Journal of Cardiology 61 (2013) 348–353

Contents lists available at SciVerse ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

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

Yoshimi Yagishita-Tagawa (MD), Dai Yumino (MD)*, Atsushi Takagi (MD, FJCC), Naoki Serizawa (MD), Nobuhisa Hagiwara (MD, FJCC)

Department of Cardiology, Tokyo Women's Medical University, Tokyo, Japan

ARTICLE INFO

Article history:
Received 28 June 2012
Received in revised form 4 November 2012
Accepted 17 December 2012
Available online 16 March 2013

Keywords:
Acute decompensated heart failure
Atrial natriuretic peptide
Central sleep apnea
Obstructive sleep apnea

ABSTRACT

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.

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 negative 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

* Corresponding author at: Department of Cardiology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. Tel.: +81 3 3353 8111; fax: +81 3 3356 0441.
E-mail addresses: dai.yumino@gmail.com, yumino@mvj.biglobe.ne.jp (D. Yumino).

0914-5087/$ – see front matter
http://dx.doi.org/10.1016/j.jjcc.2012.12.010

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 °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 SaO_2 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 $[(1-\text{sensitivity})^2+(1-\text{specificity})^2]$ [14]. Data are presented as mean ± 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 ± 12 years), and whose body mass index was 22.5 ± 2.9 kg/m^2. Ten (36%) patients had a history