Carvedilol Reduces the Severity of Central Sleep Apnea in Chronic Heart Failure

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Background Carvedilol may reduce the severity of central sleep apnea (CSA) in patients with chronic heart failure (CHF).

Methods and Results This study prospectively examined the effect of carvedilol on the severity of CSA in patients with CHF. Polysomnographic findings, left ventricular (LV) function, and plasma brain natriuretic peptide (BNP) level were evaluated before and 6 months after induction of carvedilol in 16 patients with CHF (New York Heart Association functional class II or III and LV ejection fraction <50%) who had CSA (central apnea index [CAI] >5 with dominant central apneic events). All patients tolerated carvedilol. The 6-month treatment with carvedilol increased the LV ejection fraction ($32\pm 7.4\%$ to $45\pm 9.8\%$, $P<0.001$) and decreased the BNP level (159 [69–458] pg/ml to 38 [16–193] pg/ml, $P=0.017$). The polysomnographic findings showed that the treatment decreased the apnea–hypopnea index (34 ± 13 to 14 ± 13 , $P=0.003$) and CAI (13 ± 11 to 1.9 ± 4.3 , $P<0.001$), whereas it increased the obstructive apnea index (1.1 ± 1.5 to 3.1 ± 3.4 , $P=0.04$).

Conclusion This preliminary study shows that treatment with carvedilol reduces the severity of CSA in patients with CHF, but that episodes of obstructive sleep apnea sometimes increase after the treatment. (Circ J 2009; 73: 295–298)

Key Words: Carvedilol; Central sleep apnea; Chronic heart failure

Previous studies have shown that central sleep apnea (CSA) occurs in 30–50% of patients with chronic heart failure (CHF) due to left ventricular (LV) systolic dysfunction^{1–4} and that CSA is associated with increased morbidity and mortality in those patients^{5–8}. Our study involving 44 patients with CHF recently demonstrated that (1) patients taking β -blockers (carvedilol) had a lower central apnea index (CAI) than those not taking them, (2) the dose of β -blockers was negatively correlated with the CAI, and (3) no use of β -blockers was independently associated with a higher CAI⁹. These results suggest that β -blockers may suppress CSA in a dose-dependent manner in patients with CHF. Accordingly, we prospectively examined the effect of carvedilol on the severity of CSA in 16 patients with CHF.

Methods

Study Population

Eligible patients with stable CHF who met the following criteria were considered for enrollment and underwent overnight polysomnography: age >20 years, not being treated with β -blockers, ischemic or idiopathic dilated cardiomyopathy, stable symptoms of CHF (New York Heart Association functional class II or III) within the preceding 2 months, and an LV ejection fraction (LVEF) <50%. The exclusion criteria were recent (<6 months) acute coronary syndrome,

resting angina, other concomitant heart disease, systolic blood pressure <100 mmHg, bradycardia (<50 beats/min), 2nd or 3rd degree atrioventricular block, life-threatening arrhythmia, previous cerebrovascular disease, neurological disease, chronic respiratory disease, Raynaud's phenomenon, and peripheral artery disease. Patients who had a CAI >5 with dominant central apneic events on overnight polysomnography were finally enrolled in the study. The study protocol was approved by the institutional ethics committee, and informed consent was given by each patient before the study.

Study Protocol

All patients began taking carvedilol during hospitalization, initially 1.25 mg twice daily, with the dose increasing stepwise at 1- or 2-week intervals to reach 10 mg twice daily or the maximum tolerated dose of <10 mg twice daily. Patients then took carvedilol at a fixed dose. Overnight polysomnography was performed 6 months after induction of carvedilol. In addition, echocardiography and measurement of the plasma BNP level were performed before and 6 months after induction of carvedilol. Other cardiovascular medications were unchanged during the study.

Polysomnography

Overnight polysomnography was performed using a computerized system (E-series; Compumedics Ltd, Abbotsford, Vic., Australia) that consisted of monitoring of the electroencephalogram, electro-oculogram, submental electromyogram, electrocardiogram, chest and abdominal movement using respiratory effort bands, oronasal airflow by an airflow pressure transducer, and arterial oxyhemoglobin saturation (SpO₂) by pulse oximetry. A central apnea was defined as the absence of oronasal airflow for ≥ 10 s associated with an absent inspiratory effort. An obstructive apnea was defined as the absence of oronasal airflow for ≥ 10 s associated with

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Table 1 Patients' Characteristics

<i>n</i>	16
Age (years)	63±15
Men	12 (75)
Body mass index (kg/m ²)	23±3.0
Hypertension	12 (75)
Diabetes mellitus	3 (19)
Current smoker	1 (6)
Dyslipidemia	14 (88)
Basic heart disease	
Idiopathic dilated cardiomyopathy	13 (81)
Previous myocardial infarction	3 (19)
Chronic atrial fibrillation	1 (6)
NYHA functional class	
II	1 (6)
III	15 (94)
LVEF (%)	32±7.4
BNP (pg/ml)	159 (69–458)
Polysomnography	
AHI	34±13
CAI	13±11
OAI	1.1±1.5
Loop diuretics	15 (94)
Spironolactone	13 (81)
ACEI	2 (13)
ARB	10 (63)
Digitalis	3 (19)

Data are mean±SD, median (first-third quartiles), or *n* (%).

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

continued or increased inspiratory effort. A hypopnea was defined as ≥50% reduction in oronasal airflow for ≥10s associated with ≥3% fall in SpO₂. The apnea-hypopnea index (AHI) was calculated as the mean number of apneic and hypopneic episodes per hour of sleep. In addition, the CAI or obstructive apnea index (OAI) was calculated as the mean number of central or obstructive apneic episodes, respectively. Since a central hypopnea cannot be easily distinguished from an obstructive hypopnea,¹⁰ CAI was used as an indicator of CSA.

Echocardiography

Echocardiography was performed using the standard techniques. The LVEF was calculated using a modification of Simpson's rule.¹¹

Measurement of Plasma Brain Natriuretic Peptide (BNP) Level

The plasma BNP level was measured using a specific immunoradiometric assay (Shinoria BNP kit; Shionogi Co Ltd, Osaka, Japan).

Statistical Analysis

The data are expressed as the means±SD, median (first-third quartiles), or number (%). Continuous variables were analyzed by the paired t-test or the Wilcoxon signed-rank sum test. Spearman's rank correlations were used to examine any correlations between the continuous variables. A P-value <0.05 was considered statistically significant. All analyses

Fig1. Changes in the left ventricular ejection fraction (LVEF) and the brain natriuretic peptide (BNP) levels before and 6 months after induction of carvedilol.

Fig2. Changes in the apnea-hypopnea index (AHI), central apnea index (CAI), and obstructive apnea index (OAI) before and 6 months after induction of carvedilol.

Fig 3. Associations of % changes in the central apnea index (CAI) or % changes in left ventricular ejection fraction (LVEF) before and 6 months after induction of carvedilol and % changes in plasma brain natriuretic peptide (BNP) levels before and 6 months after the induction.

were performed using SPSS 12.0J for Windows (SPSS Inc, Tokyo, Japan).

Results

A total of 16 patients (12 men, 4 women, age 63 ± 15 years) were enrolled and their characteristics are shown in **Table 1**. The etiology of CHF was idiopathic dilated cardiomyopathy in 13 patients and previous myocardial infarction in 3 patients. The frequency of hypertension, diabetes, current smoker, and dyslipidemia was 75%, 19%, 6%, and 88%, respectively. Loop diuretics, spironolactone, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and digitalis had been prescribed for 94%, 81%, 13%, 63%, and 19% of the patients, respectively.

All patients tolerated carvedilol; the maintenance dose ranged from 10 to 20 mg/day. There were no significant differences in the body mass index or total sleep time before and 6 months after induction of carvedilol (23 ± 3.0 kg/m² vs 23 ± 3.4 kg/m² and 332 ± 83 min vs 340 ± 65 min, respectively). Treatment with carvedilol increased the LVEF significantly ($32 \pm 7.4\%$ to $45 \pm 9.8\%$, $P < 0.001$) and decreased the BNP level significantly (159 [69–458] pg/ml to 38 [16–193] pg/ml, $P = 0.017$) (**Fig 1**). The treatment decreased the AHI and CAI significantly (34 ± 13 to 14 ± 13 , $P = 0.003$ and 13 ± 11 to 1.9 ± 4.3 , $P < 0.001$, respectively), and increased the OAI significantly (1.1 ± 1.5 to 3.1 ± 3.4 , $P = 0.04$) (**Fig 2**). The % changes in the CAI before and 6 months after induction of carvedilol did not correlate significantly with either the % changes in the LVEF or the % changes in the BNP levels before and 6 months after induction ($r = -0.12$, $P = 0.65$ and $r = -0.19$, $P = 0.49$, respectively) (**Fig 3**).

Discussion

Little information is available regarding the effects of standard medical therapy on CSA in patients with CHF. Tremel et al reported that the AHI did not change significantly after 2 months of optimal medical treatment in 15 patients who had been diagnosed as having CSA on polysomnography at 1 month after recovering from acute pul-

monary edema caused by LV systolic failure.¹² Their results contradict the results of the present study, which indicate that carvedilol reduces the severity of CSA in patients with CHF. The exact reasons for this discrepancy are unclear, but 2 months of medical treatment might be too short to evaluate the long-term effect of the treatment on CSA in patients with CHF. In addition, there was no description of the use or dose of β -blockers in that study.

The exact mechanisms by which carvedilol reduces the severity of CSA in patients with CHF are unclear, but the following are assumed. First, carvedilol could restore the enhanced central chemosensitivity to CO₂, resulting in suppression of CSA in patients with CHF. It is thought that enhanced central chemosensitivity to CO₂ plays a major role in the genesis of CSA in patients with CHF.¹³ In a study involving 6 healthy volunteers, Takahashi et al demonstrated that intravenous administration of isoproterenol increases the hypercapnic ventilatory response, which is an index of the central chemosensitivity to CO₂, and that intravenous administration of propranolol decreases the response.¹⁴ However, there is no evidence that carvedilol indeed restores the enhanced central chemosensitivity to CO₂ in CHF patients with CSA. Therefore, further investigations are required to clarify this point. Second, carvedilol could reduce the severity of CSA through its favorable effects on LV function in patients with CHF. Pulmonary vagal afferent nerve stimulation caused by pulmonary congestion results in brief central apnea followed by tachypnea and hyperventilation, contributing to the genesis of CSA in patients with CHF.^{15–18} Prolonged circulation time between the lungs and the chemoreceptors because of low cardiac output affects the length of both the hyperpneic phase and the total periodic breathing cycle,^{9,20} contributing to the maintenance of CSA in patients with CHF. Therefore, improvement in LV function could lead to a reduction in the severity of CSA. Solin et al demonstrated a significant reduction in the AHI associated with a significant fall in pulmonary capillary wedge pressure after intensive medical and/or nasal continuous positive airway pressure therapy in 7 patients with CHF and CSA, although they did not investigate the association between changes in the AHI and those

in pulmonary capillary wedge pressure before and after therapy.¹⁸ In the present study, the % changes in the CAI before and 6 months after induction of carvedilol did not correlate significantly with either the % changes in the LVEF or the % changes in BNP level before and after the treatment. However, the sample size of the present study was very small, so it cannot be denied that the improvement in LV function is associated with a reduction in the severity of CSA. The association between the reduction in the severity of CSA and the improvement in the indexes of cardiac function, including pulmonary capillary wedge pressure, remains to be further investigated.

Of interest, in the present study, treatment with carvedilol increased the OAI significantly, although the exact mechanisms for this phenomenon are unclear. Preexisting obstructive sleep apnea that had been masked by CSA might have appeared after the treatment and this phenomenon requires further detailed investigation.

Study Limitations

First, the sample size was very small, so further studies with a large population are needed to confirm the results. Second, we did not have a control group (ie, patients without carvedilol treatment). Because β -blocker treatment is already established as a standard therapy for CHF, no treatment with β -blockers for patients with CHF would not be ethically allowed. Third, the present study included patients with stable symptoms of CHF within the preceding 2 months of the study. The registration of patients with a longer period of stable symptoms would be more optimal: the natural time course of CHF or the therapeutic history for CHF may have, to a lesser degree, affected the results of the present study. Fourth, it is unclear whether other types of β -blockers are as effective against CSA as carvedilol. Finally, the dose of carvedilol used in the present study was smaller than that generally used in Western countries. However, the MUCHA trial demonstrated that 5–20 mg/day of carvedilol is recommended for the treatment for Japanese patients with CHF.²¹ This difference in dosage is assumed to be because β_1 -receptor sensitivity is higher in Asian than in Caucasians or African-Americans.²²

Conclusions

The present study shows that treatment with carvedilol reduces the severity of CSA in patients with CHF, but that episodes of obstructive sleep apnea sometimes increase after the treatment.

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