Effect of Adaptive Servo-Ventilation on Periodic Limb Movements in Sleep in Patients With Heart Failure

Jiang Xie, MD, PhD[a,b,*], Naima Covassin, PhD[b], Anwar A. Chahal, MD[b,c], Phillip J. Schulte, PhD[d], Prachi Singh, PhD[b], Virend K. Somers, MD, PhD[b], and Sean M. Caples, DO[e]

Periodic limb movements in sleep (PLMS) are associated with adverse outcomes in patients with heart failure (HF). The aim of this study was to investigate whether PLMS change in response to adaptive servo-ventilation (ASV) for central sleep apnea (CSA) in patients with HF. We examined polysomnographic studies conducted between 2010 and 2014 at Mayo Clinic, Rochester, Minnesota (n = 14,444). In those, 314 of 579 patients with CSA completed the sleep study with a protocol that began with diagnostic polysomnography, followed by continuous positive airway pressure, and, for persistent CSA, by ASV titration. Patients with HF (n = 118) had a significantly higher median PLM index compared with those without HF (n = 196): 33.7 versus 6.1 events/h (p <0.001). HF was associated with a significant PLM arousal index (PLMAI) increase from diagnostic trial to ASV (odds ratio [OR] = 1.79, p = 0.032) after adjusting for demographics, co-morbidities and medications. In patients aged >68 years, HF was associated with PLMI and PLMAI increases during ASV (OR = 2.16, p = 0.016 and OR = 2.05, p = 0.024), which persisted in multivariable models (OR = 2.36, p = 0.025 and OR = 2.33, p = 0.026). In multivariable analysis, patients with ejection fraction ≤45% had higher odds of increased PLMAI during ASV than those with ejection fraction >45% (OR = 1.98, p = 0.022). In conclusion, PLMS may increase in HF patients after suppression of CSA by ASV. Whereas the clinical significance of increased post-ASV PLMS in HF prognosis needs to be determined, these increases may contribute to worsening outcomes in HF patients with CSA treated with ASV. © 2018 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;123:632−637)

Periodic limb movements of sleep (PLMS) are described as episodes of nocturnal repetitive limb movements. They have been independently associated with the development of cardiovascular diseases and predict mortality in patients with heart failure (HF) and other cardiovascular diseases.[1−5] The clinical significance of PLMS may be more evident in older patients, in whom PLMS are often more prevalent.[2,6] The etiological mechanisms linking PLMS and cardiovascular risk may relate to autonomic deregulation.[7−9] Central sleep apnea (CSA) is highly prevalent in patients with HF, affecting 30%−40%[10] of this clinical population, in whom it has been associated with an adverse prognosis.[11,12] By providing breath-by-breath adjustment of respiratory pressure support to normalize breathing patterns, adaptive servo-ventilation (ASV) effectively reduces CSA. Prior data have shown PLMS decreased in patients with mild obstructive sleep apnea (OSA) after treatment of continuous positive airway pressure (CPAP), but increased in subjects with severe OSA.[13] To our knowledge, no published data are available on the changes in PLMS after treatment of CSA. Considering the high prevalence of PLMS in patients with HF[1] and its close association with long-term mortality,[4] it may be relevant to determine whether suppression of respiratory events results in heightened PLMS in this group. In the present study we investigated changes in PLMS during ASV titration for CSA in patients with HF.

Methods

A sample of 14,444 consecutive adult patients who underwent polysomnographic evaluation at the Center for Sleep Medicine at Mayo Clinic, Rochester from January 1st, 2010 to September 30th, 2014 were retrospectively investigated (Figure 1). A total of 579 patients met the criteria for CSA[14,15] during the diagnostic portion of the study. Of these, 422 had split night titration. Since most patients who accepted ASV titration underwent an unsuccessful trial of CPAP before ASV, and since the aim of study was to investigate PLMS changes after ASV, only those subjects who completed the sleep study in the sequence of diagnosis-CPAP-ASV were included (n = 314). Patients were excluded if other interventions (eg, bilevel positive airway pressure) were adopted during the study. Abnormal overnight oximetry (n = 154), observed sleep apnea or snoring (n = 102), or excessive daytime sleepiness (n = 15) were the main reasons for referral for sleep test.

All diagnoses made during any clinical visits and inpatient or outpatient procedures in the Mayo Clinic
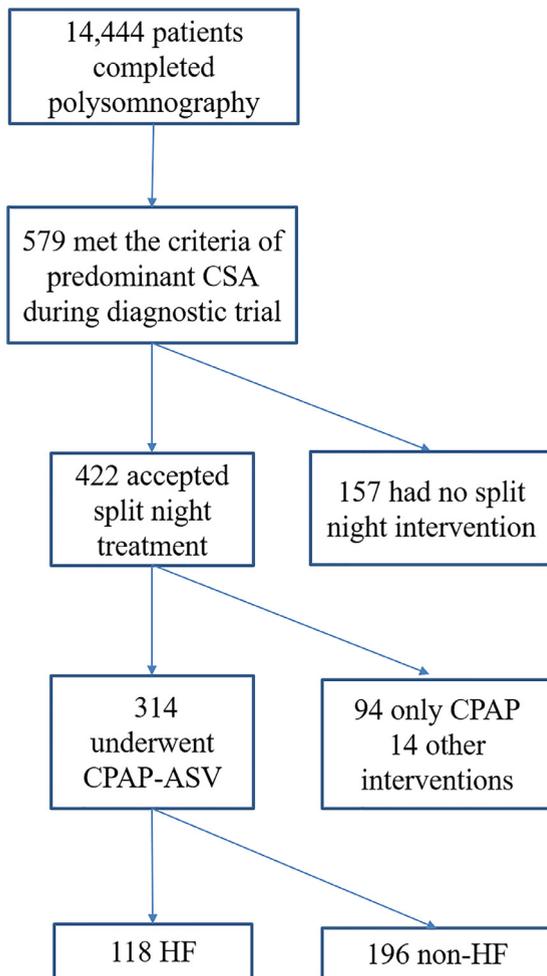
Figure 1. **Flow chart of study progress**. ASV, adaptive servo-ventilation; CPAP, continuous positive airway pressure; CSA = central sleep apnea; HF, heart failure.

were scored as central, whereas those with respiratory effort were categorized as obstructive. Apnea-hypopnea index (AHI) was calculated as the average number of apneas and hypopneas per hour of sleep. Patients with AHI ≥15 events/h were diagnosed with predominant CSA if central apneas accounted for >50% of all breathing events.[14,15] Presence of a limb movement was scored as such if its duration was between 0.5 and 10 seconds and there was a >8 μV amplitude increase from baseline in a limb electromyogram channel. A limb movement would not be scored if it occurred during a period from 0.5 seconds preceding an apnea, hypopnea, or respiratory effort-related arousal to 0.5 seconds following, according to guidelines.[21,22] To be considered periodic, at least 4 limb movements had to occur sequentially, 5 to 90 seconds apart. Periodic limb movement index (PLMI) was the total number of periodic limb movements per hour of sleep. Periodic limb movement arousal index (PLMAI) was the total number of periodic limb movements per hour of sleep in which an arousal was associated with limb movement. Arousals were scored as breathing-related arousal index if immediately preceded by any breathing event including respiratory effort-related arousal, whereas movement-related arousal index referred to the arousals promptly after any limb movement.

A proper nasal or nasal-mouth mask was selected to fit the patients and positive airway pressure titration was completed by sleep technologists. CPAP was started at 4 cm water pressure and increased to control breathing events following recommendations.[20] During ASV titration, minimum expiratory positive airway pressure was 4 or 5 cm water pressure; pressure support started at 3 cm of water and was increased to achieve optimal ventilation.

Data are presented as counts (percentage) for categorical variables or median (interquartile range [IQR]: twenty-fifth to seventy-fifth percentile) for continuous variables and compared by groups by Pearson chi-square tests or nonparametric Wilcoxon rank-sum tests, respectively. PLMI and PLMAI changes from the diagnostic portion to the ASV trial were computed, and multivariable logistic regression models were used to explore factors associated with PLMI and PLMAI increases (dependent variables) during ASV titration. Covariables included demographics (age, gender, and smoking), co-morbidities (hypertension, diabetes, coronary artery disease, cerebrovascular disease, and renal disease), and medications (antiplatelets, diuretics, angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers, beta-blockers, and statins). Note that the aforementioned medications were included in multivariable model not only for the statistical significance but also for their known beneficial effects on HF syndrome which is closely associated with PLMS prevalence. Comparison of the odds of having increased PLMS during ASV trial was conducted in HF versus non-HF subjects and in subgroups stratified by median age, since PLMS have been proved to be pathologically associated with adverse events in elderly subjects.[2,6,21] Univariable and adjusted multivariable odds ratios (OR) are provided with 95% confidence intervals (CI). Analyses were performed using JMP, version 13 (SAS Institute; Cary,

were uniformly recorded and assigned the searchable International Classification of Diseases adaptation codes.[2] Clinical information on HF diagnosis (including subjects with no-to-mild symptoms) and co-morbidities, demographics, and medications were extracted using an advanced query tool.[16] Additionally, a retrospective chart review was conducted manually to validate that the diagnosis of HF was consistent with the guidelines.[17] New York Heart Association Functional Classification within 1-year interval before or after polysomnography was noted. This study was approved by the Mayo Clinic Institutional Review Board.

Sleep evaluations were performed at the Mayo Clinic Center for Sleep Medicine, an American Academy of Sleep Medicine-accredited sleep center, using standardized scoring.[18,19] Electroencephalogram, electro-oculogram, electromyogram, electrocardiogram, thoraco-abdominal excursion, pulse oximetry, and oronasal airflow were monitored. Apneas were defined as a ≥90% decrease of airflow for at least 10 seconds, and hypopneas were defined by a ≥30% decline in airflow for at least 10 seconds accompanied by an oxygen desaturation of ≥4%. Apneas without evidence of respiratory effort

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Table 2
Sleep characteristics for subjects with central sleep apnea during diagnostic and adaptive servo-ventilation titration (n = 314)

Variable	Heart failure			ASV therapy		
	Yes (n = 118)	No (n = 196)	p Value	With heart failure (n = 118)	Without heart failure (n = 196)	p Value
Apnea-hypopnea index (events/h)	57 (42.8, 75.3)	42.0 (25.3, 63.8)	<0.001	5.0 (1.0, 14.0)	5.0 (1.0, 15.0)	0.915
CSA (events/h)	42.5 (25.8, 59.3)	29.0 (18.0, 46.0)	<0.001	0	0	0.195
Obstructive apnea (events/h)	1 (0, 4)	1 (0, 4)	0.655	0 (0, 0)	0 (0, 0)	0.760
Mixed apnea index (events/h)	1 (0, 4)	1 (0, 3)	0.196	0 (0, 0)	0 (0, 0)	0.007
Hypopnea index (events/h)	7 (3, 12)	6 (3, 10)	0.399	3 (0, 9)	2 (0, 8)	0.407
Respiratory effort-related arousal (events/h)	2 (1, 6)	5 (2, 10)	<0.001	2 (0, 6)	2 (0, 6)	0.832
Arousal index (events/h)	56.0 (42.9, 82.8)	47.5 (32.0, 65.4)	0.001	28.8 (16.5, 43.0)	27.4 (16.2, 43.8)	0.823
Percentage of movement related arousal index (%)	4.0 (0, 14.1)	1.1 (0, 13.1)	0.058	24.8 (2.3, 53.2)	2.9 (0, 28.4)	<0.001
Percentage of breathing related arousal index (%)	76.7 (58.7, 90.2)	76.8 (62.5, 85.4)	0.695	29.3 (5.9, 49.7)	26.0 (9.4, 53.1)	0.927
Sleep efficiency (%)	67.0 (52.7, 77.0)	73.9 (59.1, 83.6)	<0.001	73.9 (54.4, 86.4)	71.7 (53.8, 85.3)	0.357
Percentage of N1 sleep (%)	36.3 (20.4, 55.5)	23.8 (14.7, 39.9)	<0.001	14.3 (6.7, 27.2)	16.5 (8.6, 29.2)	0.260
Percentage of N2 sleep (%)	40.6 (27.7, 54.7)	44.6 (34.4, 59.4)	0.036	42.6 (30.3, 57.0)	43.0 (31.8, 59.5)	0.434
Percentage of N3 sleep (%)	4.9 (0, 16.1)	10.3 (0, 22.9)	0.004	11.6 (0, 25.1)	6.4 (0, 22.8)	0.048
Percentage of rapid eye movement sleep (%)	8.7 (0, 16.1)	8.8 (0, 14.7)	0.959	19.5 (7.9, 30.5)	17.7 (9.0, 25.8)	0.519
Oxygen saturation during sleep (%)	93 (92, 94)	93 (92, 94)	0.062	94 (93, 95)	94 (93, 95)	0.311
PLMI (events/h)	33.7 (2.2, 80.5)	6.1 (0, 35.9)	<0.001	32.2 (6.8, 86.3)	7.1 (0, 36.9)	<0.001
PLMAI (events/h)	2.1 (0, 8.3)	0.5 (0, 5.6)	0.028	5.1 (0.6, 13.1)	0.5 (0, 7.7)	<0.001
PLMI ≥15	74 (62.7%)	74 (37.8%)	<0.001	78 (66.1%)	81 (41.3%)	<0.001
PLMAI ≥1	71 (60.2%)	91 (46.4%)	0.018	84 (71.2%)	93 (47.5%)	<0.001

p Values refer to between-group differences in HF and non-HF patients. Data are median (interquartile range) or counts (percentage). Abbreviations: ASV = adaptive servo-ventilation; CSA=central sleep apnea; PLMI = periodic limb movement index; PLMAI = periodic limb movement arousal index.
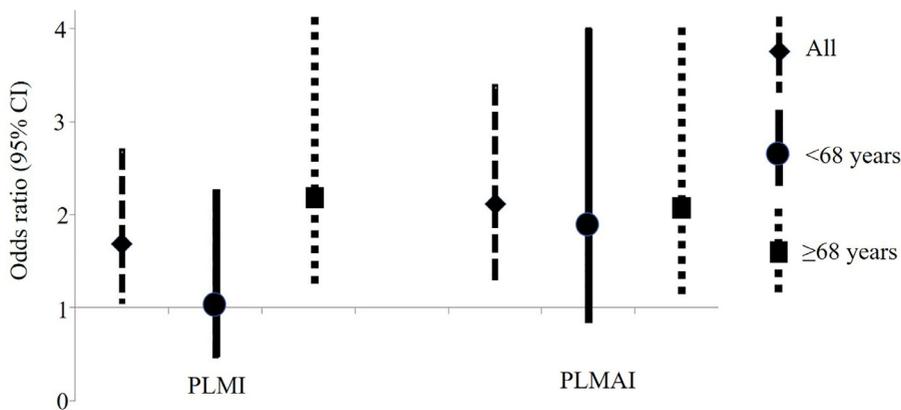
Figure 2. **Odds ratio (95% CI) of increased PLMS indexes during ASV trial in HF versus non-HF patients**. In crude logistic analysis, HF was associated with increased PLMI and PLMAI from diagnostic to ASV trial in all subjects. Stratified analysis by median age showed that the associations were statistically significantly only in those subjects ≥68 years old. ASV, adaptive servo-ventilation; HF, heart failure; PLMI, periodic limb movement index; PLMAI, periodic limb movement arousal index; PLMS, periodic limb movements in sleep.

Discussion

Our study has 2 main novel findings. First, HF patients with CSA manifest more frequent PLMS compared with CSA patients without co-morbid HF; and second, PLMS increase significantly during treatment of CSA by ASV. Since PLMS are associated with adverse cardiovascular prognosis,[4,5,22] the impact of post-ASV PLMS on cardiovascular risk warrants further investigation.

Although only patients with CSA were assessed for the purpose of the study, our results are in line with previous reports showing prevalent PLMS in HF.[23] The finding that HF subjects with CSA in our study had worse PLMS than non-HF subjects is supported by the following: (1) HF patients had higher median values of PLMS during both the diagnostic study and the ASV trial; (2) HF patients presented more PLMS than their non-HF counterparts despite higher AHI, which was shown to be inversely associated

Figure 3. Odds ratio (95% CI) of increased PLMS indexes during ASV Trial in subjects with LVEF ≤45% versus LVEF >45%. Patients with LVEF ≤45% exhibited higher PLMAI compared with those with LVEF >45%. ASV = adaptive servo-ventilation; LVEF = left ventricular ejection fraction; PLMI = periodic limb movement index; PLMAI = periodic limb movement arousal index; PLMS = periodic limb movements in sleep.
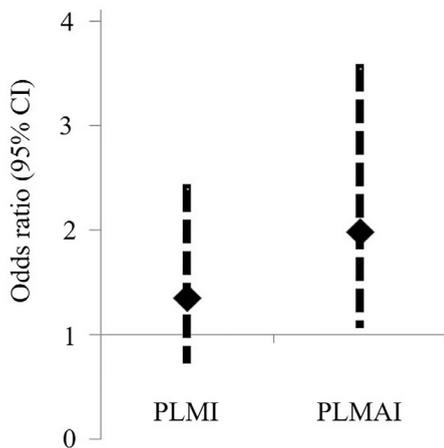
with PLMI/PLMAI in a previous study[13]; (3) A greater proportion of HF patients had increased post-ASV PLMS than non-HF subjects.

The high prevalence of post-ASV PLMS in CSA patients with HF is consistent with a previous study conducted in non-HF patients titrated on CPAP for moderate-severe OSA.[13] Spontaneous PLMS, which may be concealed by frequent breathing events, may be unmasked and become apparent after effective treatment of sleep-disordered breathing, irrespective of its obstructive or central nature, especially in subjects with severe obstructive sleep apnea and CSA. Thus, it is plausible that adequate ASV or CPAP therapy may merely unveil a preexisting sleep phenomenon, rather than increase PLMS in and of itself.

Our study indicates that age may influence the association between HF and post-ASV increase in PLMS. The significant rebound of unmasked PLMS in older HF patients is indeed noteworthy and potentially important, because both we and other investigators have shown that PLMS may be more strongly associated with cardiovascular risk in older patients than in younger ones.[2,6]

Another factor likely implicated in the observed associations is LVEF. Patients with LVEF ≤45% exhibited higher PLMS indexes compared with those with LVEF >45%, and low LVEF predicted augmented PLMS following ASV trial independently of conventional covariables. Thus, although speculative it is conceivable that PLMS may be the extraneous variable contributing to the poor outcomes reported by a recent large clinical trial[24] on HF patients with LVEF ≤45% who underwent ASV therapy for co-morbid CSA.

PLMS in isolation (ie, in the absence of symptoms of restless legs) are not typically treated. Despite the relation of PLMS with impaired cardiovascular function and adverse prognosis, it remains unknown whether treatment of PLMS impacts the cardiovascular risk profile. There is limited evidence that dopaminergic therapy may reduce atrial fibrillation burden,[25] normalize the PLMS-related heart rate response,[26] and reduce blood pressure,[27,28]

though these studies have been conducted in non-HF populations. Finally, it is worth considering that medical optimization of HF, which has been shown to attenuate CSA,[29] might also result in a similar improvement in PLMS. Indeed, there is an anecdotal evidence of resolution of PLMS after heart transplant.[30] Randomized controlled trials and experimental physiological studies are needed to test such hypotheses.

One of the strengths of our study is the inclusion of consecutive patients who underwent attended polysomnography scored by technicians who were not part of the study team and thus masked to outcomes. Meanwhile, before 2007, scoring of PLMS during breathing events was technically at the scorers' discretion with some practitioners including and others excluding this measure. The standardized approach adopted to score PLMS for our subjects reduces bias and improves generalizability. There are, however, limitations inherent to the retrospective study design. The major shortcoming is the practical split-night titration rather than separate diagnostic and titration studies on different nights. Therefore, any increase in PLMS may be a rebound from PLMS suppression by breathing events in the first part of night, and may not completely reflect a patient's usual condition. Even so, it does not diminish our finding of a close association of HF with PLMS, since HF subjects always had higher PLMI/PLMAI than their non-HF comparators in any conditions, and more HF patients had increased PLMS during ASV than non-HF patients. Second, given the high percentage of male patients and complex medical conditions of study subjects who were neither simple HF subjects nor healthy controls, but rather with medical concerns requiring referral for sleep study, generalizability of the results may be limited.

In conclusion, PLMS are prevalent in HF patients with CSA. Although treatment with ASV reduces breathing events, a paradoxical increase in PLMS is observed in HF patients, which is particularly more pronounced in elderly subjects and subjects with low LVEF. As PLMS are linked to unfavorable outcomes, these data thus reinforce the current recommendations against the use of ASV therapy in HF patients with low LVEF.

Disclosures

JX has served as a consultant for ResMed and Philips. He has spoken at meetings sponsored by Philips and ResMed. All other investigators have reported that they have no relation relevant to the contents of this study to disclose.

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