Prognostic Impact of Central Sleep Apnea in Patients With Heart Failure

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ABSTRACT

Background: Central sleep apnea (CSA) is common in patients with heart failure (HF). Earlier studies investigating the influence of CSA on mortality in HF patients, however, have yielded contradictory results.

Methods and Results: In a prospective study involving 267 patients with left ventricular (LV) ejection fractions ≤50%, we performed polysomnography and compared heart transplant−free survival rates between patients with no or mild CSA (apnea-hypopnea index [AHI] ≤15/h) and those with moderate CSA (AHI 15.1−30/h) or severe CSA (AHI >30/h). During 43 ± 18 months' mean follow-up, 67 patients (25%) died and 4 patients (1%) underwent heart transplantation. Multivariate Cox analysis identified age, male sex, chronic kidney disease, and decreased LV ejection fraction, but not moderate CSA or severe CSA, as predictors of transplant-free survival.

Conclusions: In patients with stable HF, moderate CSA as well as severe CSA do not appear to predict transplant-free survival independently from confounding factors. (*J Cardiac Fail 2015;21:126−133*)

Key Words: Central sleep apnea, heart failure, transplant-free survival, polysomnography.

Sleep-disordered breathing is a highly prevalent but underdiagnosed finding in patients with heart failure (HF). Although the frequency of obstructive sleep apnea (OSA) in CHF patients is similar to or moderately higher than that observed in the general population, central sleep apnea (CSA) has been observed in 21%−82% of patients with HF.[1−12] In patients with HF, both prevalence and severity of CSA have been associated with HF severity with increased neurohumoral activation, elevated B-type natriuretic peptide (BNP) levels, increased pulmonary capillary wedge pressure, and progression of HF.[3−8] Earlier studies investigating the influence of CSA on mortality in patients with HF, however, have yielded contradictory results.[13−26] In addition, most studies were limited by small patient populations, retrospective study designs, few end points during follow-up, no uniform use of ventilation therapy, and polygraphy instead of polysomnography as criterion standard to diagnose CSA. Therefore, we performed a prospective observational study with the use of polysomnography to determine whether untreated moderate CSA or severe CSA is associated with total mortality or need for heart transplantation compared with no CSA or mild CSA in a large patient population with stable HF.

Methods

Patients

From August 2007 to June 2011, we prospectively screened 300 adult patients for sleep-disordered breathing with the use of polysomnography at the department of internal medicine and cardiology in our hospital who fulfilled the following inclusion criteria: systolic HF due to ischemic or nonischemic cardiomyopathy, New York Heart Association (NYHA) class I−III in a stable condition with unchanged medical HF treatment for ≥1 month, and

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left ventricular (LV) ejection fraction ≤50% according to echocardiography. The LV ejection fraction cutoff of ≤50% according to echocardiography to define systolic LV dysfunction was based on the recommendations of the European Echocardiography Association[27] and European Society of Cardiology guidelines for diagnosis and treatment of HF.[28] Patients were excluded from study enrollment if they had ≥1 of the following conditions: history of sleep-disordered breathing or previous polygraphy or polysomnography for suspected sleep-disordered breathing, advanced kidney disease with an estimated glomerular filtration rate (eGFR) < 15 mL min^{-1} 1.73 m^{-2} or hemodialysis, advanced liver disease, including liver cirrhosis Child class B or C, advanced pulmonary disease, including pulmonary fibrosis and chronic obstructive lung disease Gold stage 3 or 4, pregnancy, malignancies, and current or past alcohol or drug abuse. In addition, 33 of 300 patients who underwent baseline polysomnography were subsequently excluded because of OSA despite a negative patient history for OSA, insufficient sleep studies, or withdrawal of consent, as summarized in Figure 1. The study protocol was reviewed and approved by the Ethics Committee of the University of Marburg. Patients were screened for study participation primarily at the department of Cardiology of the Hospital of the University of Marburg. Written informed consent was obtained from each of the study patients who met the inclusion criteria mentioned above at the time of study enrollment after echocardiography had confirmed that LV ejection fraction was ≤50%. Polysomnography was performed after written informed consent had been obtained within 1 week after baseline echocardiography including LV ejection fraction measurement as described below.

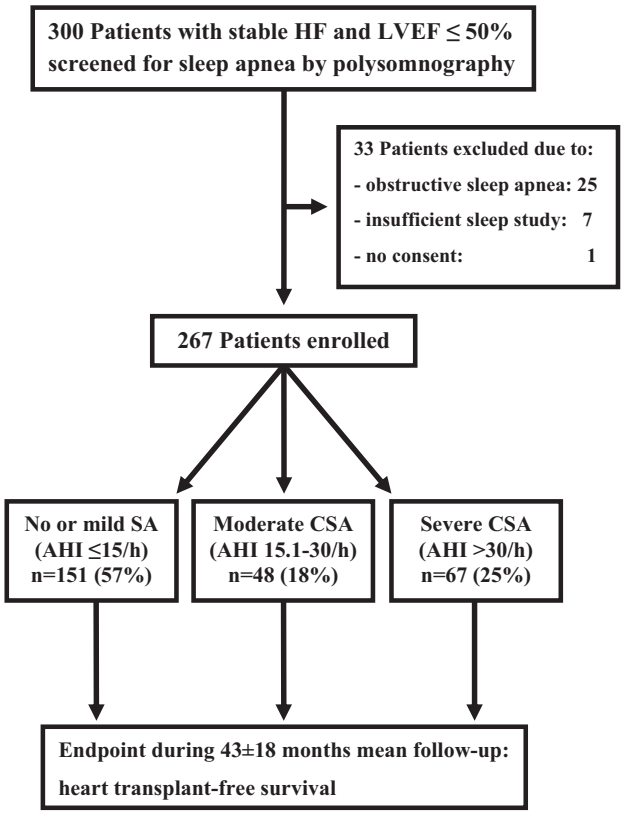

Fig. 1. Study profile. AHI, apnea/hypopnea index; CSA, central sleep apnea; HF, heart failure; LVEF, left ventricular ejection fraction.

Polysomnography

Unattended overnight cardiorespiratory polysomnography was performed during 1 night with the use of Somnocheck 2 R&K instruments (Weinmann, Hamburg, Germany) and analyzed according to the recommendations of the American Academy of Sleep Medicine.[29] Somnocheck 2 R&K is a 24-channel device to perform full polysomnography. The device includes flow measurement with the use of a nasal cannula and a respiratory flow sensor, a thorax and abdominal piezo belt to measure thoracoabdominal excursions, finger sensors for continuous measurement of oxygen saturation, blood pressure measurement, and position sensor, electrocardiograph electrodes, electromyograph electrodes at chin and leg, 3 electroencephalograph electrodes, and 2 electrooculograph electrodes. All measurements of the Somnocheck 2 R&K device were stored on an integrated, interchangeable compact flash card. The Somnocheck 2 R&K device was applied by sleep technicians in the evening before polysomnography, and the patients stayed overnight unattended in the hospital in a regular bedroom outside of the sleep laboratory. In the next morning, the Somnocheck 2 R&K device was removed by a sleep technician, and all data for a complete polysomnography were retrieved from the integrated compact flash memory card, visualized, and analyzed with the use of special software (Somnolab version 2.01 and Somnoligica version 3.3.1). All polysomnography recordings were scored by a sleep technician and with the sleep technician's scoring being overread by a sleep medicine physician, both of whom were unaware of the patients' clinical characteristics. The sleep technician who applied the Somnocheck 2 R&K device also routinely assessed daytime sleepiness with the use of the Epworth Sleepiness Scale in conjunction with polysomnography. Standard definitions were used for sleep-related disordered breathing.[29,30] An apnea was defined as cessation of inspiratory airflow >10 s. The number of apneas and hypopneas per hour of sleep is referred to as apnea/hypopnea index (AHI). No or mild sleep apnea was diagnosed in the presence of an AHI ≤15/h. An AHI >15/h but ≤30/h defined the presence of moderate sleep apnea. Severe sleep apnea was diagnosed in the presence of an AHI >30/h.[30] CSA was defined as the absence of rib cage and abdominal excursions with absence of airflow. OSA was defined as the absence of airflow in the presence of rib cage and abdominal excursions. Similarly to most previous studies, CSA was diagnosed when the number of central apneas was >50% of all apnea events.[1,2,6,8,9,11,23,30]

Echocardiography

Two-dimensional echocardiographic examinations were performed in all patients with the use of a Vingmed Vivid Seven machine (General Electronics Medical Systems, Solingen, Germany) to determine left atrial diameter, LV ejection fraction, and LV size. LV ejection fraction was measured in the apical 4-chamber view and orthogonal 2-chamber view by means of the disc summation method (modified Simpson rule algorithm). Echocardiography was performed within 1 week of study enrollment after the patient had been stable without change in HF medication for ≥4 weeks.

Kidney Function

Kidney function was assessed at study entry within 1 week of polysomnography by means of the eGFR with the use of the Modification of Diet in Renal Disease formula.[31,32]