Relationship Between β-Blocker Treatment and the Severity of Central Sleep Apnea in Chronic Heart Failure*

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Background: **We sought to examine the relationship between use of β-blockers and the severity of central sleep apnea (CSA) in patients with chronic heart failure.**

Methods: **We performed polysomnography in 45 patients with chronic heart failure (New York Heart Association functional class II/III and left ventricular ejection fraction < 50%) and examined the relationship between use of β-blockers and the severity of CSA. Central apnea index (CAI) was used as an indicator of CSA.**

Results: **Patients receiving β-blockers (*ie*, carvedilol; n = 27) had lower apnea-hypopnea index (AHI) and CAI than patients not receiving β-blockers (n = 18) [mean ± SD, 14 ± 11 vs 33 ± 17, p < 0.0001; and 1.9 ± 3.2 vs 11 ± 12, p = 0.0004, respectively]. AHI and CAI were negatively correlated with the dose of carvedilol (Spearman ρ = − 0.61, p < 0.0001; and Spearman ρ = − 0.57, p = 0.0002, respectively). Multiple regression analysis selected no use of β-blockers as an independent factor of CAI (p = 0.0006). In five patients with CAI > 5 who underwent serial sleep studies, CAI decreased significantly after 6 months of treatment with carvedilol (9.5 ± 4.9 to 1.3 ± 2.4, p = 0.03).**

Conclusions: **In patients with chronic heart failure, CAI was lower according to the dose of β-blockers, and no use of β-blockers was independently associated with CAI. In addition, 6 months of treatment with carvedilol decreased CAI. These results suggest that β-blocker therapy may dose-dependently suppress CSA in patients with chronic heart failure.**

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Key words: β-blocker; central sleep apnea; chronic heart failure

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; AHI = apnea-hypopnea index; ARB = angiotensin II receptor blocker; BNP = brain natriuretic peptide; CAI = central apnea index; CSA = central sleep apnea; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OAI = obstructive apnea index

Previous epidemiologic studies[1–4] have shown that 30 to 50% of patients with chronic heart failure due to left ventricular systolic dysfunction have central sleep apnea (CSA). CSA has been shown to be associated with increased mortality in patients with chronic heart failure.[5–8] The following mechanisms responsible for the initiation and maintenance of CSA in chronic heart failure have been proposed: enhanced central and peripheral chemosensitivity to CO_2[9,10]; prolonged circulation time, which produces a time delay between changes in blood gas tensions in the lung and their detection in the chemoreceptors[11,12]; and stimulation of pulmonary vagal irritant receptors by pulmonary congestion.[13–16] It has been believed that enhanced central chemosensitivity to CO_2 is a major determinant of CSA in chronic heart failure,[8] and it has been shown that activation of the sympathetic nervous system, which is observed in severe chronic heart failure, results in enhanced central chemosensitivity to CO_2.[17–22] Therefore,

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β-blocker therapy may reduce the severity of CSA in patients with chronic heart failure. In this study, we examined the relationship between use of β-blockers and the severity of CSA in patients with chronic heart failure.

Materials and Methods

Patients

Between January 2004 and May 2005, 45 consecutive patients (31 men and 14 women; mean age ± SD, 64 ± 13 years) with chronic heart failure who were admitted to our hospital and who met the following criteria were enrolled into this study. Inclusion criteria were chronic heart failure with New York Heart Association (NYHA) functional class II or III and left ventricular ejection fraction (LVEF) < 50%. Exclusion criteria were previous cerebrovascular disease, recent (< 6 months) acute coronary syndrome, or chronic respiratory disease. The reasons for admission to our hospital were a diagnosis of underlying heart disease together with the induction of β-blockers (n = 14) and sleep studies (n = 31). The etiology of chronic heart failure was idiopathic dilated cardiomyopathy in 25 patients and previous myocardial infarction in 20 patients. The study protocol was approved by the ethics committee at our institution, and informed consent was obtained from each patient before the study.

Polysomnography

Overnight polysomnography was performed using a computerized system (E-series; Compumedics Limited; Abbotsford, Australia). This investigation consisted of monitoring of the EEG, electrooculogram, submental electromyogram, ECG, thoracoabdominal excursions, oronasal airflow by an airflow pressure transducer, and arterial oxygen saturation by pulse oximetry. A central apnea was defined as an absence of oronasal airflow during sleep for ≥ 10 s associated with absent respiratory effort. An obstructive apnea was defined as an absence of oronasal airflow for ≥ 10 s in the presence of out-of-phase thoracoabdominal effort. Hypopnea was defined as a ≥ 50% reduction in oronasal airflow for ≥ 10 s associated with a ≥ 3% fall in oxygen saturation. The apnea-hypopnea index (AHI) was calculated as the mean number of apneas and hypopneas per hour of sleep. Also, the central apnea index (CAI) or obstructive apnea index (OAI) were calculated as the mean number of central or obstructive apneas, respectively. As a central hypopnea cannot be easily distinguished from an obstructive hypopnea, CAI was used as an indicator of CSA.

Echocardiography

Echocardiography was performed using standard techniques with an ultrasound system (model SSD-5500; Aloka; Tokyo, Japan). LVEF was calculated using a modification of the Simpson rule.[23]

Measurements of Plasma Brain Natriuretic Peptide Levels

Plasma brain natriuretic peptide (BNP) levels were measured using a specific immunoradiometric assay for human BNP (Shinoria BNP kit; Shionogi; Osaka, Japan).

Statistical Analysis

Continuous variables are expressed as mean ± SD and were analyzed by the Mann-Whitney *U* test or paired *t* test. Categorical data were analyzed using Fisher exact test or χ^2 test. Spearman correlation analysis was performed to estimate correlations between AHI or CAI and the dose of carvedilol or plasma BNP levels. Multiple regression analysis was performed to determine factors related to CAI. The variables used for the analysis were age, gender, body mass index, etiology of chronic heart failure, NYHA functional class, LVEF, BNP levels, Pa_{O_2}, Pa_{CO_2}, use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), and use of β-blockers. A p value < 0.05 was considered statistically significant.

Results

Clinical characteristics of patients studied are shown in Table 1. The β-blocker administered was carvedilol. Of 18 patients not receiving β-blockers, 14 patients received β-blockers at a later time, and 4 patients were not treated with β-blockers because of hypotension and bradycardia. Patients receiving β-blocker treatment (n = 27) had lower AHI and CAI than those not receiving β-blocker treatment (n = 18) [14 ± 11 vs 33 ± 17, $p < 0.0001$; and 1.9 ± 3.2 vs 11 ± 12, $p = 0.0004$, respectively]. There were no significant differences in age, gender, body mass index, etiology of chronic heart failure, NYHA functional class, LVEF, BNP levels, Pa_{O_2}, Pa_{CO_2}, OAI, and use of other cardiovascular drugs between patients with and without β-blocker treatment.

The dose of carvedilol was negatively correlated with AHI (Spearman $\rho = -0.61$, $p < 0.0001$) and CAI (Spearman $\rho = -0.57$, $p = 0.0002$) [Fig 1]. No patients who were treated with ≥ 10 mg/d of carvedilol had CAI > 5. Plasma BNP levels were positively correlated with CAI (Spearman $\rho = 0.30$, $p = 0.047$) but not with AHI (Spearman $\rho = 0.21$, $p = 0.18$) [Fig 2]. Multiple regression analysis selected no use of β-blockers as an independent factor of CAI ($p = 0.0006$) [Table 2].

Five patients (four men and one woman; mean age, 72 ± 5.1 years) with CAI > 5 underwent polysomnography 6 months after the induction of carvedilol. After treatment with carvedilol, AHI and CAI decreased significantly (28.8 ± 7.5 to 12.4 ± 9.1, $p = 0.02$; and 9.5 ± 4.9 to 1.3 ± 2.4, $p = 0.03$, respectively) [Fig 3]. However, OAI did not change significantly (1.8 ± 1.4 to 1.4 ± 1.5, $p = 0.54$).

Discussion

The major findings of the present study are as follows: (1) patients with chronic heart failure receiving β-blocker therapy had lower AHI and CAI than patients not receiving β-blocker therapy; (2) the dose of carvedilol was negatively correlated with AHI and CAI; (3) the multiple regression analysis selected no