Washout Rate of Cardiac Iodine-123 Metaiodobenzylguanidine is High in Chronic Heart Failure Patients With Central Sleep Apnea

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ABSTRACT

Background: The association between sleep-disordered breathing (SDB) assessed by polysomnography and cardiac sympathetic nerve activity (SNA) assessed by cardiac iodine-123 metaiodobenzylguanidine (123I-MIBG) imaging has not been investigated in patients with chronic heart failure (CHF).

Methods and Results: We performed cardiac 123I-MIBG scintigraphy and overnight polysomnography in 59 patients with stable CHF. The patients were classified into the 3 groups: 19 with no or mild SDB (NM-SDB, apnea-hypopnea index <15); 21 with central sleep apnea (CSA), and 19 with obstructive sleep apnea (OSA). The cardiac washout rate (WR) of 123I-MIBG was obtained from initial and delayed planar 123I-MIBG images. The WR was higher in patients with CSA (54.2 $\pm$ 11.6%) than in those with OSA (37.9 $\pm$ 8.6%, $P < .05$) or NM-SDB (40.8 $\pm$ 8.8%, $P < .05$). The WR correlated positively with central apnea index ($\rho = 0.40$, $P = .002$). A stepwise multiple regression analysis selected CSA and plasma brain natriuretic peptide levels as independent variables associated with the WR.

Conclusions: The WR was higher in CHF patients with CSA than in those with OSA or NM-SDB, and CSA was independently associated with the WR, suggesting a link of CSA to increased cardiac SNA in CHF. (*J Cardiac Fail 2010;16:728–733*)

Key Words: Iodine-123 metaiodobenzylguanidine, washout rate, sympathetic nerve activity, sleep-disordered breathing, central sleep apnea, obstructive sleep apnea, chronic heart failure.

In patients with chronic heart failure (CHF), sympathetic nerve activity (SNA) is initially increased as a compensatory mechanism, but chronically increased SNA itself is deleterious to the failing heart, leading to progression of CHF.[1–3] Central sleep apnea (CSA) associated with Cheyne-Stokes respiration is commonly observed in patients with CHF[4–10] and may be associated with increased morbidity and mortality in those patients.[11–16] Previous studies have shown that circulating norepinephrine levels[17,18] and muscle sympathetic nerve burst during wakefulness[19] are greater in CHF patients with CSA than in those without it. Furthermore, in a study using norepinephrine isotope dilution methodology, Mansfield et al[20] demonstrated that CHF patients with CSA have higher systemic (total body) and cardiac norepinephrine spillover than those with obstructive sleep apnea (OSA) or without sleep-disordered breathing (SDB).

Cardiac iodine-123 metaiodobenzylguanidine (123I-MIBG) imaging is a useful tool for estimating cardiac SNA and predicting an adverse prognosis in patients with CHF.[21] Little information is, however, available with regard to the association between SDB and findings of 123I-MIBG images in patients with CHF.[22,23] Meguro et al[22] reported that the washout rate (WR) of 123I-MIBG, an index of the magnitude of cardiac sympathetic drive,[21] was significantly higher in dilated cardiomyopathy patients with CSA than in those without it. However, they performed polysomnography or portable monitoring in only 14 (67%) patients with a 4% oxygen desaturation index ≥ 5 on pulse

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oximetry. Therefore, some patients who were diagnosed as not having CSA might have had CSA. Furthermore, their study did not include CHF patients with OSA. Nanjo et al[23] reported that the WR was significantly higher in dilated cardiomyopathy patients with SDB than in those without it. However, they evaluated the presence or absence of SDB using pulse oximetry, but not polysomnography. Thus, the exact association between SDB assessed by polysomnography and the WR remains unclear in patients with CHF, and no information is available as to whether there is any difference in the WR between CHF patients with CSA and those with OSA. In this study, we sought to clarify the association between SDB assessed by polysomnography and cardiac SNA assessed by 123I-MIBG images in patients with CHF from left ventricular (LV) systolic dysfunction.

Methods

Study Population

The protocol of the present study was shown in Fig. 1. Eligible patients with CHF were admitted to Oita University Hospital and underwent plasma brain natriuretic peptide (BNP) measurements, echocardiography, polysomnography, and cardiac 123I-MIBG scintigraphy. The inclusion criteria were age >20 years, ischemic or idiopathic dilated cardiomyopathy, New York Heart Association (NYHA) functional Class II or III, no changes in medications and symptoms of heart failure for preceding 2 months, and left ventricular ejection fraction (LVEF) $\leq$45%. The exclusion criteria were recent ($<$6 months) acute coronary syndrome, previous cerebrovascular diseases, neurological diseases, chronic pulmonary diseases, chronic renal failure, nonpharmacological treatment for SDB, including nasal continuous positive airway pressure, nocturnal oxygen therapy, or adaptive servo-ventilation, and use of tricyclic antidepressant drugs. In addition, the present study excluded patients in whom β-blocker treatment was planning to be initiated. The study protocol was approved by the ethics committee at Oita University Hospital, and informed consent was obtained from each patient before the study.

Polysomnography

Overnight polysomnography was performed using a computerized system (E-series; Compumedics Ltd, Abbotsford, Australia). This investigation consisted of monitoring of the electroencephalogram, electro-oculogram, submental electromyogram, electrocardiogram, chest and abdominal movement using a piezo band, airflow by a nasal pressure transducer and an oronasal thermistor, and arterial oxyhemoglobin saturation by pulse oximetry (SpO_2). Polysomnograms were manually evaluated by an experienced physician. A central apnea was defined as an absence of oronasal airflow for $\geq$10 seconds, associated with an absent inspiratory effort. An obstructive apnea was defined as an absence of oronasal airflow for $\geq$10 seconds, associated with continued or increased inspiratory effort. Hypopnea was defined as a $\geq$50% reduction in oronasal airflow for $\geq$10 seconds, associated with a $\geq$3% fall in SpO_2 or an arousal. The apnea-hypopnea index (AHI) and hypopnea index (HI) was calculated as the mean number of apneas and hypopneas per hour of sleep and the mean number of hypopneas per hour of sleep, respectively. The central apnea index (CAI) was calculated as the mean number of central apneas per hour of sleep, and the obstructive apnea index (OAI) was calculated as the mean number of obstructive apneas per hour of sleep. Because obstructive hypopneas cannot be definitely distinguished from central hypopneas, we did not calculate the central or obstructive HI. CSA was defined as an AHI $\geq$15 with CAI $>$OAI, and OSA was defined as an AHI $\geq$15 with OAI $>$CAI.

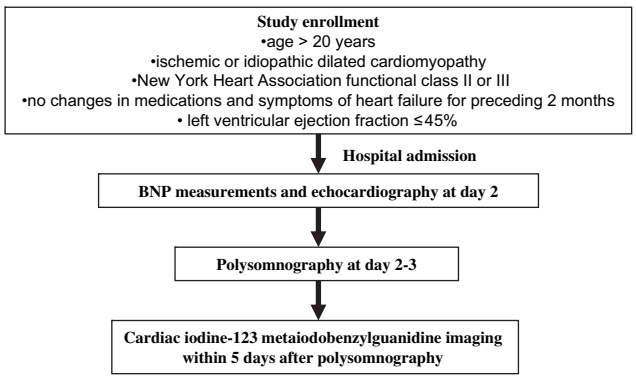

Fig. 1. The study protocol. BNP, brain natriuretic peptide.

Cardiac MIBG Imaging

Patients were placed in the supine position after an overnight fast. A dose of 111-MBq of 123I-MIBG (Fujifilm RI Pharma Co, Ltd, Tokyo, Japan) was intravenously injected and flushed with normal saline solution. 123I-MIBG images were obtained at 15 minutes (early) and 4 hours (delayed) after the injection, using a gamma camera equipped with a low- to medium-energy general-purpose collimator (E-CAM Signature, Toshiba Medical Systems, Tokyo, Japan). Anterior planar images were collected over 5 minutes in a 256 $\times$ 256 matrix. Energy discrimination was provided by a 15% window around the 159-keV photo peak 123I. LV 123I-MIBG activity was measured using a region of interest manually drawn around the LV myocardium, and the mean heart count per pixel (H) was calculated. Another region of interest was placed over the upper mediastinum, and the mean mediastinum count per pixel (M) was calculated. To evaluate the myocardium uptake of 123I-MIBG, the H/M ratio was calculated from early and delayed anterior planar 123I-MIBG images. The WR was calculated using the following formula without correction for the physical decay of 123I label: ([(H)-(M)]early $-$ [(H)-(M)]delayed) $\times$ 100/[(H)-(M)]early (%). The normal ranges of the early and delayed H/M ratios and the WR obtained from 15 normal controls (10 men and 5 women, mean age of 66.4 $\pm$ 10.1 years) at our hospital are 3.0 $\pm$ 0.3, 3.3 $\pm$ 0.3, and 28.2 $\pm$ 5.2%, respectively.

Echocardiography and Measurements of Plasma BNP Levels

Echocardiography was performed by standard techniques. LVEF was calculated using a modification of Simpson's rule.[24] Plasma BNP levels were measured using a specific immunoradiometric assay for human BNP (Shinoria BNP kit, Shionogi & Co, Ltd, Osaka, Japan). Venous blood samples for BNP measurements were taken after 20 minutes of rest in the supine position.

Statistical Analyses

Data are expressed as mean $\pm$ SD for the continuous variables. Comparisons of categorical data among the 3 groups were