Journal of Cardiac Failure Vol. ■■ No. ■■ 2016

Clinical Investigation

Prognostic Importance of Novel Oxygen Desaturation Metrics in Patients With Heart Failure and Central Sleep Apnea

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ABSTRACT

Background: Sleep-disordered breathing, particularly central sleep apnea (CSA), is highly prevalent in heart failure (HF) and an independent prognostic marker. We assessed the hypothesis that an increased hypoxemic burden during sleep may have greater prognostic value than the frequency of apneic and hypopneic episodes.

Methods and Results: We prospectively conducted overnight cardiorespiratory polygraphy on consecutive HF patients referred to our hospital from 2008 to 2011. We studied CSA defined by an apnea-hypopnea index (AHI) of ≥5 events/h with >75% of all events being central in origin. We determined the AHI, proportion of the sleep time with SpO_2 <90% (T90%), and proportion of the recording time that 4% desaturation events occurred (4%POD). We studied 112 HF patients with either systolic or diastolic dysfunction. During a follow-up period of 37 ± 25 months, 32 patients (29%) died. Nonsurvivors had a higher 4%POD compared with survivors (11 ± 6.4% vs 19 ± 13%; $P = .001$), but did not differ significantly from survivors regarding AHI and T90%. An adjusted logistic regression analysis revealed that the 4%POD was the best independent predictor of mortality.

Conclusions: The 4%POD, a novel metric for the nocturnal hypoxemic burden, is an independent prognostic marker in HF patients affected by CSA. (*J Cardiac Fail 2016;*■■*:*■■–■■)

Key Words: Sleep, heart failure, hypoxia and mortality.

Introduction

Heart failure is a major and increasing public health burden, and carries significant morbidity and mortality.[1] Better risk stratification and targeting of clinical resources might lead to an improvement in survival. Sleep-disordered breathing (SDB), both in the form of obstructive sleep apnea (OSA) and central sleep apnea (CSA) are comorbid conditions in up to 50% of heart failure patients[2–4] and have implications for heart failure progression and prognosis.[5–8]

In CSA, recurrent episodes of hypoxemic followed by hyperpnea are associated with periodic ischemia/reoxygenation, arousals, and elevations in sympathetic activity.[9–11] Unlike OSA, changes in intrathoracic pressure are only modest in CSA. Thus, the adverse effects on CSA are mainly mediated by increased sympathetic activity rather than the ventricular afterload. In an early report by Naughton et al,[12] increased sympathetic activation in patients with heart failure and CSA was shown to be related to the severity of the nocturnal oxygen desaturation rather than the frequency of apnea and hypopnea

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Manuscript received March 8, 2016; revised manuscript received August 5, 2016; revised manuscript accepted September 1, 2016.

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EW is supported by a grant from the Suzuken Memorial Foundation and JSPS KAKENHI grant no. 26461094. KK is supported by JSPS KAKENHI 23700544.VKS is supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award no. R01HL065176. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

See page ■■ for disclosure information.

1071-9164/$ - see front matter

http://dx.doi.org/10.1016/j.cardfail.2016.09.004

episodes. Mansfield et al,[13] reported that cardiac norepinephrine spillover correlated with a reduced SpO_2, but not with the apnea-hypopnea index (AHI). These studies suggest that the magnitude or severity of hypoxemia during sleep may have a greater detrimental effect on the heart than the number of apnea or hypopnea episodes.

The severity of SDB is traditionally determined by the number of apnea and hypopnea episodes per hour of sleep, ie, the AHI. However, the duration of the apnea episode and subsequent ventilation phase are inversely proportional to the cardiac function, so the AHI may not directly reflect the severity of the heart failure.[5] Although there seems little doubt that cardiovascular morbidity is associated with oxygen desaturation, few studies have explored or offered robust metrics for the nocturnal hypoxemic burden. The aim of the present study was to explore the novel oxygen desaturation metrics for risk stratification in patients with heart failure affected by CSA.

Materials and Methods

Patients

From January 2008 to December 2011, we prospectively enrolled patients who were consecutively referred to the hospital for the evaluation or treatment of either systolic or diastolic heart failure.[3] Patients were excluded if they satisfied ≥1 of the following criteria: ongoing treatment for SDB, chronic obstructive pulmonary disease (forced expiratory volume per second <70%), hypercapnia ($PaCO_2$ >45 mm Hg), pregnancy, use of sedatives/sleeping medications, ≥95 years or <20 years of age, active myocarditis, renal failure requiring dialysis, and malignancy. In addition, patients were excluded if, within the preceding 2 months, they had undergone coronary revascularization or had had an acute myocardial infarction, unstable angina, or a stroke. The study protocol conformed to the Declaration of Helsinki. The study was approved by the Ethics Committee of Fujita Health University, and patients gave their informed consents to participate.

Sleep Studies and Group Definitions

We used type 3 in-hospital unattended cardiorespiratory polygraphy (LS-300; Fukuda Denshi, Tokyo), with recording of the body position, electrocardiography, oronasal airflow, chest and abdominal effort, and pulse oximetry.[14,15] The sampling rate of the pulse oximetry was 1 Hz. Apnea was defined as a cessation of airflow that lasted ≥10 seconds, and hypopnea was defined as a ≥30% decrease in the sum of the thoracoabdominal movements lasting ≥10 seconds, followed by a reduction in the SpO_2 of ≥4%. CSA was defined as an absence of oronasal airflow during sleep for ≥10 seconds associated with an absent respiratory effort or any reduction in the oronasal airflow for ≥10 seconds associated with in-phase thoracoabdominal movement and a ≥4% fall in SpO_2. Cheyne-Stokes respiration was defined as ≥3 episodes of continuous cycles of waxing and waning tidal volumes with periods of hyperventilation separated by CSA or hypopnea episodes. In this study, Cheyne-Stokes respirations were included in CSA. OSA was defined as cessation of the oronasal airflow for ≥10 seconds in the presence of an out-of-phase thoracoabdominal effort or as a fall in the oronasal airflow for ≥10 seconds with an out-of-phase thoracoabdominal movement associated with a ≥4% fall in SpO_2. We studied CSA defined by an AHI of ≥5 events/h with ≥75% of all events being central in origin. We excluded OSA defined by an AHI of ≥5 events/h with ≥25% noncentral events. The sleep studies were performed while patients were in stable heart failure. We studied the data recorded from 22:00 h to 06:00 h, expressed as the total recording time. The sleep study analyses were performed and scored by an SDB technician (SF) and a board-certified sleep specialist (YM) who were blinded to this study.

Desaturation Index

To quantify the SDB-related variation in SpO_2 during the cardiorespiratory polygraphy, the following measures were obtained:

1. Oxygen desaturation index (ODI), defined as the number of oxygen desaturation events per hour during the sleep duration, where an event was detected if the oxygen level dropped by 3% and 4% (3%ODI and 4%ODI, respectively) from the baseline oxygen saturation.
2. The proportion of the sleep time with an SpO_2 of <90% (T90%), and area under the T90% curve (AUT90%) were determined. Also, the mean SpO_2, minimum SpO_2, and the standard deviation of the SpO_2 during sleep were analyzed.
3. The percentage of oxygen desaturation events (POD) was defined as

$$\frac{\sum_{i=1}^{n} \tau_i}{(\text{Total recording time})} \times 100\,(\%),$$

where τ_i is the duration of each oxygen desaturation event. The 3%POD and 4%POD were defined corresponding to the 3%ODI and 4%ODI, respectively. That value was normalized by the total recording time and presented as the percentage (Fig. 1).

4. The area under the oxygen desaturation event curve (AOD) was defined as

$$\frac{\sum_{i=1}^{n} S_i}{(\text{Total recording time})}\,(\%),$$

where S_i was the accumulation of (threshold – SpO_2) × (sampling interval) of each oxygen desaturation event. In this definition, the sum of S_i (numerator) could be proportional to the total recording time. Therefore, the AOD was normalized by the total recording time. The AOD value primarily reflects the depth of the apnea-induced desaturations averaged over the total recording time. The 3%AOD and 4%AOD were defined corresponding to the 3%ODI and 4%ODI, respectively. That value was measured for the total recording time and presented as the percentage (Fig. 1).