Association between sleep apnea and overnight hemodynamic changes in hospitalized heart failure patients with and without paroxysmal nocturnal dyspnea

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A B S T R A C T

Background: Paroxysmal nocturnal dyspnea (PND) is a common symptom for patients with acute decompensated heart failure (ADHF). Some symptoms of PND are similar to those of sleep apnea (SA) which might be associated with overnight worsening hemodynamics in failing hearts. However, the association between PND, SA, and overnight change in hemodynamics in patients with heart failure remains uncertain.

Methods: We studied 28 consecutive patients with reduced ejection fraction who were hospitalized with ADHF. Plasma atrial natriuretic peptide (ANP) levels were measured before and after overnight sleep study. PND was defined as having an episode of PND prior to hospitalization for ADHF.

Results: Ten (36%) patients had a history of PND. Respiratory disturbance index (the frequency and severity of sleep apnea) was an independent factor associated with a history of PND (odds ratio 1.24, 95% confidence interval 1.05–1.47, p=0.011). In those without PND, plasma ANP levels decreased from before sleep to after waking, whereas in those with PND it increased (p=0.011). In addition, overnight change in plasma ANP levels was independently associated with respiratory disturbance index (p=0.035).

Conclusion: These results thus suggest that in patients with ADHF, SA might be a predisposing cause of PND in association with overnight worsening hemodynamics.

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Introduction

Acute decompensated heart failure (ADHF) is a common and growing medical problem associated with major morbidity and mortality [1]. The difficulties surrounding treatment begin with a lack of clear definitions. Because of the heterogeneous nature of ADHF, no single finding is definitive for diagnosis, and instead a broad array of signs and symptoms are associated with the condition. Of the associated symptoms in patients with ADHF, dyspnea on exertion is the most sensitive, whereas paroxysmal nocturnal dyspnea (PND) is the most specific [2], and is characterized by “patient awakens, often quite suddenly and with a feeling of severe anxiety and suffocation, sits bolt upright, and gasps for breath” [3]. Thus, PND is a common symptom among patients with ADHF. Relieving a typical symptom as a focus of treatment for heart failure (HF) could lead to improved quality of life and be important as a therapeutic target. However, the pathophysiology of PND remains unknown. It is therefore important to achieve a better understanding of PND which might contribute to improving the clinical course. Coexisting sleep apnea (SA) may be a factor in PND.

Some symptoms of PND are similar to those of SA. SA is more common in patients with fluid retention such as in HF than in those without [4,5]. A previous study showed the possibility that rostral fluid displacement from edematous legs to the neck and lung upon assuming the recumbent position could predispose to obstructive and central apnea during sleep [6]. In addition, pulmonary capillary wedge pressure (PCWP) in patients with HF is associated with central apnea [7]. Therefore, excess fluid volume and worsening hemodynamics could be important factors coexisting with SA in patients with HF. On the other hand, SA is characterized by recurrent hypoxia, arousal, and the generation of exaggerated intrathoracic pressure during sleep, which increases sympathetic nervous system activity, reduces cardiac parasympathetic activity, and causes repetitive surges in heart rate, blood pressure, and left ventricular preload and afterload. The mechanical loading of the myocardium can also increase myocardial oxygen demand in the face of a reduced supply, causing a decrease in cardiac output in

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patients with HF [8,9]. Therefore, the failing heart could also be susceptible to the adverse hemodynamic consequences of SA.

Thus, it is likely that the pathophysiology of PND may be associated with SA through worsening hemodynamics during sleep in patients with HF. However, the relationship among PND, SA, and overnight change in hemodynamics in patients with HF remains uncertain. A number of studies have shown that plasma atrial natriuretic peptide (ANP) levels are elevated in patients with HF, which are positively correlated with right atrial pressure (RAP) or PCWP, or both [10,11]. Therefore, plasma ANP levels could be useful as a cardiac biomarker predicting overnight changes in general hemodynamics in patients with HF. We hypothesized that coexisting SA in patients referred for ADHF might be associated with PND accompanied by increased plasma ANP levels at baseline and its overnight increment during pathologic sleep disturbance.

Methods

Patients and study design

We prospectively recruited consecutive HF patients with reduced ejection fraction who were hospitalized with ADHF in our institute between May 1, 2006 and October 30, 2006. After their conditions had been improved by medical treatment and their HF had been stabilized [New York Heart Association (NYHA) class II and III], each patient underwent complete assessment during overnight sleep. Plasma ANP levels were measured before and after the overnight sleep study.

Inclusion criteria were: (1) age 18 years or older and (2) left ventricular ejection fraction (LVEF) \( \leq 40\% \) as confirmed by echocardiography. Exclusion criteria included: (1) unstable status, including unstable angina, NYHA class IV, receiving any intravenous drip infusions, oxygen supplementation, or positive airway pressure treatment; (2) hospitalization with acute coronary syndrome; (3) congenital heart disease; and (4) having renal dysfunction defined as an estimated glomerular filtration rate < 60 ml/min, because renal function directly contributes to elevated natriuretic peptide levels [12]. No patients were selected on the basis of possible underlying SA. The study was approved by the local institutional review boards and all patients gave written informed consent for participation in the study.

Data collection

Data on demographic characteristics, medical history, and medication use were obtained with the use of a standardized questionnaire and patient medical records obtained by a physician at the time of the sleep study. PND was defined as having an episode that ‘patient suddenly awakens with a feeling of suffocation or a gasp for breath’ prior to hospitalization for ADHF. Atrial fibrillation was defined by its presence on the continuous electrocardiographic recording during the sleep study. LVEF was determined using Simpson’s method with echocardiography in the stable condition. Right catheterization was performed by experienced cardiologists on the day of the sleep study.

Plasma ANP levels were determined in samples obtained at 22:00 (before sleep) and 06:00 (after waking). The patients lay quietly for at least 30 min before the baseline samples were collected before sleep. At the end of the sleep study, samples were collected immediately after the patients awoke, but before they arose from bed. Blood was first collected in a heparinized plastic syringe to clear the tubing volume. Thereafter, the blood samples collected for the determination of ANP were transferred to chilled disposable tubes containing aprotinin and ethylenediaminetetraacetic acid and immediately centrifuged. The plasma was then frozen at \(-20^\circ C\) and stored until quantitative ANP analysis was performed. Plasma ANP levels were measured using a standard peptide radioimmunoassay kit (Shionogi ANP kit, Shionogi & Co., Ltd., Osaka, Japan).

Sleep study

The overnight sleep study was performed using a cardiopulmonary monitoring device (Morpheus, Teijin Inc., Tokyo, Japan) consisting of a pressure sensor for nasal flow, two stress-sensitive belts for the ribcage and abdomen, respectively, and a continuous pulse oximeter. An episode of apnea was defined as the complete cessation of the sum of thoracoabdominal movements and air flow for \( \geq 10\ s \). An episode of hypopnea was defined as a \( \geq 50\% \) decrease in the sum of thoracoabdominal movements and air flow lasting for \( \geq 10\ s \), followed by a reduction in SaO2 of at least 4%. Apnea was classified as obstructive or central in the presence or absence of flow and thoracoabdominal motion, respectively, and hypopnea as obstructive or central in the presence or absence of out-of-phase thoracoabdominal motion, respectively [13]. The total respiratory disturbance index (RDI) was quantified as the total frequency of apnea and hypopnea per hour of time in bed and subclassified into either central-RDI or obstructive-RDI based on the above definitions. The sleep study was manually analyzed by an expert technician who was blinded to the patients’ baseline clinical characteristics.

Statistical analysis

Comparisons between the two groups were performed using Student’s t-test for continuous variables that were normally distributed and the Mann–Whitney U-test for variables that were not normally distributed. The chi-square or Fisher’s exact test was used to compare nominally scaled variables. To evaluate the independent factors associated with PND, multivariate analysis was performed using the logistic regression model with the best subset variable selection method including older age, male sex, body mass index, LVEF, atrial fibrillation, ischemic etiology, and total RDI. To determine the independent factors associated with RDI, multivariate analysis was performed using the generalized linear regression model with the best subset variable selection method including older age, male sex, body mass index, LVEF, atrial fibrillation, ischemic etiology, plasma ANP level before sleep, and overnight change in plasma ANP level. Odds ratios (ORs) and regression coefficients are reported with 95% confidence intervals (CIs). The best cutoff values for variables predicting increasing plasma ANP levels during overnight sleep were identified based on receiver operating characteristic (ROC) curves at regular intervals as the value that minimized the expression \( [(1 – sensitivity)^2 + (1 – specificity)^2] \) [14]. Data are presented as mean \( \pm SD \) or SEM unless indicated otherwise. The influence of profile, linearity, interaction, and collinearity was assessed in all models by regression diagnostic analysis. A two-tailed p-value of less than 0.05 was considered to indicate a statistically significant difference. The analyses were performed using Statistical Analysis System ver. 9.1 software (SAS Institute Inc., Cary, NC, USA).

Results

Of 50 consecutive hospitalized patients with ADHF, 23 patients were excluded from the study: 2 patients died, 15 patients had normal ejection fraction, 1 had congenital heart disease, 4 had renal dysfunction, and 1 was receiving supplemental oxygen. Thus, a total of 28 patients hospitalized for ADHF were included in the final analysis. There were 15 (54%) men and 13 (46%) women, whose ages ranged from 33 to 77 years (mean 59 \( \pm 12 \) years), and whose body mass index was 22.5 \( \pm 2.9 \) kg/m\(^2\). Ten (36%) patients had a history...
of PND. All patients had NYHA class II and III, and mean LVEF was 27.1 ± 11.5%. There was a history of hypertension in 21% of patients and diabetes in 11%. The etiology of HF was ischemic in 18%. At the time of assessment, 93% were taking angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers, 96% beta-blockers, and 86% thiazide or loop diuretics. The period from hospitalization to the sleep study ranged from 4 to 36 days (mean 14 ± 6 days). RDI ranged from 0.4 to 37.7/h (mean 14.9 ± 10.8/h).

The characteristics of the patients with and without PND are shown in Table 1. Patients with PND had a significantly higher percentage of ischemic etiology, higher total RDI and central-RDI, and lower SaO2 than those without PND. Patients with PND tended to be older, have a higher body mass index, and have a lower LVEF compared with those without PND. There were no differences in the proportion of male sex, atrial fibrillation, and medication use between the two groups. In multivariate analysis using the logistic regression model with the best subset variable selection method including older age, male sex, body mass index, LVEF, atrial fibrillation, ischemic etiology, and total RDI, only total RDI was an independent factor associated with a history of PND (per one event/h increase, OR 1.24, 95% CI 1.05–1.47, p = 0.011). The ROC curve demonstrating the sensitivity and specificity of total RDI in patients with HF shows that the best total RDI cutoff value to predict for PND was ≥20/h (area under the curve 0.88 ± 0.07, p < 0.001, sensitivity 90.0%, specificity 88.9%).

Of the 28 patients analyzed, 20 underwent right catheterization before sleep study. Plasma ANP levels at baseline (before sleep) significantly correlated with RAP (r = 0.04x + 1.8, R = 0.55, p = 0.026) and PCWP (r = 0.09x + 4.5, R = 0.71, p = 0.002).

Both plasma ANP levels obtained before sleep and after waking were more than two-fold higher in patients with PND than in those without (Fig. 1A). In addition, in the non-PND group, plasma ANP levels decreased from before sleep to after waking, whereas in the PND group it increased (Fig. 1B).

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>PND (N = 18)</th>
<th>Yes (N = 10)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56 ± 13</td>
<td>64 ± 9</td>
<td>0.118</td>
</tr>
<tr>
<td>Male (%)</td>
<td>9 (50)</td>
<td>6 (60)</td>
<td>0.627</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>21.8 ± 2.3</td>
<td>23.7 ± 3.6</td>
<td>0.100</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>30.2 ± 11.5</td>
<td>21.5 ± 9.5</td>
<td>0.056</td>
</tr>
<tr>
<td>Left ventricular diastolic diameter (mm)</td>
<td>62.1 ± 11.2</td>
<td>67.6 ± 9.5</td>
<td>0.201</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>7 (39)</td>
<td>5 (50)</td>
<td>0.586</td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>1 (6)</td>
<td>4 (40)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
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<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
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</thead>
<tbody>
<tr>
<td>Coefficient (95% CI)</td>
<td>p-Value</td>
<td>Coefficient (95% CI)</td>
</tr>
<tr>
<td>Older age (per 10-yr increase)</td>
<td>4.72 (1.73–7.70)</td>
<td>0.003</td>
</tr>
<tr>
<td>Male sex</td>
<td>11.70 (4.54–18.85)</td>
<td>0.002</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>1.30 (–0.09–2.68)</td>
<td>0.065</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>−0.15 (−0.52–0.23)</td>
<td>0.428</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4.89 (3.52–13.29)</td>
<td>0.243</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>6.23 (0.80–12.43)</td>
<td>0.048</td>
</tr>
<tr>
<td>ANP before sleep (per 10-pg/ml increase)</td>
<td>0.71 (0.10–1.33)</td>
<td>0.025</td>
</tr>
<tr>
<td>Overnight change in ANP (per 10-pg/ml increase)</td>
<td>0.81 (0.13–1.49)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

The above variables were all evaluated using the generalized linear regression model with the best subset variable selection method. ANP, atrial natriuretic peptide; 95% CI, 95% confidence interval.
in plasma ANP levels was associated with central-RDI (R = 0.54, p = 0.004).

Plasma ANP levels were higher in the RDI ≥ 20 group than in the RDI < 20 group regardless of the sampling time point (Fig. 2A). In addition, in the RDI < 20 group, the overnight change in plasma ANP levels showed a decreasing pattern, whereas in the RDI ≥ 20 group it increased (Fig. 2B).

Discussion

This observational study yielded several novel observations. First, in patients referred for ADHF, the frequency and severity of SA (total RDI) was an independent factor associated with the presence of prior PND. Second, patients with PND had increased ANP levels at baseline and overnight increases in ANP; conversely, those without PND did not. Third, we found that increased ANP at baseline and increasing overnight change in ANP were independent factors associated with RDI. To the best of our knowledge, this is the first study that determined the relationship between PND and SA with a surrogate hemodynamic marker.

The relationship between PND and SA was described in the 1930s by Harrison et al., who reported that the hyperpneic phase of central apnea could produce dyspnea [15]. On the other hand, Montuschi reported four HF cases in which the symptoms of PND were alleviated by volume reduction using diuretics [16]. Our results provided further support for a direct link between PND and SA, and overnight change in hemodynamics. In patients with HF, venous return to the right heart at bedtime when moving from the upright to the recumbent position is increased and this might lead to a further worsening of hemodynamics including increased RAP and PCWP [17,18]. Their conditions might predispose to central apnea due to the stimulation of pulmonary irritant receptors that can cause hyperventilation, which might then lead to PND. Indeed, a previous study showed that in patients with HF, overnight rostral fluid displacement from the legs did not only contribute to the pathogenesis of both obstructive and central SA, but also with progressively greater overnight rostral fluid shift, and there was a gradation from no sleep apnea to obstructive SA to central SA [6]. Solin et al. showed that PCWP and pulmonary artery pressure were markedly higher in the central-predominant SA group than in the obstructive-predominant SA and no SA groups when comparing hemodynamics via right heart catheterization [7]. In addition, positive airway pressure treatment and cardiac resynchronization therapy reduced plasma ANP levels and the frequency and severity of SA through improvement of cardiac function in patients with central SA [19,20]. Furthermore, a recent study showed that ANP levels are increased among patients with HF and central SA compared with those without CSA [21]. Our results were consistent with those in the previous studies. The frequency and severity of SA were positively correlated with plasma ANP levels at baseline in central-RDI. Therefore, central apnea more likely arises as a consequence of poor hemodynamics in HF than obstructive apnea. A key factor predisposing to CSA is hyperventilation, setting eupneic PaCO2 close to the apnea threshold. Hemodynamic congestion is a significant factor triggering hyperventilation and CSA. And other factors, including impaired cerebral blood flow, prolongation of circulation time, metabolic alkalosis, low functional residual capacity, upper airway instability, and hypoxia, may further contribute to respiratory instability and CSA.

On the other hand, SA itself might contribute to deteriorating cardiac hemodynamics overnight in patients with HF. To our knowledge, there has been no previous study of overnight changes in hemodynamics among HF patients with and without SA. Nevertheless, during obstructive apnea, the generation of exaggerated negative intrathoracic pressure against the occluded upper airway, hypoxia and hypercapnea, and sympathetic nerve activation leads to increased right ventricular preload and increased left ventricular afterload, both of which increase myocardial oxygen demand [9,22], thereby causing distention of the right atrium and ventricle. This distention also shifts the interventricular septum, impairs left ventricular diastolic filling, and reduces stroke volume during each apnea episode. Bradley et al. showed that during awake periods, Mueller maneuvers were associated with significantly greater reductions in cardiac index in patients with HF than in healthy individuals [9]. In severe apnea cases, the cycles of apnea can recur several hundred times each night and could worsen hemodynamics during overnight sleep. Also, as a result of these vaccinations, atrial intragranular stores of ANP are released immediately due to intrathoracic pressure swings that modify the atrial distention pressure, as our results showed [23–25]. In addition, short-term randomized trials demonstrated that treating obstructive SA with positive airway pressure in HF patients reduced sympathetic nervous system activity, blood pressure, and nocturnal ventricular ectopy, increased vagal modulation of the heart rate, and improved LVEF and the quality of life [26–29]. In contrast to obstructive apnea, in which inspiratory efforts are made against the occluded upper airway owing to the continued presence of respiratory drive, no respiratory effort is generated during central apnea due to the cessation of respiratory drive. Thus, unlike obstructive apnea, no negative intrathoracic pressure is generated during central apnea. Therefore, its impact on afterload might be less than in obstructive
apnea. However, it remains uncertain whether central apnea contributes to the deterioration of cardiac hemodynamics overnight.

From these viewpoints, we suggest that in HF patients poor hemodynamics and a rostral fluid shift at bedtime are important factors causing SA, which itself constitutes an adaptive adverse effect on the worsening hemodynamics during sleep, and thus may be closely associated with the predisposing to PND.

Our observations are subject to some limitations. First, the present study examined PND in patients who were in a stable condition after a mean 14 days of hospitalization for initial ADHF.

Nevertheless, previous studies showed that the severity and types of SA remained unchanged between decompensated and stable HF status [30,31]. Second, the cardiorespiratory monitoring device used in this study cannot record electroencephalograms, unlike polysomnography. However, the Morpheus device can distinguish between obstructive and central apneas and hypopneas and like polysomnography meets the recommendations for the quality of evidence obtained using methods for measuring breathing disorders during sleep [32]. In addition, several reports showed a close correlation between data obtained with polysomnography and this device [33]. Third, we only included patients with reduced ejection fraction. Further research is needed to determine association between PND and SA for patients with preserved ejection fraction.

Clinical implications and conclusions

From a pathophysiological viewpoint, it is likely that PND is associated with coexisting SA and worsening hemodynamics in patients with ADHF. From a therapeutic viewpoint, it may be inferred from the present results that interventions aiming at reducing plasma ANP levels and the frequency and severity of SA, independent of specific treatment for cardiac hemodynamics, could help to relieve symptoms in patients with HF [34]. Increased LV filling pressure is the main reason for ADHF admission and readmission. The goal of tailored therapy for ADHF has been to reduce RAP and PCWP filling pressures [35]. Therefore, our results suggest that treatment for SA appears more likely to have beneficial effects on symptoms and quality of life in HF patients. The presence of SA should thus be determined and treated as a target condition.

Author’s contribution

Y. Yagishita-Tagawa collected data and analyzed it, and assisted in designing the study, and drafting and revising the manuscript. D. Yumino, A. Takagi, and N. Serizawa collected data, assisted in designing the study and revising the manuscript. N. Hagiwara provided collected data and assisted in its analysis, and assisted in designing the study, and drafting and revising the manuscript.

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