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Night-to-night alterations in sleep apnea type in patients with heart failure

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SUMMARY In patients with heart failure, apnea type can shift overnight from mainly obstructive to mainly central in association with reductions in PCO_2 and increases in periodic breathing cycle length, indicative of a fall in cardiac output. We hypothesized that the predominant apnea type could also vary from one night to another in association with alterations in PCO_2 and cycle length. We studied 12 men with heart failure in whom the predominant apnea type changed from one night to the next over periods of at least 1 month, and two groups with either predominantly obstructive or central sleep apnea (OSA or CSA) in whom apnea type remained stable over time. In patients with unstable apnea type ($n = 12$, duration between sleep studies 9.0 ± 4.4 months), PCO_2 was significantly lower (37.6 ± 1.6 mmHg versus 41.7 ± 1.9 mmHg, $P < 0.01$), and cycle length significantly longer (61.9 ± 3.4 s versus 51.0 ± 1.9 s, $P < 0.001$) during nights with predominantly central than nights with predominantly obstructive apnea. In contrast, in both the stable central ($n = 8$, duration between sleep studies 11.9 ± 5.3 months) and the stable obstructive ($n = 8$, duration between studies 6.9 ± 5.2 months) sleep apnea groups, neither PCO_2 nor cycle length changed significantly between the baseline and follow-up sleep studies. We conclude that in some patients with heart failure, OSA and CSA are part of a spectrum of periodic breathing that can shift over time in association with alterations in PCO_2, cycle length and probably cardiac function.

KEYWORDS cardiopulmonary interactions, control of breathing, sleep-disordered breathing

INTRODUCTION

Obstructive and central sleep apneas (OSA and CSA respectively) are commonly seen in patients with heart failure (Bradley and Phillipson, 2000; Javaheri *et al*., 1998; Sin *et al*., 1999). Growing evidence indicates that both of these breathing disorders are part of a vicious pathophysiological cycle involving the cardiovascular, pulmonary, and autonomic nervous systems that can contribute to the progression of heart failure (Hanly and Zuberi-Zokhar, 1996; Lanfranchi *et al*., 1999; Tkacova *et al*., 2001). Although there is usually a predominance of either obstructive or central apneas in patients with heart failure, both types may occur in the same individual (Lanfranchi *et al*., 1999; Tkacova *et al*., 2001).

One factor related to apnea type is PCO_2. In patients with heart failure, CSA is triggered by reductions in PCO_2 below the apneic threshold (Lorenzi-Filho *et al*., 1999; Naughton *et al*., 1993; Xie *et al*., 2002), whereas OSA is not associated with a fall in PCO_2 (Bradley and Phillipson, 2000; Sin *et al*., 1999). Low PCO_2 during sleep in patients with heart failure and CSA is related to increased left ventricular (LV) volumes (Tkacova *et al*., 1997), and elevated LV filling pressures; PCO_2 is inversely proportional to pulmonary capillary wedge pressure both while awake (Lorenzi-Filho *et al*., 2002) and asleep (Solin *et al*., 1999). Taken together, these data suggest that hyperventilation and the subsequent lowering of PCO_2 that

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triggers central apneas is due, at least in part, to stimulation of pulmonary vagal afferents by pulmonary congestion secondary to elevated LV filling pressure.

In a study involving patients with heart failure and both OSA and CSA, we demonstrated that over the course of a single night, obstructive events predominated at the beginning and central events predominated at the end of the night (Tkacova *et al*., 2001). The overnight shift from OSA to CSA occurred in association with an overnight reduction in PCO_2, and was accompanied by increases in lung-to-chemoreceptor circulation time, and lengthening of the periodic breathing cycle. As there is a close inverse relationship between these latter two variables and cardiac output (Hall *et al*., 1996), it was proposed that the shift from OSA to CSA over the course of a single night was related to an overnight deterioration in cardiac function. This is in keeping with the suggestion that alterations in the hemodynamic profile of heart failure may predispose to alterations in the predominant type of apnea as well (Somers, 1999). The aim of the present study was to assess the relationships between the change in type of sleep apnea (from OSA to CSA or from CSA to OSA), and changes in PCO_2 and periodic breathing cycle length over time. We hypothesized that, in some individuals, OSA and CSA constitute parts of a spectrum of periodic breathing in which the predominant apnea type can vary from night to night depending on the prevailing PCO_2.

METHODS

Subjects

The study was performed retrospectively on a database of heart failure patients who were referred to the sleep laboratory over a 5-year period from 1996 to 2001. Inclusion criteria were: (1) chronic heart failure (LV ejection fraction, LVEF < 45% at the baseline sleep study) secondary to ischemic or idiopathic dilated cardiomyopathy; (2) exertional dyspnea (New York Heart Association Classes II or III); (3) appropriate pharmacologic therapy for heart failure; (4) stable clinical status without any medication changes for at least 1 month prior to the baseline sleep study; and (5) a baseline sleep study demonstrating either predominantly CSA or OSA (see below), followed at least 1 month later by a follow-up sleep study during which sleep apnea was not treated. Patients who participated in this study were not treated for their sleep apnea after the initial sleep study at their request. The reason we preformed repeat sleep studies in these patients was because the patients or their referring physicians were reconsidering whether they should be treated for their sleep apnea. We, therefore, felt it important to reassess their sleep apnea before recommending treatment for sleep apnea. Exclusion criteria were: (1) a history of myocardial infarction, unstable angina or cardiac surgery within 3 months of the study; (2) presence of neurological lesions; and (3) a history of pulmonary disease. Alcohol, sedatives, and caffeinated beverages were not permitted during the 48 hours prior to sleep studies. This protocol was approved by the local institutional review board and all patients gave written informed consent prior to participation.

Sleep studies

Subjects underwent overnight polysomnography using standard techniques and scoring criteria described before (Chadha *et al*., 1982; Naughton *et al*., 1993; Rechtschaffen and Kales, 1968; Tkacova *et al*., 2001). Thoracoabdominal movements were measured by a calibrated respiratory inductance plethysmograph (Respitrace, Ambulatory Monitoring, Inc., White Plains, NY, USA). Transcutaneous PCO_2 ($PtcCO_2$) was recorded with a capnograph (Kontron Medical; Hoffman LaRoche, Basel, Switzerland) with the electrode placed on the anterior chest wall. It was calibrated against test gases before and after the sleep study. This technique has been validated against direct measurements of arterial PCO_2, both acutely and during serial measurements over several hours, and provides an accurate and stable measure of PCO_2 (Naughton *et al*., 1993). Oxyhemoglobin saturation (SaO_2) was measured with an oximeter.

Central apneas were identified by the absence of tidal volume for at least 10 s with no movements of the rib cage or abdomen. Central hypopneas were defined as a 50% or greater reduction in tidal volume from the baseline value for at least 10 s with proportional in-phase reductions in rib cage and abdominal movements (Gould *et al*., 1988; Naughton *et al*., 1993). Obstructive apneas and hypopneas were similarly defined except that out-of-phase thoracoabdominal motion had to be present (Tkacova *et al*., 2001). Mixed apneas were defined as apneas that began with a central component and ended with an obstructive component. They were classified as central in this study because in all cases, more than half the apnea was central. In no case did mixed apneas make up more than 15% of all apneas or more than 5% of all events. Calibrated respiratory inductance plethysmography has been validated against esophageal pressure and has been recommended as an accurate and reliable non-invasive means of distinguishing between central and obstructive apneas and hypopneas in patients with HF (Staats *et al*., 1984; The Report of the American Academy of Sleep Medicine Task Force, 1999). Thoracoabdominal motion has been widely used for this purpose (Ahmed *et al*., 1994; Javaheri *et al*., 1998; Mansfield *et al*., 2003; Solin *et al*., 1999; Wilcox *et al*., 1993; Wilcox *et al*., 1998). The apnea–hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. The diagnosis of CSA was based on the presence of an AHI ≥10 per hour of sleep, of which > 50% had to be central. OSA was similarly defined except that ≥50% of events had to be obstructive.

Statistical analysis

The mean SaO_2 and $PtcCO_2$ during sleep were calculated as previously described (Tkacova *et al*., 2001). Periodic breathing

cycle length was calculated from the beginning of inspiration of the first breath terminating one apnea to the onset of inspiration of the first breath terminating the next apnea. The mean cycle length was obtained by averaging the lengths of five consecutive periodic breathing cycles (Hall *et al*., 1996; Tkacova *et al*., 2001). The analyses of $PtcCO_2$ and periodic breathing cycle length were confined to stage 2 sleep to avoid any confounding influence of changes in sleep stage on breathing.

Two-tailed paired *t*-tests were used to compare variables during the first and second sleep study. $P < 0.05$ was considered statistically significant. All results are expressed as mean ± SEM.

RESULTS

Characteristics of the subjects

Twenty-eight subjects with heart failure met the inclusion criteria. The reason that treatment for sleep apnea was not initiated between the baseline and follow-up sleep studies was that subjects chose not to be treated at that time. Subjects were divided into three groups: (1) a group whose predominant apnea type changed from the first to the second sleep study (unstable apnea group); (2) a group which had predominantly OSA on both sleep studies (stable OSA group); and (3) a group which had predominantly CSA on both sleep studies (stable CSA group) (Table 1). The unstable group consisted of 12 men whose type of sleep apnea changed from the baseline to the follow-up sleep study 9.0 ± 4.4 months later. In seven subjects, the apnea type shifted from CSA to OSA, and in five from OSA to CSA. All data collected during the CSA nights were averaged irrespective of whether CSA occurred during the baseline or the follow-up night. The same held true for data collected during the OSA nights. The cause of heart failure was coronary artery disease in all subjects. There were no changes in medical therapy for heart failure between the baseline and follow-up sleep study nights. In addition, there was no significant difference in the percentage of time spent in the supine position during the nights in which CSA predominated versus nights during which OSA predominated (53.4 ± 11.4% versus 62.0 ± 9.4% of the time asleep, $P = 0.57$). Therefore, changes in predominant apnea type are not explained by changes in the amount of time supine.

The stable OSA group consisted of eight subjects (six men and two women), the stable CSA group consisted of eight men. No differences were seen in the time elapsed between the first and the follow-up polysomnography between the unstable group (9.0 ± 4.4 months), the stable OSA (6.9 ± 5.2 months) and stable CSA groups (11.9 ± 5.3 months) ($P = 0.80$). There was no change in prescribed medical therapy for heart failure between the baseline and follow-up sleep studies in either of the stable sleep apnea groups. Weights did not change significantly in either the unstable group (from 88.2 ± 4.2 kg on the OSA night to 89.0 ± 4.5 kg on the CSA night, $P = 0.90$), the stable OSA group (from 84.7 ± 9.3 kg at baseline to 85.3 ± 9.5 kg at follow-up, $P = 0.96$), or the stable CSA group (from 80.2 ± 4.2 kg at baseline to 78.4 ± 3.5 kg at follow-up, $P = 0.75$).

Table 1 Demographic data and the use of medication in patients with unstable sleep apnea, and in patients with stable obstructive and patients with stable central sleep apnea

Variable	*Unstable sleep apnea group (n = 12)*	*Stable OSA group (n = 8)*	*Stable CSA group (n = 8)*
Age (years)	61.6 ± 3.7	60.6 ± 4.0	63.4 ± 3.8
BMI (kg m^{-2})	29.1 ± 1.0	32.4 ± 3.5	27.3 ± 2.2
LVEF (%)	20.7 ± 4.0	27.3 ± 3.6	16.6 ± 4.3
Digoxin	8	3	7
Diuretics	12	8	8
ACE inhibitors	8	5	6
Beta-blockers	2	2	3

OSA, obstructive sleep apnea; CSA, central sleep apnea; BMI, body mass index; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme. There were significant differences in these variables between groups.

Table 2 Sleep study data from subjects with unstable apnea type

Variable	*OSA*	*CSA*	P-*value*
Total time asleep (min)	279.8 ± 24.6	285.8 ± 21.3	0.942
Sleep stage (%)			
Stage 1	10.2 ± 1.9	13.0 ± 2.2	0.282
Stage 2	71.8 ± 2.5	68.3 ± 2.6	0.156
Slow wave	4.9 ± 1.7	3.2 ± 1.0	0.325
REM	13.1 ± 2.5	15.5 ± 2.1	0.470
AHI (number per hour)	29.6 ± 3.9	41.5 ± 6.8	0.162
Proportion obstructive (%)	91.3 ± 2.8	23.2 ± 5.6	< 0.001
Proportion central (%)	8.6 ± 2.7	76.8 ± 5.6	< 0.001
Movement arousals (number per hour)	23.3 ± 3.1	25.4 ± 3.8	0.539
Mean SaO_2	93.1 ± 0.6	92.9 ± 1.0	0.958
Mean lowest SaO_2 (%)	83.0 ± 2.3	84.0 ± 2.3	0.604
Mean awake $PtcCO_2$ (mmHg)	39.6 ± 1.8	37.0 ± 1.5	0.027

OSA, obstructive sleep apnea; CSA, central sleep apnea; REM, rapid eye movement; AHI, apnea–hypopnea index; SaO_2, oxyhemoglobin saturation; $PtcCO_2$, transcutaneous PCO_2.

Polysomnographic findings

As illustrated in Tables 2–4, no significant differences were found in the total time asleep, sleep structure, mean, and mean lowest SaO_2 between the two nights in any of the three groups. There was no relationship between AHI and LVEF in the unstable sleep apnea group ($r = 0.162$, $P = 0.86$), stable OSA group ($r = 0.131$, $P = 0.76$) or stable CSA group ($r = 0.009$, $P = 0.98$). In the group with unstable apnea type, there was a tendency for the AHI to be higher during the CSA night ($P = 0.16$, Table 2). There was no significant difference in AHI from baseline to follow-up in the stable OSA group ($P = 0.58$, Table 3). In the stable CSA group, AHI was significantly lower during the follow-up sleep study compared with the baseline ($P < 0.001$, Table 4).

PCO_2 and periodic breathing cycle length

In the 12 subjects with unstable apnea type, mean $PtcCO_2$ during stage 2 sleep was significantly lower during the CSA than the OSA night (37.6 ± 1.6 mmHg versus 41.7 ± 1.9 mmHg, $P < 0.01$) (Fig. 1). Periodic breathing cycle length was also longer during the CSA than the OSA night (61.9 ± 3.4 s versus 51.0 ± 1.9 s, $P < 0.001$). In addition, the change in $PtcCO_2$ from one night to the next correlated inversely with the change in periodic breathing cycle length ($r = -0.584$, $P = 0.046$). It was not possible to compare cycle lengths of obstructive events on the two nights in the unstable patients because on the CSA night, two patients had no obstructive events and the rest had only sporadic obstructive apneas during stage 2 sleep such that cycle length could not be determined, or had obstructive events only in REM sleep which could not be compared with events occurring in stage 2 sleep. Importantly, all Cheyne–Stokes respiration was captured by the AHI; Cheyne–Stokes respiration did not occur without apneas and hypopneas.

In contrast, in the stable OSA and stable CSA groups, there were no significant differences in mean $PtcCO_2$ during stage 2 sleep or in periodic breathing cycle length between the baseline and follow-up sleep studies (stable OSA group: 44.9 ± 1.4 mmHg versus 45.4 ± 1.6 mmHg, $P = 0.82$; 45.0 ± 4.0 s versus 40.3 ± 2.5 s, $P = 0.34$ respectively; and stable CSA group: 37.7 ± 1.9 mmHg versus 38.3 ± 1.5 mmHg, $P = 0.81$; 63.5 ± 4.2 s versus 66.2 ± 4.2 s, $P =$

Table 3 Sleep study data from the stable obstructive sleep apnea group

Variable	*Baseline*	*Follow-up*	P-*value*
Total time asleep (min)	288.3 ± 28.4	300.3 ± 19.8	0.711
Sleep stage (%)			
Stage 1	10.1 ± 1.8	10.2 ± 1.5	0.967
Stage 2	63.2 ± 3.6	63.5 ± 5.5	0.964
Slow wave	13.6 ± 3.3	11.5 ± 3.7	0.678
REM	12.6 ± 2.6	11.1 ± 1.9	0.649
AHI (number per hour)	40.1 ± 5.8	44.7 ± 5.6	0.577
Proportion obstructive (%)	99.7 ± 0.3	96.8 ± 2.1	0.193
Proportion central (%)	0.3 ± 0.3	3.2 ± 2.1	0.193
Movement arousals (number per hour)	39.6 ± 4.7	40.2 ± 6.4	0.941
Mean SaO_2	93.2 ± 1.1	93.1 ± 0.8	0.942
Mean lowest SaO_2 (%)	91.3 ± 1.4	91.4 ± 1.0	0.954
Mean awake $PtcCO_2$ (mmHg)	43.9 ± 1.5	44.7 ± 1.5	0.712

OSA, obstructive sleep apnea; CSA, central sleep apnea; REM, rapid eye movement; AHI, apnea–hypopnea index; SaO_2, oxyhemoglobin saturation; $PtcCO_2$, transcutaneous PCO_2.

Table 4 Sleep study data from the stable central sleep apnea group

Variable	*Baseline*	*Follow-up*	P-*value*
Total time asleep (min)	291.1 ± 34.6	243.6 ± 8.2	0.203
Sleep stage (%)			
Stage 1	19.2 ± 4.4	11.7 ± 8.6	0.450
Stage 2	55.5 ± 6.1	60.6 ± 3.2	0.471
Slow wave	1.3 ± 1.0	1.4 ± 1.1	0.947
REM	9.4 ± 2.2	12.0 ± 3.2	0.514
AHI (number per hour)	53.9 ± 6.2	39.2 ± 5.6	< 0.001
Proportion obstructive (%)	3.8 ± 1.5	7.6 ± 3.1	0.288
Proportion central (%)	96.2 ± 1.5	92.4 ± 3.1	0.288
Movement arousals (number per hour)	47.3 ± 5.1	42.2 ± 5.7	0.516
Mean SaO_2	93.5 ± 0.5	93.3 ± 0.6	0.802
Mean lowest SaO_2 (%)	91.4 ± 0.6	91.5 ± 0.8	0.922
Mean awake $PtcCO_2$ (mmHg)	36.5 ± 1.9	37.2 ± 1.5	0.777

OSA, obstructive sleep apnea; CSA, central sleep apnea; REM, rapid eye movement; AHI, apnea–hypopnea index; SaO_2, oxyhemoglobin saturation; $PtcCO_2$, transcutaneous PCO_2.

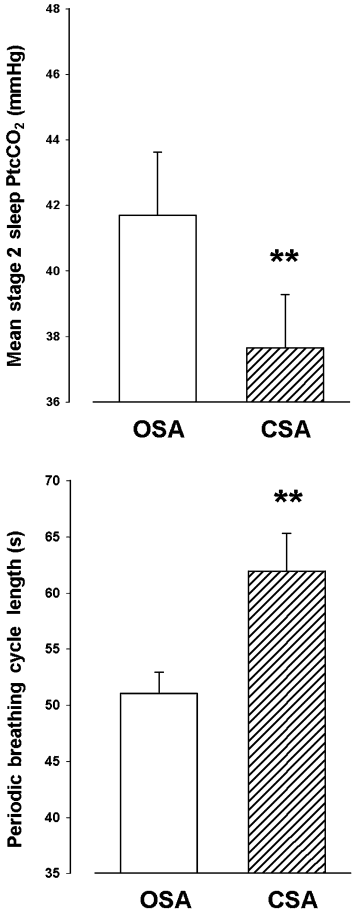

Figure 1. In patients with congestive heart failure and unstable sleep apnea type ($n = 12$), mean stage 2 sleep transcutaneous PCO_2 ($PtcCO_2$) was significantly lower during the night with predominantly central sleep apnea (CSA) compared with the night with predominantly obstructive sleep apnea (OSA) ($*P < 0.01$). Periodic breathing cycle length was significantly longer during the CSA compared with the OSA night ($**P < 0.001$).

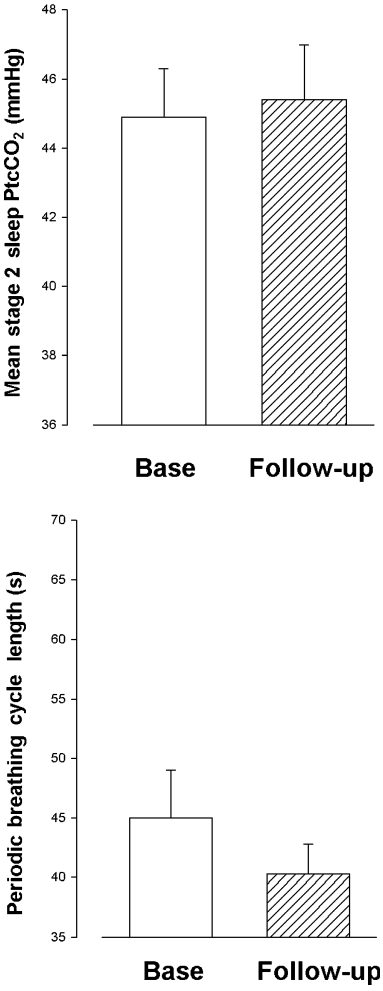

Figure 2. In patients with stable obstructive sleep apnea (OSA) ($n = 8$), there were no significant differences between the baseline and follow-up studies in either mean stage 2 sleep transcutaneous PCO_2 ($PtcCO_2$) ($P = 0.817$) or periodic breathing cycle length ($P = 0.336$).

0.66 respectively) (Figs 2 and 3). In the unstable group, awake $PtcCO_2$ was also lower during the CSA night than the OSA night ($P = 0.027$, Table 1). However, in the stable OSA and CSA groups, awake $PtcCO_2$ did not differ significantly between the baseline and follow-up studies ($P = 0.71$ and 0.78 respectively) (Tables 3 and 4).

DISCUSSION

Our data demonstrate that the predominant type of sleep apnea in patients with heart failure may vary within an individual from one night to the next over periods of one to several months. Changes from predominantly OSA to predominantly Cheyne–Stokes respiration with CSA are associated with reductions in $PtcCO_2$, both awake and asleep, and lengthening of the periodic breathing cycle, while changes from CSA to OSA are associated with increases in $PtcCO_2$ and shortening of the periodic breathing cycle. These data are consistent with previous observations that in heart failure patients whose apnea type shifted from OSA to CSA during a single night, $PtcCO_2$ fell and cycle length increased (Tkacova *et al*., 2001). The present findings extend those findings in three important ways. First, the change in predominant apnea type occurred over longer periods of time. Secondly, the shift in apnea type occurred in both directions. Thirdly, we included two stable groups with either OSA or CSA neither of whose predominant apnea type, $PtcCO_2$ nor periodic breathing cycle lengths changed over time. As, in patients with heart failure, cycle length is inversely proportional to cardiac output (Hall *et al*., 1996), and as PCO_2 is inversely related to LV filling pressure (Lorenzi-Filho *et al*., 2002), the present data add to the evidence that in some patients with heart failure, OSA and CSA are part of a continuum of breathing disorders that vary over time in association with alterations in cardiac function. In contrast, our data indicate that where PCO_2 and cycle length did not change, there was no associated change in apnea type.

The present data suggest that a shift from OSA to CSA occurs in association with a deterioration in cardiac function characterized by an increase in LV filling pressure and a fall in

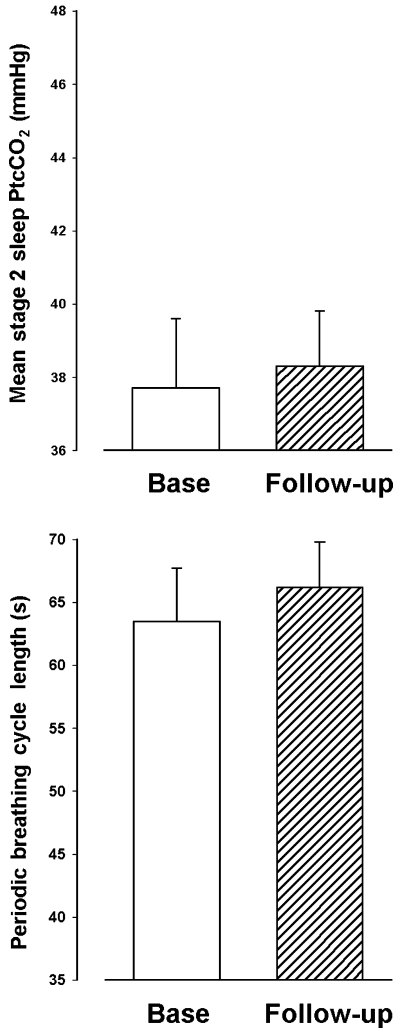

Figure 3. In patients with stable central sleep apnea (CSA) ($n = 8$), there were no significant differences between the baseline and follow-up studies in either mean stage 2 sleep transcutaneous PCO_2 ($PtcCO_2$) ($P = 0.808$) or periodic breathing cycle length ($P = 0.656$).

cardiac output (Hall *et al*., 1996; Lorenzi-Filho *et al*., 2002; Solin *et al*., 1999; Tkacova *et al*., 2001). Consequently, long-term changes in cardiac function may influence the nature of sleep apnea. Therefore, differences in the relative proportions of OSA and CSA among epidemiological studies (Javaheri *et al*., 1998; Sin *et al*., 1999) may reflect, in part, differences in hemodynamic function and the intensity of medical therapy for heart failure. If so, as medical therapy for heart failure improves, the prevalence of CSA should decrease.

Five of the 12 patients in the unstable apnea group changed from predominantly OSA to predominantly CSA from the baseline to the follow-up study. An important pathophysiologic feature of CSA in patients with heart failure is a tendency to chronically hyperventilate thus maintaining $PaCO_2$ close to the apneic threshold (Naughton *et al*., 1993; Xie *et al*., 2002). In this setting, abrupt increases in ventilation drive $PaCO_2$ below the apneic threshold triggering apneas (Naughton *et al*., 1993; Xie *et al*., 2002). Consistent with these considerations, we observed that in patients with heart failure, the nights during which CSA predominated were associated with lower PCO_2 than the nights on which OSA predominated.

The mechanisms responsible for nocturnal hypocapnia in patients with heart failure and CSA have not been fully elucidated. One possible mechanism is hypoxia. However, in the present study there was no difference in SaO_2 between the OSA and CSA nights (Table 4). Another possible explanation would be a primary increase in chemoresponsiveness (Ahmed *et al*., 1994; Javaheri, 1999; Wilcox *et al*., 1993; Wilcox *et al*., 1998) or the development of pulmonary congestion because of increases in LV filling pressures (Lorenzi-Filho *et al*., 2002).

While drug prescriptions did not change over the study period, subtle degrees of pulmonary congestion were likely present when CSA predominated. Patients with heart failure are not always adherent to salt and fluid restrictions, and to diuretic prescriptions. It is, therefore, possible that patients developed some pulmonary congestion when CSA predominated as a result of alterations in salt and water intake and diuretic usage. However, any such fluid retention must have been minimal because weight did not change over the study period. Consequently, any development of pulmonary congestion would most likely occur as a result of a shift in fluid to the intrathoracic compartment, rather than to marked fluid retention *per se*.

Seven of the 12 patients changed from predominantly CSA to OSA on the follow-up sleep study night in association with an increase in PCO_2 and a decrease in cycle length. These observations suggest that the shift from CSA to OSA occurs in conjunction with an improvement in cardiac function (Hall *et al*., 1996; Lorenzi-Filho *et al*., 2002; Tkacova *et al*., 2001).

Our findings raise two intriguing questions. First, can periodic breathing associated with CSA in heart failure predispose to OSA as PCO_2 rises above the apneic threshold? Secondly, can OSA predispose to periodic breathing and CSA in patients with heart failure? Regarding the first question, it has been proposed that an underlying tendency to periodic breathing could destabilize the upper airway and predispose to its collapse (Alex *et al*., 1986; Hudgel *et al*., 1987; Naughton *et al*., 1993; Younes, 1989). Alternatively, heart failure may give rise to increased neck vein distension and pharyngeal edema that could increase pharyngeal collapsibility (Shepard *et al*., 1996). Accordingly, one might expect that as cardiac function deteriorated, the likelihood of OSA would increase. Our data are not consistent with this hypothesis. Instead, we found that conversion from CSA to OSA was associated with a decrease in the periodic breathing cycle length and an increase in PCO_2; findings consistent with improvements in cardiac function (Hall *et al*., 1996; Tkacova *et al*., 2001). These data, coupled with those showing that conversion from OSA to CSA is associated with an increase in cycle length and a reduction in PCO_2, therefore suggest, that in some patients with heart failure, OSA predisposes to the development of CSA as cardiac function deteriorates (Bradley *et al*., 2001; Hall *et al*., 1998). Therefore, if cardiac function improved, apnea type could revert to obstructive (Tkacova *et al*., 2001).

In both the stable OSA and CSA groups, stability of PCO_2 and cycle length were accompanied by stability in apnea type. Mean AHI did not change from the first to the follow-up night in the stable OSA group, similar to the findings of Bittencourt *et al*. (2001) in OSA patients without heart failure. In addition, there was a gradation of baseline LVEF related to apnea type, with the highest LVEF in the stable OSA group (LVEF = 27.3 ± 3.6%), intermediate LVEF in the unstable group (LVEF = 20.7 ± 4.0%), and the lowest LVEF in the stable CSA group (LVEF = 16.6 ± 4.3%) (Table 1). Intermediate LVEF in the unstable group suggests that apnea type could shift either way depending on whether LV function deteriorated or improved. Mansfield *et al*. (2003) reported that following cardiac transplantation, CSA either resolved or converted to OSA. In the few patients in whom CSA did not resolve, the cycle length decreased, because of improved cardiac function and reduced circulation time. These findings are consistent with those in our unstable group who converted from CSA to OSA in conjunction with a reduction in cycle length and circulation time.

Other factors may influence sleep apnea type besides alterations in PCO_2. First, in some patients with CSA, but without heart failure, the pharynx can collapse passively during central apneas (Badr *et al*., 1995, 1997). However, it has not been shown that this can lead to obstructive apneas. Nevertheless, if the pharynx collapsed when PCO_2 was above the apnea threshold, the patient would generate inspiratory efforts against the occluded airway causing obstructive apneas.

Secondly, changes in sleep state and arousals from sleep can destabilize respiratory control and predispose to CSA. The transition from wakefulness to sleep is accompanied by an increase in the set-point for a ventilatory response to CO_2 (Xie *et al*., 1994). During this time, PCO_2 may remain below the apneic threshold causing cessation of airflow. If shifts from wakefulness to sleep occurred frequently because of frequent arousals, repetitive central apneas could occur. Arousals can also trigger hyperventilation and, therefore, repetitively drive PCO_2 below the apnea threshold provoking periodic breathing (Xie *et al*., 1994). Thus frequent arousals might favor development of CSA. However, in our patients with unstable apnea type, no differences were seen in the arousal index between the nights during which obstructive or central apneas predominated. Therefore, alterations in the frequency of arousals from sleep, and sleep state changes are unlikely explanations for the shift from one type of sleep apnea to another.

One limitation of our study was that we had no direct measure of cardiac or pulmonary function on the follow-up studies to confirm that changes in apnea type were related to changes in cardiac function or lung water. Nevertheless, we have previously shown a strong inverse relationship between periodic breathing cycle length and cardiac output (Hall *et al*., 1996), and between PCO_2 and LV filling pressure (Lorenzi-Filho *et al*., 2002; Solin *et al*., 1999). Consequently, alterations in apnea type were likely related to changes in cardiac function. However, even if they were not, our data demonstrate an unequivocal relationship between changes in $PtcCO_2$ and changes in apnea type (Tkacova *et al*., 2001). Another limitation of our study is that esophageal pressure was not measured during sleep studies to distinguish obstructive from central hypopneas. Because an esophageal catheter is not well tolerated by patients with heart failure, it was not feasible to use it in all patients studied over the 5-year study period. Respiratory inductance plethysmography is an acceptable technique for scoring central and obstructive apneas (Staats *et al*., 1984; The Report of the American Academy of Sleep Medicine Task Force, 1999), but is not completely reliable for distinguishing between central and obstructive hypopneas. It is, therefore, possible that some of the events scored as central hypopneas actually had some obstructive component. Accordingly, we used only episodes of periodic breathing with apneas to calculate the periodic breathing cycle length during both OSA and CSA. Importantly, respiratory inductance plethysmography and other types of thoracoabdominal motion detectors have been the standard method used to score apneas and hypopneas in patients with HF and CSA in previous studies (Javaheri *et al*., 1998; Mansfield *et al*., 2003; Tkacova *et al*., 1997). Nasal pressure could also be used, but they have not been validated to distinguish central from obstructive hypopneas. Another limitation of the study is that, over the past decade, the treatment of heart failure has changed. Therefore, it remains unclear whether predominant apnea type can change in the presence of optimal contemporary heart failure therapy.

In conclusion, in some patients with heart failure, the predominant type of sleep apnea can change over time in association with changes in nocturnal PCO_2 and periodic breathing cycle length. Therefore, in such patients, conversion of one predominant apnea type to another over time suggests that OSA and CSA represent extremes on a continuum of periodic breathing that can shift in conjunction with alterations in PCO_2, and possibly cardiac function (Somers 1999; Tkacova *et al*., 2001). In contrast, stability of apnea type over time, whether predominantly obstructive or central, is associated with stability of nocturnal PCO_2 and cycle length, and possibly, cardiac function. These observations point to the need, in patients with heart failure, for a more flexible approach to classification of sleep apnea and for more research into the relationship between alterations in hemodynamic function and changes in apnea type.

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