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Assessment of central chemosensitivity and cardiac sympathetic nerve activity using I-123 MIBG imaging in central sleep apnea syndrome in patients with dilated cardiomyopathy

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Objective: Iodine-123 MIBG imaging has been used to study cardiac sympathetic function in various cardiac diseases. Central sleep apnea syndrome (CSAS) occurs frequently in patients with chronic heart failure (CHF) and is reported to be associated with a poor prognosis. One of the mechanisms of its poor prognosis may be related to impaired cardiac sympathetic activity. However, the relationship between chemosensitivity to carbon dioxide, which is reported to correlate with the severity of CSAS, and cardiac sympathetic activity has not been investigated. Therefore, this study was undertaken to assess cardiac sympathetic function and chemosensitivity to carbon dioxide in CHF patients. ***Methods:*** The oxygen desaturation index (ODI) was evaluated in 21 patients with dilated cardiomyopathy (male/female: 19/2, LVEF < 45%, 65 ± 12 yr). Patients with an ODI > 5 times/h underwent polysomnography. Patients with an apnea hypopnea index > 15/h but without evidence of obstructive apnea were defined as having CSAS. Early (15 min) and delayed (4 hr) planar MIBG images were obtained from these patients. The mean counts in the whole heart and the mediastinum were obtained. The heart-to-mediastinum count ratio of the delayed image (H/M) and the corrected myocardial washout rate (WR) were also calculated. The central chemoreflex was assessed with the rebreathing method using a hypercapnic gas mixture (7% CO_2 and 93% O_2). ***Results:*** Ten of the 21 patients had CSAS. The H/M ratio was similar in patients both with and without CSAS (1.57 ± 0.18 vs. 1.59 ± 0.14, p = 0.82). However, the WR was higher in patients with CSAS than in patients without CSAS (40 ± 8% vs. 30 ± 12%, p < 0.05). ODI significantly correlated with central chemosensitivity to carbon dioxide. Moreover, there was a highly significant correlation between WR and central chemosensitivity (r = 0.65, p < 0.05). However, there was no correlation between ODI and the WR (r = 0.36, p = 0.11). ***Conclusions:*** Cardiac sympathetic nerve activity in patients with CHF and CSAS is impaired. However, central sleep apnea might not directly increase cardiac sympathetic nerve activity. We suggest that central chemosensitivity, which is considered to be one of the mechanisms of CSAS, is correlated with cardiac sympathetic nerve activity.

Key words: central chemosensitivity, I-123 MIBG imaging, cardiac sympathetic nerve activity, sleep apnea syndrome

INTRODUCTION

IN PATIENTS with chronic heart failure (CHF), it has been demonstrated that plasma norepinephrine concentrations are increased and significantly correlate with mortality.[1] Furthermore, sympathetic nerve activity in CHF patients has been proposed to play a major role in CHF progression. Iodine 123 (^{123}I) metaiodobenzylguanidine (MIBG)

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is an analog of the adrenergic blocking agent guanethidine and shares many cellular transport properties with norepinephrine,[2] and ^{123}I-MIBG imaging has been used to study cardiac sympathetic nerve activity. Cardiac uptake of ^{123}I-MIBG and left ventricular ejection fraction have been shown to correlate,[3,4] and MIBG imaging can be a useful prognostic marker in patients with CHF.[4]

Central sleep apnea syndrome (CSAS), which is also known as Cheyne-Stokes respiration, occurs with a prevalence of about 50% in patients with CHF.[5–7] In addition, patients with CHF and CSAS have a poor prognosis compared with those without CSAS.[8,9]

Central and peripheral chemosensitivity play an important role in causing CSAS in patients with CHF.[10–12] Elevated chemoreceptor responsiveness destabilizes the respiratory control system, both by decreasing the prevailing $PaCO_2$ and by increasing the tendency to hyperventilate. In this situation, hyperventilation, decreased PaO_2 and arousal occur, and, through sympathetic nerve activation, increased catecholamine concentrations, increased heart rate and increased blood pressure occur. In patients with obstructive sleep apnea syndrome, cardiac sympathetic function is reported to be impaired.[13] However, cardiac sympathetic nerve activity assessed by ^{123}I-MIBG scintigraphy has not been investigated in CSAS and CHF patients.

Chemosensitivity to carbon dioxide plays an important role in causing the CSAS.[10–12] However, the mechanisms responsible for augmented chemosensitivity and the relationship between chemosensitivity and cardiac sympathetic nerve activity are not fully investigated. In the present study, we assessed chemosensitivity and cardiac sympathetic nerve activity in patients with CHF and CSAS using MIBG cardiac scintigraphy.

MATERIALS AND METHODS

Subjects

Twenty-one consecutive patients (19 men, 2 women; mean age: 65 ± 12 y) with CHF due to idiopathic dilated cardiomyopathy (DCM) were enrolled in this study (from April 2001 to April 2003). All patients had at least one episode of heart failure requiring short-term hospitalization, and had an echocardiographic left ventricular ejection fraction (LVEF) ≤45%. All patients gave informed consent in accordance with the guidelines of our hospital's Human Clinical Study Committee before participating in this study. The clinical condition of all patients was stable when they were enrolled.

Coronary angiography showed normal coronary arteries in all of the patients. Acute or chronic myocarditis was excluded in all patients based on the results of left ventricular endomyocardial biopsy. None of the patients was suspected of alcohol abuse. Moreover, congenital heart disease, valvular heart disease, and hypertensive heart disease were also excluded.

Measurement of ejection fraction

All patients underwent echocardiographic evaluation (SONOS 5500 or 2000, Philips Medical Systems, Andover, MA) and LVEF was calculated by the Simpson method.

Central chemosensitivity to carbon dioxide

Central hypercapnic chemosensitivity was assessed during rebreathing of carbon dioxide[14,15] in 14 patients (6 patients with CSAS and 8 patients without CSAS). Seven patients did not undergo this assessment. Patients rebreathed through a 6-liter bag containing a gas mixture of 7% carbon dioxide and 93% oxygen for 4 minutes. This examination was stopped rapidly if patients became too short of breath to continue or if the $P_{ET}CO_2$ exceeded 10%. This examination estimates the sensitivity of central chemoreceptors, since the peripheral hypercapnic response is known to be very small or negligible at high oxygen concentrations.[16] Breath-by-breath tidal volume and $P_{ET}CO_2$ were measured continuously using a gas analyzer (Minato AE300S, Minato Ikagaku, Osaka, Japan). The linear slope described by the relationship between ventilation and $P_{ET}CO_2$ was calculated using linear regression analysis and expressed in terms of liters per minute per millimeters of mercury (*l*/min/mm Hg).

Sleep study

All patients underwent pulse oxymetry (Pulsox-M24, TEIJIN, Tokyo, Japan) during the night. The oxygen desaturation index (ODI) was calculated, which was defined as the frequency of desaturations ≥4% in the arterial oxyhemoglobin saturation per hour, and the ODI was used to evaluate the severity of sleep apnea.[17] Patients with an ODI < 5 times per hour were not felt to have sleep apnea syndrome (SAS) (7 patients). If a patient had an ODI ≥ 5 times per hour (14 patients), the patient underwent further evaluation with polysomnography (PS2 plus, Compumedics Sleep pty, Victoria, Australia) or using a computerized sleep apnea diagnosis set (Morpheus, TEIJIN, Tokyo, Japan) to evaluate the presence of SAS and to exclude obstructive SAS.

Polysomnography was performed in 6 patients. The electroencephalogram, body position, eye and leg movements, electrocardiogram, nasobuccal air flow, chest and abdominal effort, and pulse oximetry were recorded. An episode of apnea was defined as cessation of airflow for at least 10 seconds. A computerized sleep apnea diagnosis set was performed in the other 8 patients, which includes ECG measurements and measurements of nasobuccal air flow, chest and abdominal effort, and pulse oximetry. An episode of obstructive apnea was defined as the absence of airflow in the presence of rib-cage and abdominal excursion. An episode of central apnea was defined as not only the absence of airflow, but also the absence of both rib-cage and abdominal excursion. Hypopnea was defined as a reduction in airflow lasting at least 10 sec, which was accompanied by at least a 3% decrease in the arterial

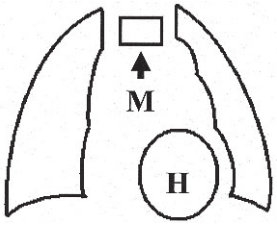

Fig. 1 Anterior planar image was obtained 15 minutes and 4 hours after I-123 MIBG intravenous injection. Cardiac I-123 MIBG uptake was quantified as the H/M activity ratio, with regions of interest positioned over the heart (H) and over the upper mediastinum (M).

Table 1 Demographics and clinical characteristics of CHF patients with and without central sleep apnea

	Patients with CSAS	Patients without CSAS	p value
Patients (women)	10 (1)	11 (1)	
Age (y)	69 ± 11	60 ± 13	0.13
Weight (kg)	61 ± 11	69 ± 15	0.22
Height (cm)	162 ± 5	163 ± 7	0.91
BMI (kg/m^2)	23 ± 4	26 ± 5	0.22
NYHA class II/III	7/3	9/2	0.53
LVEF (%)	25 ± 12	26 ± 8	0.76
ODI (times/h)	26 ± 6	6 ± 5	<0.01
Beta-blocker	9/10	10/11	0.94
ACEI or ARB	8/10	10/11	0.47

CSAS = central sleep apnea syndrome, BMI = body mass index, NYHA = New York Heart Association, LVEF = left ventricular ejection fraction, ODI = oxygen desaturation index, ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker.

oxyhemoglobin saturation.

The frequency per hour of episodes of apnea and hypopnea was defined as the apnea hypopnea index (AHI). Patients with obstructive sleep apnea ≥5 times per hour were excluded from the present study. Patients with an AHI ≥15 per hour were defined as patients with CSAS and the others were defined as patients without CSAS.[5]

^{123}I-MIBG scintigraphy

^{123}I-MIBG scintigraphy was used to evaluate the cardiac sympathetic nerve activity. The ^{123}I-MIBG was obtained commercially (Daiichi Radioisotope Laboratories, Chiba, Japan). The patients were injected intravenously with 111 MBq of ^{123}I-MIBG while in an upright position. Anterior planar images were acquired 15 min after injection and repeated 4 h later using a gamma camera (PRISM 300; Picker International, Cleveland, OH). Energy discrimination was provided by a 20% window around the 159-keV photo peak of ^{123}I. Using the anterior planar delayed ^{123}I-MIBG images, the heart-to-mediastinum (H/M) activity ratio was obtained with regions of interest positioned over the heart (H) and over the upper mediastinum (M) (Fig. 1).

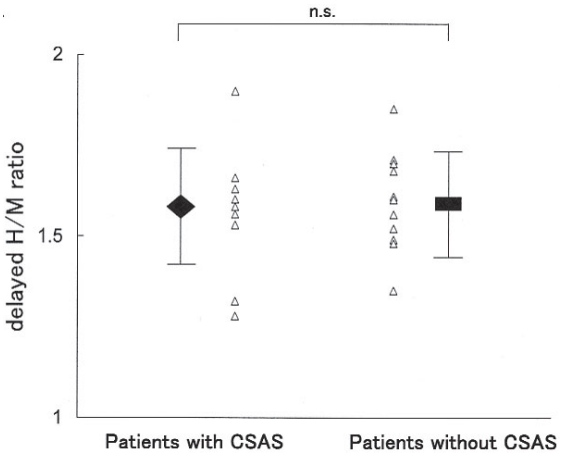

Fig. 2 Delayed H/M ratio for the ^{123}I-MIBG images in patients with and without CSAS. Black diamond represents mean ± SD of delayed H/M ratio in patients with CSAS. Black bar represents mean ± SD of delayed H/M ratio in patients without CSAS. There was no significant difference between patients with and without CSAS (1.57 ± 0.18 vs. 1.59 ± 0.14, p = 0.82).

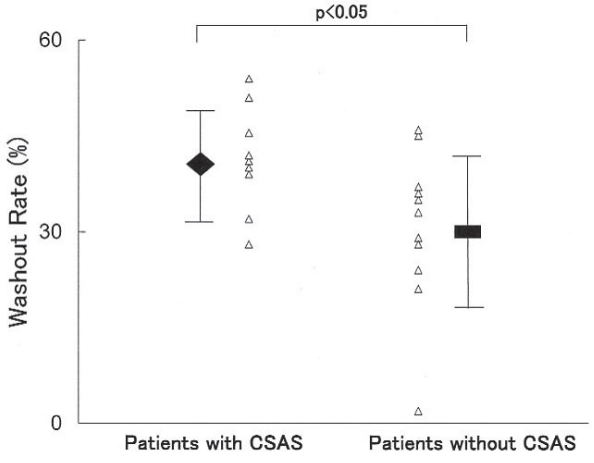

Fig. 3 Washout rate (WR) for the ^{123}I-MIBG images in patients with and without CSAS. Black diamond represents mean ± SD of WR in patients with CSAS. Black bar represents mean ± SD of WR in patients without CSAS. WR in patients with CSAS is significantly higher than that in patients without CSAS (40 ± 8% vs. 30 ± 12%, p < 0.05).

The washout rate (WR) was calculated using the following formula: $\{(H - M)_{early} - (H - M)_{delayed)}\}/(H - M)_{early} \times 100$.

Statistical analysys

All descriptive data are expressed as the mean ± SD. Unpaired Student's t tests were used to compare values in patients with and without CSAS. The χ^2 test was used to compare dichotomous variables. Correlations between the central chemosensitivity to carbon dioxide, WR and ODI were assessed by the Pearson least-squares correlation test. A value of $p < 0.05$ was considered statistically significant. All calculations were performed using

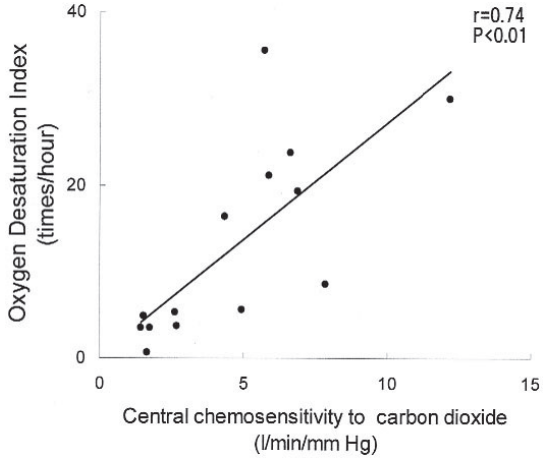

Fig. 4 Relationship between oxygen desaturation index and chemosensitivity to carbon dioxide. Central chemosensitivity to carbon dioxide was measured in 14 patients. ODI was significantly correlated with central chemosensitivity to carbon dioxide ($r = 0.74$, $p < 0.01$).

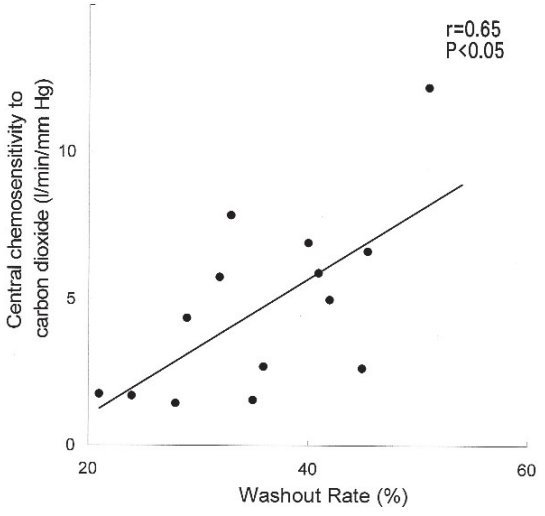

Fig. 5 Relationship between chemosensitivity and washout rate (WR) for the ^{123}I-MIBG images. Central chemosensitivity to carbon dioxide was measured in 14 patients. There was a significant correlation between central chemosensitivity to carbon dioxide and WR ($r = 0.65$, $p < 0.05$).

STATVIEW software, version 5.0 (SAS Institute Inc., Cary, NC).

RESULTS

Twenty-one patients were enrolled in this study. No one had obstructive SAS. Ten patients, 9 men and 1 woman, were patients with CSAS, and the remaining 11 patients, 10 men and 1 woman, were patients without CSAS. The ODI in patients with CSAS was significantly higher than that in patients without CSAS (26 ± 12 vs. 6 ± 5 times/h, $p < 0.01$). There were no significant differences between the two groups with respect to age, anthropometric data, severity of CHF, or medical therapy (Table 1).

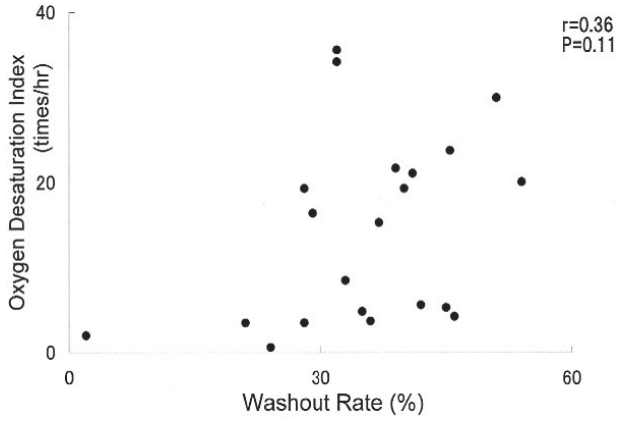

Fig. 6 Relationship between oxygen desaturation index and washout rate (WR) for the ^{123}I-MIBG images. No significant correlation between the ODI and the WR was observed ($r = 0.36$, $p = 0.11$).

The H/M ratios for the delayed ^{123}I-MIBG images in both groups did not show a significant difference (1.57 ± 0.18 vs. 1.59 ± 0.14, $p = 0.82$) (Fig. 2). In patients with CSAS, the WR was significantly higher (40 ± 8%) than that in patients without CSAS (30 ± 12%, $p < 0.05$) (Fig. 3).

ODI, which represents the severity of CSAS, was significantly correlated with central chemosensitivity to carbon dioxide (Fig. 4). There was a significant correlation between central chemosensitivity to carbon dioxide and the WR for the ^{123}I-MIBG images ($r = 0.65$, $p < 0.05$, Fig. 5). However, no correlation between the ODI and WR was observed ($r = 0.36$, $p = 0.11$, Fig. 6).

DISCUSSION

This is the first study to investigate cardiac sympathetic nerve activity in patients with DCM and SAS using ^{123}I-MIBG scintigraphy. There were two important findings in this study. First, cardiac sympathetic nerve activity in CHF and CSAS patients was activated to a greater extent than in patients without CSAS. Second, cardiac sympathetic nerve activity correlated with the central chemosensitivity to carbon dioxide, which is reported to be responsible for CSAS.

Myocardial scintigraphy with ^{123}I-MIBG, an analog of norepinephrine, has been reported to provide images that reflect cardiac sympathetic function. This is the first study to evaluate the influence of CSAS on cardiac sympathetic nerve activity using this method. The H/M activity ratio[3,4] and WR[18,19] are reported to be useful for evaluating cardiac sympathetic nerve activity. In this study the H/M ratio was similar in both groups. However, the WR was significantly higher in CSAS patients than in patients without CSAS. There are some controversies about the uptake ability of ^{123}I-MIBG in CHF patients. There are

some papers which support both normal and reduced neuronal uptake of norepinephrine by cardiac adrenergic nerves.[20–22] Moreover, in contrast to the H/M activity ratio, the WR is more useful as an index of sympathetic nerve activity because it is independent of the number of neurons available, whereas the H/M activity ratio is not.[18] Therefore, although we failed to show a significant difference in the H/M ratio between patients with and without CSAS, cardiac sympathetic nerve activity in patients with CHF and CSAS is considered to be impaired. ^{123}I-MIBG scintigraphy can be used to evaluate prognosis,[4] as well as the severity of CHF.[18,23] Augmented sympathetic nerve activity may be responsible for the poor prognosis of patients with CSAS and impaired exercise tolerance.[8,9,12]

It has been reported that enhanced chemosensitivity to carbon dioxide plays an important role in causing CSAS.[10,11] During sleep, the threshold for a ventilatory response to carbon dioxide increases[24] and apnea begins. During CSAS cycles, augmented chemosensitivity decreases the $PaCO_2$ below the apneic threshold, and breathing stops. As the $PaCO_2$ increases above the apnea threshold in the chemoreceptors, hyperpnea begins and drives the $PaCO_2$ below the apnea threshold. In the present study, ODI was significantly correlated with central chemosensitivity to carbon dioxide. Our finding supports these former reports.

Chemosensitivity to carbon dioxide is considered to be one of the most important mechanisms responsible for CSAS. However, the mechanisms underlying the augmentation of chemosensitivity are not fully understood. Some factors are reported to be responsible for the development of the augmented chemosensitivity. First, increased pulmonary vascular pressure, which stimulates J receptors and increases pulmonary vagal nerve activity, is reported to increase ventilation.[25–27] Second, elevated ventilatory responses may be secondary to enhanced sympathetic nerve activation.[28] It has been reported that minute ventilation increases after intravenous infusion of norepinephrine, which can be blocked by prior treatment with propranolol.[29] In this study, central chemosensitivity to carbon dioxide was significantly correlated with the WR of ^{123}I-MIBG scintigraphy. Two reasons for this result are possible. First, enhanced sympathetic nerve activity, which is reported to be correlated with the WR,[30] plays an important role in increasing chemosensitivity. Second, increased pulmonary vascular pressure increases ventilation through impaired cardiac function, which is reported to be correlated with the WR.[18,23]

Increased sympathetic nerve activity is correlated with mortality in patients with CHF[31] and occurs in association with apnea, hypoxemia, and arousal.[32,33] Patients with CSAS have a poor prognosis.[34,35] However, continuous positive airway pressure, which improves disordered breathing, has been reported to reduce sympathetic nerve activity.[36] In this study, we failed to show a significant correlation between WR and ODI, which represents the severity of CSAS. Two reasons for this result can be considerable. First, because the WR was significantly correlated with chemosensitivity, sleep disturbance may not have a strong influence on cardiac sympathetic nerve impairment contrary to obstructive SAS.[13] This might have been explained by a previous study, which showed that cardiac norepinephrine spillover did not correlate with apnea severity, but with pulmonary artery pressure.[28] Therefore, the severity of heart failure might be responsible for cardiac sympathetic nerve activation. Second, in this study the number of patients who underwent all of the examinations might not be sufficient to show a significant correlation.

Limitations of this study

In this study, not all of the patients underwent polysomnography. Polysomnography was used to distinguish patients with CSAS from patients with obstructive SAS and normal sleep patterns. ODI may not sufficiently reflect the severity of CSAS. In the future, we need to perform polysomnography in all of the patients.

The population of this study is small, and not all patients (14 patients participated) underwent measurement of central chemosensitivity to carbon dioxide. To demonstrate more accurately the pathophysiological mechanisms for CSAS in CHF patients, a larger population may be needed.

CONCLUSION

In conclusion, cardiac sympathetic nerve activity in patients with CHF and CSAS is impaired. However, central sleep apnea may not directly increase cardiac sympathetic nerve activity. In this study, we suggest that augmented cardiac sympathetic nerve activity might be one of the mechanisms responsible for augmented central chemosensitivity, which is considered to be one of the mechanisms of CSAS.

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