	92 (95)	0.38
Loop diuretics	98 (91)	83 (86)	0.25
Beta blockers	85 (79)	75 (77)	0.81
Digoxin	61 (56)	50 (52)	0.48
Aspirin	57 (53)	49 (51)	0.75
Statins	43 (40)	41 (42)	0.72
Spironolactone	41 (38)	33 (34)	0.56
Amiodarone	19 (18)	22 (23)	0.36
Calcium channel blockers	16 (15)	13 (14)	0.77

Values are means ± SD or number (%).
Totals in table may not equal 100% due to rounding.
Abbreviations: ACEIs = angiotensin converting enzyme inhibitors, AHI = apnea-hypopnea index, ARBs = angiotensin II receptor blockers, BMI = body mass index, CSA = central sleep apnea, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, SaO_2 = oxygen saturation.

frequency and sleep structure, we analyzed data in a subgroup of 58 subjects in whom CPAP reduced the AHI to < 15 after 3 months (CPAP-CSA-suppressed group, Table 3). Although the AHI fell by 82% in this subgroup, ArI did not change significantly compared to the control or the CPAP-CSA-unsuppressed groups (P = 0.15). Similarly, none of the sleep structure variables improved in CPAP-CSA-suppressed group compared to the other two groups (P ≥ 0.08 for all variables). Even among the subset of 22 patients in whom CPAP reduced the AHI to < 5 (from 30.1 ± 12.4 to 2.5 ± 1.5, P < 0.001), there was no significant reduction in the ArI (from 24.9 ± 16.3 to 19.3 ± 15.9, P = 0.17).

In the patients who underwent the 2 year assessment, the ArI in those randomized to CPAP (n = 33) did not change significantly from baseline compared to the control group (n = 38) (from 26.3 ± 18.3 to 24.6 ± 18.4 vs. from 27.1 ± 16.0 to 32.0 ± 16.5, respectively, P = 0.11), despite a reduction in AHI (from 38.7 ± 16.1 to 15.5 ± 16.2 vs. from 36.1 ± 15.8 to 34.8 ± 16.6, respectively, P = 0.001). There was also no significant change in total, slow wave, or REM sleep time, or sleep efficiency compared to the control group (all P ≥ 0.18).

DISCUSSION

In this multicenter randomized controlled trial, we found that treating CSA in HF patients with CPAP for 3 months reduced the AHI by 55%, but that this was not accompanied by any significant reduction in the frequency of arousals from sleep or any increases in the amounts of total, slow wave, or REM sleep, or improvement in sleep efficiency. Even among the subgroup in whom CPAP suppressed the AHI by 82% to below 15 after 3 months, the ArI did not decrease significantly. These data suggest that in HF patients with CSA, arousal from sleep is not mainly a consequence of central apneas and hypopneas, but may be incidental to, or play a causative role in the development of CSA by rendering the respiratory control system unstable.[11,12,28]

Previous studies have reported inconsistent effects of CPAP and other interventions on arousal frequency and sleep structure in HF patients with CSA. In some studies, these interventions lowered the AHI by 40% to 87% in association with 47% to 75% decrease in ArI and an increase in the proportion of both slow wave and REM sleep.[13-15] In contrast, other studies report-

Table 2—Sleep Data at Baseline and 3 Months after Randomization

	Control group (n = 108)		CPAP treated group (n = 97)		Between group P-value
	Baseline	3 months	Baseline	3 months	
Effect on CSA					
Total AHI, no/h	37.8 ± 15.1	37.6 ± 25.7	38.9 ± 15.0	17.6 ± 16.3*	< 0.001
Central AHI, no/h	33.0 ± 15.0	30.7 ± 23.6	35.4 ± 15.1	16.1 ± 16.3*	< 0.001
Obstructive AHI, no/h	4.8 ± 4.9	6.9 ± 10.7	3.5 ± 4.1	1.6 ± 3.9*	< 0.001
Mean SaO_2, %	93.1 ± 3.3	93.5 ± 2.8†	93.2 ± 3.6	94.9 ± 2.7*	< 0.001
Lowest SaO_2, %	81.9 ± 6.3	83.0 ± 6.0†	81.4 ± 8.1	86.3 ± 6.4*	< 0.001
Effect on Arousals					
Arousal index, no/h	24.8 ± 19.3	26.3 ± 18.6	28.8 ± 23.7	24.3 ± 19.5	0.15
Effect on Sleep Structure					
Time in bed, min	452.4 ± 51.4	457.5 ± 48.9	454.5 ± 51.7	454.5 ± 44.9	0.49
Sleep period time, min	421.4 ± 52.7	423.7 ± 55.9	428.8 ± 54.4	423.7 ± 48.7	0.57
Total sleep time, min	310.5 ± 84.3	308.9 ± 77.6	318.2 ± 75.6	318.0 ± 73.9	0.55
Sleep efficiency, %	68.4 ± 16.5	67.8 ± 16.6	70.3 ± 16.4	70.2 ± 15.7	0.45
Sleep onset latency, min	30.8 ± 30.8	33.7 ± 36.5	25.3 ± 27.7	30.6 ± 29.3	0.99
Wake after sleep onset, min	111.0 ± 65.4	114.8 ± 70.0	110.6 ± 70	105.7 ± 65.5	0.29
Stage 1 percentage, %	18.2 ± 12.8	18.9 ± 12.9	19.1 ± 13.5	16.8 ± 15.3	0.14
Stage 2 percentage, %	58.8 ± 13.5	58.0 ± 14.4	56.6 ± 15.5	59.0 ± 15.3	0.27
SWS percentage, %	9.6 ± 11.0	10.3 ± 10.8	10.8 ± 10.1	10.8 ± 11.7	0.77
REM sleep percentage, %	13.1 ± 6.8	12.7 ± 7.9	13.6 ± 7.0	13.3 ± 7.0	0.69
PLMI, no/h	25.8 ± 38.9	24.1 ± 33.2	24.9 ± 40.4	26.4 ± 38.7	0.48

Values are expressed as means ± SD.
Abbreviations: AHI = apnea-hypopnea index, CSA = central sleep apnea, PLMI = periodic leg movement index, SaO_2 = oxygen saturation, SWS = slow wave sleep; *P < 0.001 compared to their baseline; †P = 0.04 compared to their baseline

ed that although CPAP and other treatments reduced the AHI by 62% to 89%, they had no effect on ArI or the amounts of slow wave or REM sleep.[16-21] In this regard, the most interesting study was that of Mansfield and colleagues.[29] They studied 13 HF patients with CSA in an uncontrolled study before and 6 months after cardiac transplantation. Their LVEF increased from 19% to 54% and their AHI decreased significantly from 28 to 7. However, neither arousal frequency nor sleep structure changed. These findings suggest the possibility that in some HF patients with CSA, there is an underlying arousal disorder, accompanied by sleep disruption that is neither mainly a consequence of CSA, nor of impaired cardiac function.

The reasons for discrepancies on the effects of treating CSA on arousal frequency and sleep structure between the above studies are not clear. One possibility is that some studies reported only "respiratory-related" arousals. It follows that if the AHI is reduced by an intervention, then respiratory-related arousals must also fall, even if the overall frequency of arousals is unchanged. This can be misleading since, in that case, arousals deemed respiratory-related at baseline would be considered spontaneous when a treatment lowered the AHI. This suggests that some arousals deemed respiratory-related at baseline were not caused by apneas and hypopneas, but that their spontaneous nature was unmasked by treatment of CSA.[17] Because all the above studies were small, single-centered, and of short duration, and in none was the significance of arousal frequency and sleep structure in response to interventions discussed as an outcome, the discrepancy in their findings remains a source of controversy, which we have addressed.

Our study has several strengths. First, it specifically addressed, in HF patients with CSA, the long-term effects of an intervention that reduces the AHI (i.e., CPAP) on arousal frequency and sleep structure as a trial outcome, and considered the physiological and clinical ramifications of these findings. Our data are consistent with those previous studies, discussed above, in which interventions that suppressed CSA had no effect on ArI, or the amounts of slow wave and REM sleep. Second, because ours was a prospective, randomized, multicenter (11 sites) trial with the largest number of subjects studied to date (n = 205), our results are liable to be generalizable to the broad population of HF patients with CSA. Because there was a slight tendency for ArI to decrease from baseline to 3 months in the CPAP group, it is possible that if we had studied more patients a significant difference might emerge. However, even at 2 years in a smaller sample, there was no reduction in the ArI in CPAP treated patients, and given the high variance of the measurement, the sample size required to detect such a small difference would have to be several-fold greater than in our study. In addition, if the magnitude of the difference in such a scenario was similar to that in the present study, it would be of little or no physiological or clinical significance. Third, we used uniform, state-of-the-art noninvasive techniques for classifying apneas and hypopneas at all centers with use of respiratory inductive plethysmography and nasal pressure cannulae. A limitation of our study was that we did not classify arousals as being respiratory or non-respiratory related, and did not examine their timing. Nevertheless, since the arousal index did not decrease in the CPAP-treated group despite a 55% reduction in the AHI, our findings imply that HF patients with CSA might have a predisposition to hyperarousability.

In contrast to CSA, in randomized trials involving CPAP-treated patients with OSA, but without HF, reductions in the

Table 3—Sleep Data at Baseline and 3 Months after Randomization According to CPAP-Response

	Control group (n = 108)		CPAP-CSA-suppressed (n = 58)		CPAP-CSA-unsuppressed (n = 39)		Between group P-value
	Baseline	3 months	Baseline	3 months	Baseline	3 months	
Effect on CSA							
Total AHI, no/h	37.8 ± 15.1	37.6 ± 25.7	33.8 ± 12.7	6.2 ± 3.9	46.9 ± 14.9	34.6 ± 12.4	< 0.001*
Effect on Arousals							
Arousal index, no/h	24.8 ± 19.3	26.3 ± 18.6	24.0 ± 16.6	18.4 ± 15.5	36.4 ± 30.3	33.1 ± 21.5	0.15
Effect on Sleep Structure							
Time in bed, min	452.4 ± 51.4	457.5 ± 48.9	456.1 ± 52.2	450.8 ± 44.6	452.8 ± 51.8	464.3 ± 44.9	0.14
Sleep period time, min	421.4 ± 52.7	423.7 ± 55.9	426.6 ± 57.3	420.9 ± 47.1	432.4 ± 50.3	432.0 ± 47.4	0.47
Total sleep time, min	310.5 ± 84.3	308.9 ± 77.6	321.4 ± 77.0	326.1 ± 65.3	314.9 ± 74.7	309.9 ± 83.0	0.88
Sleep efficiency, %	68.4 ± 16.5	67.8 ± 16.6	70.6 ± 16.2	72.4 ± 13.3	70.1 ± 16.9	67.3 ± 18.3	0.40
Sleep onset latency, min	30.8 ± 30.8	33.7 ± 36.5	28.9 ± 31.0	29.7 ± 29.6	19.9 ± 21.1	32.0 ± 29.4	0.08
Wake after sleep onset, min	111.0 ± 65.4	114.8 ± 70.0	105.3 ± 62.8	94.8 ± 51.5	117.4 ± 79.8	122.1 ± 80.1	0.36
Stage 1 percentage, %	18.2 ± 12.8	18.9 ± 12.9	18.4 ± 12.0	15.2 ± 14.2	20.3 ± 15.5	18.8 ± 16.9	0.27
Stage 2 percentage, %	58.8 ± 13.5	58.0 ± 14.4	55.8 ± 14.6	57.3 ± 14.8	57.8 ± 16.7	61.9 ± 16.1	0.20
SWS percentage, %	9.6 ± 11.0	10.3 ± 10.8	11.4 ± 10.7	12.6 ± 12.2	9.8 ± 9.3	8.4 ± 10.4	0.37
REM sleep percentage, %	13.1 ± 6.8	12.7 ± 7.9	14.4 ± 6.6	14.8 ± 6.3	12.3 ± 7.4	10.9 ± 7.3	0.45
PLMI, no/h	25.8 ± 38.9	24.1 ± 33.2	22.2 ± 32.8	23.3 ± 28.5	29.8 ± 49.8	32.3 ± 50.4	0.37

Values are expressed as means ± SD.
Abbreviations: AHI = apnea-hypopnea index, CSA = central sleep apnea, PLMI = periodic leg movement index, SWS = slow wave sleep.
*Compared the changes over time between; Control vs. CPAP responder P < 0.001, Control vs. CPAP non responder P = 0.01, CPAP responder vs. CPAP non responder P = 0.002.

AHI of 88% to 94% were consistently accompanied by reductions in ArI of 25% to 74%.[6-8] CPAP also reduced the amount of stage 1 sleep and increased the amounts of slow wave and REM sleep.[8,30] Similarly, in HF patients with OSA, CPAP reduced the AHI significantly by 74% to 79% in association with a significant 53% to 59% reduction in ArI after one month.[31-33] Interestingly, however, unlike patients without HF, the CPAP-induced reduction in ArIs were not accompanied by any increases in the amounts of slow wave or REM sleep. These observations support the findings of Artz et al[34] that even in the absence of sleep apnea, HF patients have poor sleep structure with reduced sleep efficiency, and amounts of total, slow wave and REM sleep compared to the general population. Thus factors other than sleep apnea, such as pulmonary congestion during the night, other comorbidities or medications, may contribute to poor sleep quality in patients with HF.

Although not all obstructive apneas and hypopneas are terminated by arousals, and upper airway opening can occur in their absence in a small minority of cases,[35] arousal is an important defense mechanism for terminating obstructive apneas. The combination of inspiratory efforts against the occluded airway,[36] hypoxemia,[37] and hypercapnia[38] provoke arousal both in spontaneous and experimentally induced obstructive apneas.[36,39,40] In contrast to obstructive apneas, central apneas are not accompanied by negative intrathoracic pressure swings, cause less severe oxygen desaturation,[41] and are typically accompanied by hypocapnia[41] rather than hypercapnia. Therefore, stimuli for arousals from central apneas are generally less potent than those arising from obstructive apneas. In keeping with this view, the ratio of the ArI to the AHI was only 68% in our patients, which is lower than the ratio of 85% to 90% reported in HF patients with OSA in our previous studies.[31-33] Furthermore, in HF patients with CSA, arousal is often not necessary for resumption of airflow following central apneas.[9,42] In the present study, however, we did not analyze the timing of arousals.

Arousals from sleep provoke respiratory control system instability. They augment ventilation abruptly by increasing the ventilatory response to chemical respiratory stimuli and by causing sudden reinstitution of the non-chemical waking neural drive to breathe.[28] This sudden increase in ventilation can cause hypopcapnic apnea.[11,12] Indeed, in HF patients with CSA, more than 90% of episodes of Cheyne-Stokes respiration with cyclic hyperpneas and central apneas are precipitated by arousals from sleep and hyperventilation.[11] Similarly, it has been postulated that arousals following obstructive apneas might also destabilize the respiratory control system and predispose to upper airway collapse by causing withdrawal of upper airway dilator muscle activity in patients with OSA.[35] Thus arousals may act both as a defense mechanism to terminate obstructive events, and perhaps in some instances, as an agent that provokes respiratory instability and facilitates upper airway collapse. However, there is little experimental evidence to support this latter possibility.

Previous small studies, in which attempts were made to suppress arousals, and thus to dampen hyperventilation, yielded inconsistent results. Bonnet et al[43] studied the effects of triazolam on arousals and AHI in patients with CSA, but without HF. They observed that a triazolam-induced reduction in the frequency of arousals was accompanied by a decrease in the frequency of central respiratory events. In contrast, in a study involving HF patients with CSA, administration of temazepam decreased the arousal index but did not suppress CSA.[44] Taken together, these findings suggest that the presence of arousals in HF patients with CSA is not entirely a consequence of central apneas and hypopneas, but that such arousals may be incidental

to, or play a causative or aggravating role in the pathogenesis of CSA in HF patients. Another possibility is that even though CPAP reduced the AHI, and might have reduced respiratory-related arousals, this was offset by arousals caused by discomfort from the CPAP mask. However, this seems unlikely for 3 reasons. First, subjects had 3 months to 2 years during which to habituate to CPAP and used it, on average, for 4.6 h per night during this time, indicating that it was well tolerated. Second, preserved amounts of total, slow wave, and REM sleep times, and sleep efficiency while on CPAP compared to baseline, suggest that CPAP was not disrupting sleep. Third, other interventions such as inhaled CO_2 and O_2 that reduced the AHI in patients with CSA, but which did not require a tight-fitting face mask, were also reported not to reduce the frequency of arousals or improve sleep structure.[45,46]

In conclusion, our data demonstrate that despite lowering of the AHI, CPAP had no significant effect on the frequency of arousals, sleep efficiency, or on the amounts of total, slow wave, or REM sleep in HF patients with CSA. Thus, in such patients, arousals from sleep do not appear to be primarily a consequence of central apneas and hypopneas, and thus may not be acting as a defense mechanism to terminate these events in the same way they do obstructive apneas in OSA. It therefore seems possible that HF is a condition that predisposes to pathological hyperarousability or sleep disruption, even in the absence of sleep related breathing disorders.[34] In addition, the lack of improvement in sleep structure we observed may be one factor that contributed to the lack of effect that CPAP had on quality of life that we previously reported, despite lowering of the AHI, and improvements in left ventricular systolic function and exercise capacity.[22] It would therefore be interesting to further examine interventions that alleviate arousals to see whether this would attenuate CSA, and improve sleep structure.

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DISCLOSURE STATEMENT

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APPENDIX

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