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ORIGINAL ARTICLE

In patients with heart failure the burden of central sleep apnea increases in the late sleep hours

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Abstract

Study Objectives: Periodic breathing with central sleep apnea (CSA) is common in patients with left ventricular systolic dysfunction. Based on the pathophysiological mechanisms underlying CSA, we hypothesized that the frequency of CSA episodes would increase in the late hours of non-rapid eye movement (NREM) of sleep.

Methods: Forty-one patients with left ventricular ejection fraction <40% underwent full-night-attended polysomnography scored by a central core lab. Because central apneas occur primarily in NREM sleep, total NREM sleep time for each patient was divided into 8 equal duration segments. Segment event counts were normalized to an events/hour index based on sleep segment duration.

Results: Central apnea index (CAI) varied among sleep segments ($p = 0.001$). As expected CAI was higher in segment 1 compared to segments 2 and 3, increasing during later segments. The minimum CAI occurred in segment 2 with mean ± *SD* of 21 ± 3 events/hour and maximum CAI was in segment 8 with 37 ± 4 events/hour. We also determined central apnea duration which varied among segments ($p = 0.005$), with longer durations later in the night (segment 1: 22 ± 1 seconds; segment 8: 26 ± 1 seconds, $p < 0.001$). Data were also analyzed including rapid eye movement (REM) sleep, with similar results. Further, comparison of CAI between the first and second half of the night showed a significant increase in the index. Circulation time did not change across the segments ($p = 0.073$).

Conclusions: In patients with left ventricular dysfunction and CSA, central apnea burden (number and duration) increases during later hours of sleep. These findings have pathophysiological and therapeutic implications.

Statement of Significance

This study reports that in patients with heart failure and predominantly central sleep apnea (CSA) and with minimal obstructive sleep apnea, the burden of disordered breathing increases during later hours of sleep, characterized by both an increase in number and duration in the central apneas. These findings have important physiological implications for the treatment of CSA in the heart failure population, as treatment will need to be effective throughout the night.

Clinical Trial Registration: NCT01124370.

Key Words: central sleep apnea; heart failure; apnea burden; lung

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Introduction

Central sleep apnea (CSA) with Hunter-Cheyne-Stokes breathing is common in patients with chronic, stable heart failure and reduced left ventricular ejection fraction (HFrEF), with a reported prevalence of 30%–40% [1–4]. Similar prevalence has been observed in patients with asymptomatic left ventricular dysfunction [5]. Polysomnographically, CSA is characterized by the simultaneous absence of airflow and respiratory effort followed by hyperventilation. Each cycle is accompanied by mild hypoxemia and reoxygenation with subsequent arousals that disrupt sleep [1, 3, 4]. Arousals can occur during hyperventilation, and in the presence of congested lungs and a stiff respiratory system, larger than normal negative swings in the esophageal pressure are observed [6]. These adverse pathophysiological consequences of CSA could lead to progressive left ventricular dysfunction, further aggravating cardiac failure and ultimately could contribute to increased morbidity and mortality [3–10].

While the mechanisms underlying the development of CSA in patients with left ventricular systolic dysfunction have been investigated and reviewed [7–10], little is known about the overnight changes in the frequency and duration of central apnea events in patients with predominantly CSA. In individuals with obstructive sleep apnea (OSA), Charbonneau *et al.* and Montserrat *et al.* observed lengthening of obstructive apneas during later hours of non-rapid eye movement (NREM) sleep, and Montserrat proposed increasing arousal threshold as the underlying mechanism [11, 12].

In another study, in patients with HFrEF and mixed OSA and CSA, obstructive events predominated at the beginning and central events predominated at the end of the night. This overnight shift in apnea type was linked to deterioration in cardiac function as measured by circulation time [13]. Based on the aforementioned studies, we hypothesized that there would be an overnight increase in the frequency and duration of central apneas in patients with left ventricular systolic dysfunction and predominantly CSA. Initial findings were previously reported in abstract form [14].

Materials and Methods

As part of a worldwide pilot study (Chronic Evaluation of the remedē System; NCT01124370), whose design and results have been previously reported [15], patients with evidence of sleep-disordered breathing by a screening polygraphy underwent full night attended diagnostic polysomnography (PSG) prior to receiving any therapy. Patients had moderate to severe CSA with minimal obstructive apneas, defined as an apnea-hypopnea index (AHI) ≥ 20 events/hour, with at least 50% of the apneas central in origin [13]. Polysomnographically, CSA has been arbitrarily defined when CAI is 5 or more per hour of sleep [7]. In this study, the minimum CAI was 6 events/hour of sleep.

The present analysis includes the subset of these patients who had a left ventricular ejection fraction (LVEF) <40%, and at least 3 hours of NREM sleep. Subjects were on guideline-directed medical therapy and stable for at least 30 days prior to the PSG. Ethics committees at all participating centers approved the study, and patients provided written informed consent before study procedures. This study was conducted in accordance with the amended Declaration of Helsinki.

PSG was performed with the use of standard techniques, as described previously [15]. To determine the stages of sleep, an electroencephalogram (with two channels), chin electromyogram (with one channel), and electrooculogram (with two channels) were obtained. Thoraco-abdominal excursions were measured qualitatively by respiratory inductance plethysmography placed over the rib cage and abdomen. Airflow was assessed using temperature and pressure sensitive probes. Arterial-blood oxyhemoglobin saturation was recorded with the use of a pulse oximeter. These variables were recorded on a multichannel polygraph.

Obstructive apnea was defined as the absence of airflow in the presence of respiratory effort for ≥10 seconds. Central apnea was defined as the absence of respiratory effort and airflow for ≥10 seconds. Mixed apnea was defined as the absence of inspiratory effort at the beginning of the episode, followed by occluded breaths. Hypopnea was defined as a >30% reduction in airflow lasting at least 10 seconds, associated with at least a 4% decrease in arterial oxyhemoglobin saturation. Hypopneas were not further classified, in view of difficulty in accurately differentiating obstructive from central hypopnea. As noted above, the focus of this study was on central apnea which is more easily differentiated from obstructive apnea (compared to hypopneas), and also more accurate to define the start and the end to determine its duration. Central apnea duration was measured in the standard manner. Circulatory delay was measured as the time from the end of the apnea to the nadir in oxygen level [13]. An electroencephalographic arousal from NREM sleep was defined as the appearance of alpha waves or a shift to a greater frequency for at least 3 seconds after at least 10 seconds of sleep [16]. The AHI was defined as the number of episodes of apnea and hypopnea per hour of sleep. For the purpose of this study, we analyzed the data in different ways, although the focus was on NREM sleep.

Because central apneas occur primarily in NREM sleep [2, 9, 17], total NREM sleep time was divided into 8 equal duration segments and all NREM events were assigned to the corresponding segment for each patient. We chose eight segments in order to isolate changes throughout different parts of the night. Due to the impact of sleep onset CSA in the first few minutes of NREM sleep (segment 1) it was expected that during transition from wakefulness to light sleep, the first segment would have a higher CAI relative to the next few sleep segments. If our hypothesis is correct, the frequency of central apneas should then increase in the late segments of sleep. We also compared the first half of sleep to the second half of the sleep. In a second analysis, in order to assess the impact of including rapid eye movement (REM) sleep on the results, we repeated the analysis including REM sleep in each segment.

Statistical analysis

For comparison of the segments, disordered breathing events during each segment were normalized to an events/hour index based on sleep segment duration. Overall differences in sleep indices and central apnea duration among sleep segments were analyzed using repeated measures ANOVA with sleep segment as the independent variable [18].

A test for an overall segment effect was performed to assess if there were differences among segments during the night. Additionally, to further assess if differences were temporally

related to early portions versus late portions in the night, the differences between sleep segments 1 through 4 versus 5 through 8 were compared using general linear combinations from the ANOVA. p values less than 0.05 were considered significant. Within each segment, the correlation between change in duration of central apnea and change in circulatory delay was assessed. Data are presented as mean and standard deviation for clinical characteristics and mean and standard error for sleep results.

Results

Patient characteristics

Forty-one patients met the inclusion criteria for this analysis including a LVEF < 40%. The mean age was 66 ± 9 years. Mean LVEF was 26 ± 7%. The majority of patients (78%) were New York Heart Association functional class II and III, and 56% of patients had a concomitant implanted cardiac device (Table 1).

Polysomnographic findings

Over the entire night of the study, patients had an average of 4.7 ± 1.0 hours of NREM sleep, translating to average NREM sleep segment duration of 35.1 ± 7.6 minutes for each of the eight segments. The minimum duration of an NREM sleep segment was 27 minutes and the maximum was 51 minutes. Examination of the whole night NREM sleep time prior to division into segments showed severe CSA with an overall AHI of 51 ± 2 events per hour of sleep, comprised of a CAI of 28 ± 2 events per hour, obstructive apnea index of 4 ± 1 events per hour, hypopnea index of 15 ± 2 events per hour, and mixed apnea index of 4 ± 1 events per hour (Table 2). All patients had a CAI >5 events per hour.

Table 1. Baseline patient characteristics

Characteristic	Result (N = 41)
Age (years)	66 ± 9
Body mass index (kg/m^2)	29 ± 4
Male	39 (95%)
Concomitant implanted device	23 (56%)
Cardiac resynchronization therapy	24% (10)
Implantable cardioverter-defibrillator	27% (11)
Pacemaker	5% (2)
Atrial fibrillation	16 (39%)
Hypertension	30 (73%)
New York Heart Association	
Functional Class I/II/III/IV (NA)	10% / 59% / 20% / 2% (10%)
LVEF %	26 ± 7
Ischemic and/or CAD	29 (71%)
Systolic Blood Pressure (mmHg)	124 ± 21
Diastolic Blood Pressure (mmHg)	75 ± 11
Heart rate (bpm)	72 ± 11
Respiratory rate (breaths/min)	16 ± 3
Creatinine (mg/dL)	1.2 ± 0.4
Heart failure medications	
ACE Inhibitor or ARB	36 (88%)
Beta-blocker	39 (95%)
Diuretic	36 (88%)
Aldosterone antagonist	19 (46%)

Values presented as mean ± SD or n (%). ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; NA = no history of heart failure symptoms.

Figure 1 shows the pattern of changes in burden of CSA across the night during NREM sleep. Repeated measures ANOVA showed a statistically significant difference in CAI among the sleep segments (p = 0.001), with CAI burden increasing during later segments of sleep. As demonstrated in Table 3, CAI was 25 events/hour in the very first segment and, as expected, decreased somewhat in the second and third segments before a progressive increase in the remaining segments. The minimum CAI occurred in the second segment (21 ± 3 events/hour) and the maximum CAI was in the eighth segment (37 ± 4 events/hour). Comparison of NREM CAI during the first half of the night (segments 1–4) versus the second half of the night (segments 5–8) showed a significant increase from 23 ± 3/hour of sleep to 33 ± 3/hour of sleep, respectively (p < 0.001).

AHI showed a similar trend as CAI with the nadir at segment 3, and the increase in later segments was driven by CAI. The number of hypopnea events decreased later in the night but did not account for the overall increase in CAI. Obstructive and mixed apnea indices did not change throughout the night (Figure 1 and Table 2). The analysis including REM and NREM sleep in the eight segments produced similar results (Supplementary Table).

The average duration of central apneas varied among sleep segments (p = 0.005), with durations lengthening later in the night (minimum was segment 1: 22 ± 1 seconds; maximum was segment 8: 26 ± 1 seconds, p < 0.001). Comparison of central apnea during the first half of the night (segments 1–4) versus the second half of the night (segments 5–8) showed a significant increase from 24 ± 1 seconds to 25 ± 1 seconds, respectively (p = 0.003). The difference was small, because the duration of central apneas began to increase in segment 2 onward. The duration of hypopnea events also showed a statistically significant difference among segments (p = 0.014), whereas there were no significant changes in obstructive event duration. However, the paucity of obstructive events in this study may have prevented identification of a significant change (Table 3).

Arousal index increased significantly across the night, driven primarily by an increase in disordered breathing events (Table 2). Respiratory arousal index started high in segment 1, dropped for segments 2–5, and then was higher during the later segments of the night, though statistical significance was not achieved. The pattern of changes in the CAI and respiratory arousal index across the night is depicted in Figure 2, showing a close trend. In contrast, spontaneous arousal index showed a nonsignificant decrease as the night progressed. Because of increasing CAI density, the 4% oxygen desaturation index was higher later in the night, but this finding was not significant.

Discussion

In this study of 41 patients with left ventricular systolic dysfunction who suffered predominantly from CSA, we found that both the number and duration of central apneas increased during the later segments of NREM sleep. We analyzed the data both with and without including REM sleep and in the first and second half of the night. The results were consistent showing that the burden of sleep-disordered breathing increases in the later part of sleep, primarily because of the increased burden of central apneas. In concert with these changes, respiratory-related arousals increased.

Table 2. Overnight sleep-disordered breathing indexes during NREM sleep by sleep segment

Parameter	Episodes/hour by sleep segment (n = 41)								P-value*	Whole night average†
	1	2	3	4	5	6	7	8		
Apnea-hypopnea index	50 ± 4	48 ± 4	44 ± 4	47 ± 4	49 ± 3	57 ± 3	57 ± 3	56 ± 3	0.015	51 ± 2
Central apnea index	25 ± 3	21 ± 3	22 ± 3	25 ± 3	26 ± 3	34 ± 4	35 ± 3	37 ± 4	0.001	28 ± 2
Obstructive apnea index	4 ± 2	4 ± 1	2 ± 1	3 ± 1	2 ± 1	4 ± 1	4 ± 1	4 ± 1	0.343	4 ± 1
Hypopnea index	17 ± 3	19 ± 3	16 ± 3	14 ± 3	17 ± 3	15 ± 3	13 ± 3	11 ± 2	0.017	15 ± 2
Mixed apnea index	4 ± 1	5 ± 1	3 ± 1	5 ± 1	4 ± 1	4 ± 1	4 ± 1	5 ± 1	0.695	4 ± 1
Oxygen desaturation index 4%	42 ± 4	44 ± 4	41 ± 4	42 ± 4	45 ± 4	46 ± 4	47 ± 4	47 ± 4	0.448	44 ± 4
Arousal index	48 ± 4	41 ± 4	40 ± 4	40 ± 4	38 ± 4	44 ± 4	45 ± 4	49 ± 4	0.023	43 ± 3
Respiratory arousal index	42 ± 4	36 ± 4	35 ± 4	36 ± 4	34 ± 4	41 ± 4	40 ± 4	45 ± 4	0.097	39 ± 3

Data reported as mean ± standard error.
*Repeated measures ANOVA for overall segment effect.
†Excludes REM sleep.

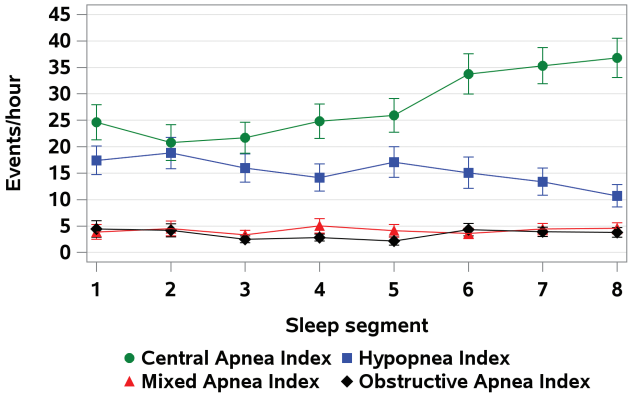

Figure 1. Overnight AHI composition by sleep segment (least square means ± standard error), N = 41.

To our knowledge, this is the first polysomnographic study to show the pattern of changes in CAI burden across the night in patients with predominantly CSA. We had expected a higher CAI during the first segment of NREM sleep in view of transition from wakefulness to sleep and the expected observation of the so-called sleep onset central apneas. This notion was reflected in a higher CAI in the first segment of sleep, a reduction in the following two segments and a progressive increase as the night progressed (Table 2). As noted, the main reason for the increasing burden of sleep-disordered breathing was an absolute increase in the number of central apneas. The number of hypopneas during NREM sleep decreased suggesting that hypopneas might have converted to central apneas as the night progressed. However, the increase in the number of central apneas exceeded the reduction in the number of hypopneas, indicating a real increase in the burden of events over the night (6 events/hour reduction in hypopneas between segment 1 and 8 compared to a 12 events/hour increase in CAI).

In a study of 12 patients with HFrEF, Tkacova *et al.* [13] showed an overnight shift from OSA to CSA. These patients suffered from severe sleep apnea with an average AHI of 32 events/hour of sleep, with 70% of the events considered obstructive in the early portion of sleep. As the night progressed, the number of central apneas increased whereas obstructive apneas diminished. In contrast, our patients had primarily severe CSA (average AHI of 50 events/hour of sleep, CAI of 25 events/hour of sleep and obstructive apnea index of 4 events/hour of sleep). We found the burden of CSA (both number of apneas and the duration) worsened across the night, with no significant change in the burden of obstructive events. The latter finding was not surprising because very few obstructive apneas were present at the beginning of the night in contrast to the Tkacova population [11].

The mechanisms driving the burden of CSA increasing in later hours of NREM sleep remains to be elucidated fully. However, there are several shared physiological processes that could underlie the late NREM increased burden of both CSA and OSA with a unified mechanism.

Increased circulation time

One possibility could be worsening of cardiac function across the night, in which case, we would have expected to observe increasing circulation time as occurred in heart failure patients with predominantly OSA [13]. We calculated circulation time during each segment in a similar manner [13] but observed no clear trend of changes throughout the night. This finding may be best explained by the differences in the phenotype of sleep apnea between the two studies, with our study primarily CSA whereas the study of Tkacova *et al.* [13] included a mixture of OSA and CSA with 70% of the early events being obstructive in nature. We suggest that the larger negative swings in intrathoracic pressure and severe hypoxemia seen in obstructive apnea (compared with that in CSA) during the first part of the night have more profound acute effects on cardiac dysfunction, explaining the increase in circulation time with ongoing sleep in OSA versus CSA [13]. These two features of OSA (exaggerated negative intrathoracic pressure changes and hypoxemia) could account for the acute worsening of cardiac function in heart failure patients with predominantly OSA [11], in contrast to those with CSA.

Ventilatory control instability

Another possibility to explain the increase in central apnea events is that ventilatory control instability (loop gain) increases during the course of the night. Given that loop gain is defined by the ventilatory response to a ventilatory disturbance, one would predict longer apneas with increasing loop gain as a result of marked ventilatory overshoots following a

Table 3. Duration of events

Event duration (n = 41)	1	2	3	4	5	6	7	8	P-value*
Central apnea (seconds)	21.9 ± 1.1	23.0 ± 1.2	24.1 ± 1.2	25.5 ± 1.2	25.0 ± 1.2	24.7 ± 1.8	25.9 ± 1.1	26.2 ± 1.3	0.005
Obstructive apnea (seconds)	20.3 ± 1.3	22.9 ± 1.3	21.2 ± 1.3	23.0 ± 1.2	23.5 ± 1.7	22.7 ± 1.2	23.1 ± 1.3	23.6 ± 1.3	0.653
Hypopnea (seconds)	29.2 ± 1.0	31.0 ± 1.2	32.3 ± 1.3	31.2 ± 1.6	32.2 ± 1.3	32.7 ± 1.4	32.9 ± 1.4	31.4 ± 1.4	0.014
Mixed apnea (seconds)	30.8 ± 2.5	28.8 ± 2.4	31.4 ± 2.2	32.8 ± 2.2	30.7 ± 2.2	31.7 ± 2.2	32.5 ± 2.0	33.3 ± 1.9	0.883

Data reported as mean ± standard error.
*Repeated measures ANOVA for overall segment effect.

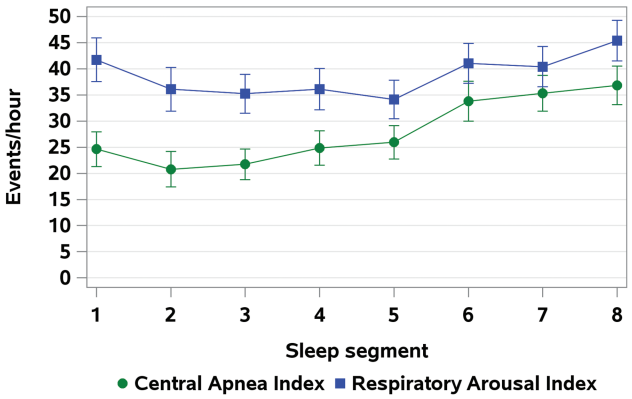

Figure 2. Central apnea index and respiratory arousal index by segment (least square means ± standard error), N = 41.

given respiratory event. This speculation is consistent with increased circulation time, one of the three components of the loop gain [7], as reported in above study [13]. However, changes in circulation time across the night were not significant in the current study. On the other hand, pulmonary congestion, if it were to occur progressively during the night, could increase ventilatory drive and therefore increase loop gain. In this regards, with recumbency to sleep, rostral redistribution of fluid from lower extremities to the lung could increase the loop gain by two processes: With fluid replacing air, lung volume decreases increasing the plant gain [7], and at the same time due to pulmonary congestion and elevated pulmonary capillary pressure, PCO_2 reserve decreases [19], both increasing the loop gain [7].

In the presence of sleep-disordered breathing, there is a third mechanism by which loop gain could increase. While asleep, apnea-related intermittent hypoxemia could result in respiratory plasticity promoting periodic breathing and central apnea. In naturally sleeping human, Chowderi *et al.* [20] have shown that exposure to intermittent hypoxia induces a significant increase in hypocapnic ventilatory response decreasing the PCO_2 reserve, destabilizing breathing and promoting central apneas. In passing, we note that it is conceivable, that endogenous circadian rhythms could influence various aspects of ventilatory control, but definitive research is still lacking [21, 22]. An important recent study by Landry *et al.* [22] has demonstrated that ventilatory control sensitivity in patients with OSA is sleep stage dependent. These investigators have shown that loop gain increases in NREM sleep late in the night, and is lower in REM sleep than NREM sleep. The difference in the loop gain between REM and NREM sleep is consistent with our early study [23] in patients with heart failure consistently [1, 17] showing a much higher prevalence of central apneas in NREM than REM sleep, a finding confirmed by others [3]. Importantly, the increase in loop gain late in NREM sleep, reported by Landry *et al.* [22] is consistent with the results of the current study showing increased burden of CSA in NREM sleep as night progressed.

Arousals

Finally, because of the cyclical nature of CSA, the increase in the number of NREM sleep arousals, driven by an increase in respiratory-related arousals later in the night, could have facilitated further development of central apneas as part of a feedback loop [7].

Interestingly, our results somewhat resemble those of OSA patients without heart failure [11, 12]. In 66 patients with OSA, Charbonneau *et al.* observed that as the night progressed, the mean apnea duration increased by about 8 seconds from about 27 to 35 seconds ($p < 0.0001$), mainly from increases during NREM sleep [11]. Similarly, Montserrat *et al.* [12] reported an increase of an average of 6 seconds in the apnea duration from 26.6 to 32.6 seconds. In the current study, we report an increase of 4 seconds in duration of central apneas from 22 to 26 seconds in NREM sleep in patients with heart failure, consistent with the OSA population without known heart disease. It appears that there may be a unifying mechanism to account for increasing duration of apneas across the night, independent of the mechanism underlying apnea. As suggested by Montserrat [12], the potential mechanism could be related to changes in the arousal threshold which could increase in NREM sleep in the latter segments of the night. In patients with OSA, Montserrat and associates proposed that a progressive decline in the arousal response to neural stimuli plays a major role in apnea lengthening across the night [12].

Limitations

One limitation of this study is that there is no reliable information available on sleep position across the night, as it is known that the number of, but not necessarily the duration of, central apneas increases in the supine position compared to lateral posture [24]. However, based on the following reasons we believe our finding are unrelated to position. In the present study, we found that not only the number but also duration of central apneas increased progressively in later hours of sleep, and we are not aware of any evidence that the arousal threshold is position dependent and increases in supine position. Further, as noted, the number of obstructive apneas did not change significantly across the night, and the number of hypopneas decreased. Collectively, these data suggest that the reported

findings are probably unrelated to sleep position and random changes in body posture would tend to obscure any systematic findings observed.

Clinical implications

If central apneas are indeed compensatory and protective in heart failure, as one of the speculated conclusions of the SERVE-HF has been [25], then our data could be interpreted for further cardiac protection as sleep progresses. However, based on pathophysiological consequences of CSA, and the mortality associated with CSA [4, 10, 26], we believe that CSA is not a protective mechanism [27, 28]. We have discussed the potential pitfalls of the SERVE-HF which may have contributed to excess cardiovascular mortality [29]. Among these, one factor discussed [29], could have been poor adherence (3.5 hours). If this is true, we speculate that worsening burden of CSA in the later hours of sleep, which is normally when most subjects take the mask off and sleep for few hours without using the positive airway pressure device, could be another factor contributing to excess mortality. As such, in theory, a full use of PAP therapy throughout sleep may be required to realize the cardiovascular benefits.

We should note that in the present study, the change in the pattern of arousals more or less paralleled the changes in central apneas. Arousals are associated with increased sympathetic activity with consequent adverse cardiovascular effects. In addition, the burden of CSA was associated with a nonsignificant increase in oxygen desaturation index, perhaps related to small number of patients.

Conclusions

Patients with reduced LVEF and predominantly CSA experience a significant increase in the AHI and CAI during NREM sleep later in the night compared to earlier in the night. In addition to the increase in the frequency, the duration of CSAs lengthens. The increase in the number of central apneas was associated with an increase in the number of associated arousals.

Supplementary material

Supplementary material is available at *SLEEP* online.

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Conflict of interest statement. S.J. is a consultant to Respicardia; S.W.M. and R.E.G. are employees of Respicardia; N.C. has no conflicts; A.M.—ResMed provided a philanthropic donation to UCSD.

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