Clinical research
Heart failure/cardiomyopathy

Evaluation of cardiac sympathetic nerve activity and left ventricular remodelling in patients with dilated cardiomyopathy on the treatment containing carvedilol

Shu Kasama1*, Takuji Toyama1, Takashi Hatori1, Hiroyuki Sumino2, Hisao Kumakura2, Yoshiaki Takayama2, Shuichi Ichikawa2, Tadashi Suzuki1, and Masahiko Kurabayashi1

1Department of Cardiovascular Medicine, Gunma University School of Medicine, 3-39-15, Showa-machi, Maebashi, Gunma 371-0034, Japan and 2Department of Internal Medicine, Cardiovascular Hospital of Central Japan, Gunma, Japan

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Aims It has been reported that carvedilol improves cardiac sympathetic nerve activity (CSNA) in patients with dilated cardiomyopathy (DCM). However, the influence of carvedilol on cardiac 123I-meta-iodobenzylguanidine (MIBG) scintigraphic findings and left ventricular (LV) remodelling has not been determined in DCM patients.

Methods and results In 30 patients with DCM and 10 normal controls, the delayed heart/mediastinum count (H/M) ratio, delayed total defect score (TDS), and washout rate (WR) were determined by 123I-MIBG scintigraphy. In addition, the left ventricular end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV ejection fraction (LVEF) were calculated by echocardiography. In the DCM patients, the regional defect score index (RDSI), regional washout rate index (RWRI), and wall motion score index (WMSI) were also determined to evaluate regional adrenergic dysfunction and wall motion. Examinations were repeated in all DCM patients after standard treatment containing carvedilol at a dose of 10–20 mg/day (mean dose: 16 ± 4 mg/day) for a mean of 12 ± 1 months. Both the 123I-MIBG scintigraphic and echocardiographic parameters were significantly worse in the DCM patients than the normal control subjects. After treatment, all of these parameters improved significantly in the DCM patients. There was a significant correlation between the changes of 123I-MIBG findings and changes of the LVEDV and LVESV after treatment. Moreover, there was a significant correlation between changes of the WMSI and those of the RDSI or RWRI in DCM patients.

Conclusion Both 123I-MIBG scintigraphic parameters and echocardiographic parameters were improved in the DCM patients. There was a significant correlation between the changes of 123I-MIBG scintigraphic and echocardiographic findings after treatment. These findings implicate that long-term, including carvedilol, therapy can improve both CSNA and LV remodelling in patients with DCM.

KEYWORDS 123I-meta-iodobenzylguanidine; Dilated cardiomyopathy; Carvedilol

Introduction

The prognosis of patients with idiopathic dilated cardiomyopathy (DCM) remains poor. Activation of the sympathetic nervous system is one of the cardinal pathophysiological abnormalities associated with congestive heart failure (CHF). Since Waagstein et al. reported that some patients with decompensated CHF showed clinical improvement after administration of β-blockers, various studies have demonstrated that β-blocker therapy can have a beneficial effect in selected patients with CHF. Cardiac imaging with 123I-meta-iodobenzylguanidine (MIBG), an analogue of norepinephrine, is a useful tool for detecting abnormalities of the myocardial adrenergic nervous system in patients with CHF. A large number of studies have suggested that treatment of heart failure can improve cardiac sympathetic nerve activity (CSNA) in CHF patients, as demonstrated by cardiac 123I-MIBG scintigraphy. The third-generation β-blocker carvedilol has been reported to improve CSNA in a rat model of DCM as well as in DCM patients with heart failure. However, the effect of carvedilol on cardiac 123I-MIBG scintigraphic parameters and left ventricular (LV) remodelling has not been determined in patients with DCM.

Accordingly, the present study was performed to evaluate whether standard treatment containing carvedilol could improve both CSNA and LV remodelling in patients with idiopathic DCM.

Methods

Patients

Forty-two patients with DCM and a left ventricular ejection fraction (LVEF) <45% were admitted to our institution with their first...
episode of CHF between November 2000 and August 2003. A
detailed history and physical examination were obtained prior to
enrollment in this prospective, non-randomized, open-label study.
Chest radiography, standard electrocardiography, echocardiography,
and $^{201}$TI and $^{123}$I-MIBG scintigraphy were performed in all patients.
The patients were in New York Heart Association (NYHA) functional
class II or III at the time of enrollment. Patients were excluded from
the study for the following reasons: heart failure NYHA functional
class IV (three patients were excluded); coronary artery disease
diagnosed with evidence of any coronary artery stenosis $>50\%$
by angiography (one patient); active myocarditis diagnosed by LV endo-
myocardial biopsy specimens (two patients); systemic arterial
hypertension (one patient); and diabetes or glucose intolerance
(three patients). Furthermore, none of the patients had a history
of alcohol abuse, congenital heart disease, and severe liver or
kidney disease. Therefore, 32 of 42 patients were enrolled in this
trial at subacute phase.

Five patients were already taking $\beta$-blockers when admitted to
our institution, but their $\beta$-blockers were discontinued immediately
after hospitalization. None of the patients was using spironolactone
before being hospitalized. During the acute phase, all of the
patients were treated with standard therapy for heart failure.
After heart failure was controlled, all of the patients were being
treated with an angiotensin-converting enzyme (ACE)-inhibitor
and with diuretics, whereas some were also receiving digitalis
($n = 2$) and vasodilators (isosorbide dinitrate; $n = 3$). None of the
patients was treated with tricyclic anti-depressants or other serotonin
reuptake inhibitors.

All control subjects (seven men and three women aged 48–62
years) who had been hospitalized for suspected angina pectoris
had low-risk profiles with normal cardiovascular examination
results, including echocardiography, coronary angiography, and
left ventriculography. No control subject was on any drug treatment
for cardiac disease or had a cardiac disease that could possibly
affect haemodynamic studies. The study was approved by the
Ethical Review Board of our institution, and written informed
consent was obtained from each subject.

Study protocol
Carvedilol was started at a dose of 1.25–2.5 mg/day in all of the
DCM patients and the dose was gradually increased to a maximum
of $10–20$ mg/day (mean: $16 \pm 4$ mg/day). Examinations were performed
before and after carvedilol treatment for a mean of $12 \pm 1$
months in all of the DCM patients, while examinations were
done only once (at the time when haemodynamics was normal) in
the control group.

Echocardiography
Echocardiography was performed with a commercially available
sector scanner (SONOS 5500, Hewlett-Packard) and the images were
recorded on half-inch 5-VHS tape. Two experienced echocardiogra-
phers who had no knowledge about the study performed all the
measurements independently. Left ventricular end-diastolic volume
(LVEDV), left ventricular end-systolic volume (LVESV), and LVEF
were calculated using the modified method of Simpson.\textsuperscript{20} The mean
interobserver and intraobserver differences of LVEDV were $2 \pm 4$
and $0 \pm 2$ mL, respectively, those of LVESV were $1 \pm 5$ and $0 \pm 2$
ml, respectively, and those of LVEF were $2 \pm 4\%$ and $0 \pm 3\%$
respectively. Moreover, interobserver and intraobserver variability
in these measurements were assessed by linear regression, and
the levels of agreement were very high [LVEDV: $r = 0.90$ ($P = 0.002$) and $r = 0.94$ ($P = 0.000$), respectively; LVESV: $r = 0.90$
($P = 0.004$) and $r = 0.93$ ($P = 0.000$), respectively; LVEF: $r = 0.90$
($P = 0.002$) and $r = 0.93$ ($P = 0.000$), respectively].
Regional wall motion was assessed by using the 17-segment
method recommended by American Heart Association.\textsuperscript{21} In each
segment, systolic wall motion was visually graded with the following
scale: 0, normal; 1, mild hypokinesis; 2, moderate hypokinesis; 3,
severe hypokinesis or akinesia; 4, dyskinesia. The regional wall
motion score index (WMSI) was calculated as an average of the
wall motion scores in these 17 segments.

Cardiac $^{123}$I-MIBG scintigraphy
The method of $^{123}$I-MIBG imaging has been described previously.\textsuperscript{16–18}
In brief, patients were injected intravenously with $111$ MBq of
$^{123}$I-MIBG (Daichii Radioisotope Laboratories, Tokyo, Japan) while
in the supine position. At 15 min and at 4 h after injection, the
anterior planar and single photon emission computed tomography
(SPECT) images were obtained with a single-head gamma camera
(Millennium MPR, GE Medical Systems, Waukesha, WI, USA).

Global analysis of $^{123}$I-MIBG scintigraphy
The heart/mediastinum count ratio (H/M ratio) was determined from
the delayed anterior planar $^{123}$I-MIBG image. The global
washout rate (WR) was calculated using the following formula:
$((H - [M])_{early} - ([H] - [M])_{delayed}) / ([H] - [M])_{early} \times 100\%$,
where $[H] = \text{mean count per pixel in the LV}$ and $[M] = \text{mean count per pixel in the upper mediastinum}$.
Myocardial SPECT images of each subject were divided into 17
segments as was done for echocardiography. Regional tracer
uptake was assessed semi-quantitatively using the following
5-point scale: 0, normal uptake; 1, mildly reduced uptake; 2, mod-
erate reduced uptake; 3, severely reduced uptake; 4, no uptake.
In addition, the delayed total defect score (TDS) was calculated as
the sum of all segmental defect scores.
Analysis was done in a blinded fashion by two independent obser-
vers with no knowledge of the clinical status or therapy of the sub-
jects. The mean interobserver and intraobserver differences of TDS
were $2 \pm 3$ and $0 \pm 1$, respectively. Moreover, interobserver and
intraobserver variability of TDS were assessed by linear regression,
and the levels of agreement were very high ($r = 0.90$, $P = 0.001$
and $r = 0.94$, $P = 0.000$, respectively).

Regional analysis of $^{123}$I-MIBG scintigraphy
To evaluate regional adrenergic dysfunction in the DCM patients on
SPECT images, we calculated a regional defect score (RDS) for each
of the 17 segments, as was done in the echocardiographic study. In
addition, the regional washout rate (RWR) was calculated for each
of the 17 segments using the following formula: $\text{[(mean count per}
\text{pixel in early images)} - (\text{mean count per pixel in delayed images})]$
/ (mean count per pixel in early images). Then the regional defect
score index (RDSI) and regional washout rate index (RWRI) were cal-
culated as the average RDS and RWR of the 17 segments, respectively.

Plasma brain natriuretic peptide concentration
Blood samples were collected in test tubes containing EDTA after the
subjects had rested in a supine position for at least 30 min. Plasma
was separated by centrifugation and frozen at $-84$ C until measure-
ment. Then the plasma concentration of brain natriuretic peptide
(BNP) was measured with a specific immunoradiometric assay
for human BNP using a commercial kit (normal range $<20$ pg/mL)
(Shionogi, Osaka, Japan), as previously reported.\textsuperscript{17,18,22}

Statistical analysis
Statistical analysis was performed using SPSS 12.0 for Windows (SPSS
Inc.). Numerical results are expressed as the mean $\pm$ SD. Compari-
sion of baseline categorical data between the two groups was done
by the one-sided chi-square contingency table method and differ-
ences between continuous variables were evaluated using the
unpaired t-test and one-way ANOVA. The effects of carvedilol treat-
ment were assessed by the paired t-test. Changes of NYHA func-
tional class were assessed using the Wilcoxon matched pairs
signed ranks test. Linear regression analysis was employed to determine the relationship between continuous variables. The relationships between changes of WMSI and both changes of RDSI and RWRI were assessed using the Spearman rank correlation coefficient ($r_s$). In all analyses, $P < 0.05$ was considered statistically significant.

**Results**

**Clinical characteristics**

One DCM patient developed cerebral embolism and one patient died of CHF after 3 months of the treatment. Thus, 30 out of 32 patients (20 men and 10 women with a mean age of $55 \pm 11$ years, range: 38–70 years) enrolled in the trial completed the entire protocol (Table 1). None of the 30 patients changed their baseline cardiac medication (apart from gradually increasing the dose of carvedilol) during the follow-up period. The mean dose of the ACE-inhibitor enalapril was $7.3 \pm 2.8$ mg/day ($n=16$), while that of perindopril was $2.3 \pm 0.7$ mg/day ($n=14$). The mean dose of furosemide was $53 \pm 21$ mg/day ($n=30$), while the mean dose of spironolactone was only $25$ mg/day ($n=10$). In this study, no patients were treated with angiotensin-receptor blockers.

The $^{123}$I-MIBG scintigraphic data, echocardiographic data, and plasma BNP concentrations of the DCM patients and normal control subjects are shown in Table 1. All of these parameters were significantly worse in the DCM patients when compared with the normal controls.

**Heart rate, blood pressure, and NYHA functional class of the DCM patients before and after treatment**

The heart rate was significantly reduced in the DCM patients group ($68 \pm 11$ b.p.m.) when compared with the baseline value ($79 \pm 13$ b.p.m.) ($P=0.000$). However, there were no significant changes of the systolic and diastolic blood pressures ($123 \pm 17$ mmHg vs. $120 \pm 14$ mmHg, and $74 \pm 9$ mmHg vs. $71 \pm 7$ mmHg, respectively).

The NYHA functional class of the DCM patients is shown in Table 2. Significant improvement of the NYHA functional class relative to baseline occurred after the treatment.

**BNP concentration of the DCM patients before and after treatment**

Plasma BNP concentrations are shown in Table 2. The plasma BNP concentration was significantly decreased after the treatment relative to baseline.

**Cardiac $^{123}$I-MIBG scintigraphic and echocardiographic findings of the DCM patients before and after treatment**

The TDS, H/M ratio, and WR data for the DCM patients are listed in Table 3 and Figure 1. The TDS and WR were significantly decreased by the treatment when compared with the baseline value. The H/M ratio was significantly increased by the treatment when compared with baseline.

The LVEDV, LVESV, and LVEF data for the DCM patients are displayed in Table 3. The LVEDV and LVESV were significantly decreased after the treatment when compared with the baseline value, while LVEF significantly increased after the treatment.

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### Table 1 Clinical characteristics of the DCM patients and normal control subjects

<table>
<thead>
<tr>
<th>DCM patients ($n=30$)</th>
<th>Control subjects ($n=10$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55 $\pm$ 11</td>
<td>54 $\pm$ 5</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>20/10</td>
<td>7/3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160 $\pm$ 8</td>
<td>162 $\pm$ 10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59 $\pm$ 9</td>
<td>57 $\pm$ 11</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>I/II/III 5/25</td>
<td>0.000</td>
</tr>
<tr>
<td>I-123 MIBG scintigraphy data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDS</td>
<td>38 $\pm$ 8</td>
<td>8 $\pm$ 4</td>
</tr>
<tr>
<td>H/M ratio</td>
<td>1.66 $\pm$ 0.16</td>
<td>2.44 $\pm$ 0.26</td>
</tr>
<tr>
<td>WR (%)</td>
<td>52 $\pm$ 10</td>
<td>25 $\pm$ 5</td>
</tr>
<tr>
<td>Echocardiographic data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>206 $\pm$ 33</td>
<td>86 $\pm$ 14</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>137 $\pm$ 23</td>
<td>28 $\pm$ 8</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>33 $\pm$ 6</td>
<td>67 $\pm$ 7</td>
</tr>
<tr>
<td>Plasma BNP (pg/mL)</td>
<td>270 $\pm$ 249</td>
<td>14 $\pm$ 5</td>
</tr>
</tbody>
</table>

Data are presented as the mean value $\pm$ SD.

NYHA, New York Heart Association; MIBG, meta-iodobenzylguanidine; TDS, total defect score; H/M, heart/mediastinum count; WR, washout rate; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide.

### Table 2 NYHA functional class and plasma BNP concentration of the DCM patients

<table>
<thead>
<tr>
<th>NYHA functional class</th>
<th>Baseline</th>
<th>After treatment</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I/II/III 0/5/25</td>
<td>9/19/2</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Plasma BNP (pg/mL)</td>
<td>270 $\pm$ 249</td>
<td>148 $\pm$ 125</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data are presented as the mean value $\pm$ SD.

NYHA, New York Heart Association; BNP, brain natriuretic peptide.

### Table 3 Changes of $^{123}$I-MIBG scintigraphic and echocardiographic findings in the DCM patients

<table>
<thead>
<tr>
<th>I-123-MIBG scintigraphy</th>
<th>Baseline</th>
<th>After treatment</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDS</td>
<td>38 $\pm$ 8</td>
<td>26 $\pm$ 11</td>
<td>0.000</td>
</tr>
<tr>
<td>H/M ratio</td>
<td>1.66 $\pm$ 0.16</td>
<td>1.88 $\pm$ 0.23</td>
<td>0.000</td>
</tr>
<tr>
<td>WR</td>
<td>52 $\pm$ 10</td>
<td>41 $\pm$ 13</td>
<td>0.000</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDV</td>
<td>206 $\pm$ 33</td>
<td>171 $\pm$ 29</td>
<td>0.000</td>
</tr>
<tr>
<td>LVESV</td>
<td>137 $\pm$ 23</td>
<td>104 $\pm$ 21</td>
<td>0.000</td>
</tr>
<tr>
<td>LVEF</td>
<td>33 $\pm$ 6</td>
<td>39 $\pm$ 6</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are presented as the mean value $\pm$ SD.

TDS, total defect score; H/M, heart/mediastinum count; WR, washout rate; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction.
Relationship between LV volume and global $^{123}$I-MIBG scintigraphic findings before and after treatment

There were significant correlations between the changes of $^{123}$I-MIBG scintigraphic findings after the treatment and the changes of the LVEDV (Figure 2) or the LVESV (Figure 3).

Relationship between WMSI and regional $^{123}$I-MIBG scintigraphic findings before and after treatment

According to Spearman’s rank correlation coefficient analysis, there was a significant correlation between the changes of the WMSI after the treatment and the changes of the RDSI or RWRI (Figure 4).

Discussion

Idiopathic DCM is characterized by ventricular dilation and systolic dysfunction, and it generally has a poor prognosis. The 1-year mortality rate of patients with idiopathic DCM can be as high as 25%, while the 5-year mortality ranges from 20 to 50%.23 Earlier detection of this disease and introduction of β-blocker therapy may have led to a recent improvement of the prognosis.3-7 The beneficial effects of β-blockers on DCM include the following: (i) increased supply of energy to the myocardium for synthesis and repair; (ii) improvement of diastolic relaxation, filling, and compliance; (iii) inhibition of sympathetically mediated vasoconstriction via prostaglandin and renin; and (iv) protection against catecholamine-induced myocardial damage and necrosis.24,25 It has been reported that β-blockers have various haemodynamic and energetic benefits,26 as well as enhancing cell-mediated immunity and improving T cell function.27 These multiple actions lead to a reduction in the risk of death and the risk of hospitalization for cardiovascular disease.3-7

$^{123}$I-MIBG is an analogue of the adrenergic neuron blocking agent guanethidine, and it is thought to utilize the same myocardial uptake and release mechanisms as norepinephrine.28 The myocardial norepinephrine concentration and $^{123}$I-MIBG imaging findings are correlated in patients with DCM,8 so cardiac $^{123}$I-MIBG imaging is a useful tool for detecting abnormalities of the myocardial adrenergic nervous system in these patients.8,9 Several reports have suggested that ACE-inhibitors,10,11,18 β-blockers,11-15 spironolactone,16 and angiotensin-receptor blockers17 can improve CSNA in patients with heart failure, based on cardiac $^{123}$I-MIBG scintigraphic findings. The basic pharmacological action of the third-generation β-blocker carvedilol differs considerably from that of other β-blockers. Carvedilol is a relatively non-selective β1-, β2-blocking agent, while it also blocks α1-receptors29 and has antioxidant activity.30 Carvedilol may inhibit the cardiac adrenergic drive more potently than other β-blockers, because Gilbert et al.31 have reported that carvedilol does not upregulate β1-adrenergic receptors and that it blocks all adrenergic receptors. Furthermore, Watanabe et al.19 reported that carvedilol directly improves cardiac neuronal uptake of

![Figure 1](image1.png)  
Cardiac $^{123}$I-meta-iodobenzylguanidine (MIBG) scintigraphic findings before and after carvedilol treatment in 30 patients with dilated cardiomyopathy (DCM). TDS, total defect score; H/M, heart/mediastinum count; WR, washout rate; 1Y, after 1 year of therapy.

![Figure 2](image2.png)  
Correlations between the changes of $^{123}$I-MIBG scintigraphic findings and left ventricular end-diastolic volume (LVEDV) after carvedilol treatment in 30 patients with dilated cardiomyopathy. $\Delta$LVEDV = the value of LVEDV after treatment – pretreatment value of LVEDV; $\Delta$TDS = the value of TDS after treatment – pretreatment value of TDS; $\Delta$H/M ratio = the value of H/M ratio after treatment – pretreatment value of H/M ratio; $\Delta$WR = the value of WR after treatment – pretreatment value of WR.

$P=0.000$

$P=0.000$

$P=0.000$

$r=0.638$

$r=-0.610$

$r=0.586$

Figure 1  
Cardiac $^{123}$I-meta-iodobenzylguanidine (MIBG) scintigraphic findings before and after carvedilol treatment in 30 patients with dilated cardiomyopathy (DCM). TDS, total defect score; H/M, heart/mediastinum count; WR, washout rate; 1Y, after 1 year of therapy.

Figure 2  
Correlations between the changes of $^{123}$I-MIBG scintigraphic findings and left ventricular end-diastolic volume (LVEDV) after carvedilol treatment in 30 patients with dilated cardiomyopathy. $\Delta$LVEDV = the value of LVEDV after treatment – pretreatment value of LVEDV; $\Delta$TDS = the value of TDS after treatment – pretreatment value of TDS; $\Delta$H/M ratio = the value of H/M ratio after treatment – pretreatment value of H/M ratio; $\Delta$WR = the value of WR after treatment – pretreatment value of WR.
norepinephrine in a rat model of DCM and that this action may increase the exposure of cardiac myocytes to norepinephrine. In this study, we examined whether standard treatment containing carvedilol could improve CSNA in DCM patients using $^{123}$I-MIBG scintigraphy, and we found that the TDS, H/M ratio, and WR were all improved by the treatment.

Kramer et al.\textsuperscript{32} have previously reported that sympathetic denervation of the adjacent non-infarcted regions contributes to LV remodelling in animal models with myocardial infarction. The same group also demonstrated that $\beta$-blocker therapy improves adjacent regional innervation and preserves cardiac function.\textsuperscript{13} Although our subjects included patients with non-ischaemic DCM, we did not include any patients with myocardial infarction. Accordingly, we will need to study the effects of carvedilol on CSNA and LV remodelling after myocardial infarction in the future.

The plasma BNP level is a useful prognostic indicator in patients with CHF,\textsuperscript{34} since BNP is a ventricular hormone.\textsuperscript{35} Plasma BNP is reported to show a correlation with abnormalities of LV EF and LV end-diastolic pressure,\textsuperscript{35} as well as with LV mass.\textsuperscript{36} The decrease of circulating BNP that we detected after carvedilol treatment was presumably due to a decrease of LV filling pressure, improvement of LV remodelling, or both factors. The decrease of plasma BNP with carvedilol therapy may also have reflected improvement of LV diastolic function secondary to the amelioration of cardiac hypertrophy and fibrosis by this drug. Treatment of CHF guided by the plasma BNP level has been reported to reduce cardiovascular events,\textsuperscript{34} so a decrease of BNP may be associated with a better outcome, as has been shown in the previous studies of carvedilol.\textsuperscript{5–7} In the present study, plasma BNP was significantly decreased by the therapy in our patients with DCM, and the patients also showed improvement of heart failure as measured by the NYHA functional class.

In some previous studies, carvedilol was found to improve CSNA evaluated by $^{123}$I-MIBG scintigraphy in patients with DCM.\textsuperscript{13–15} Gerson et al.\textsuperscript{13} reported that there was no significant improvement of the H/M ratio and WR by carvedilol in patients with DCM, despite marked improvement of LV function and CSNA in patients with severe heart failure. In contrast, we found that the TDS, H/M ratio, and WR were all improved by the treatment. Such discrepancies may be partly due to differences of the patient population between the two studies, particularly a difference in the severity of heart failure. For example, the LVEF of our subjects was better than that of Gerson’s group\textsuperscript{13} (33 ± 6\% vs. 25 ± 8\%, $P = 0.000$). Agostini et al.\textsuperscript{14} have also reported that carvedilol increases the H/M ratio and improves cardiac function in patients with DCM. Moreover, Cohen-Solal et al.\textsuperscript{15} found that carvedilol improves $^{123}$I-MIBG SPECT findings and decreases the LV diameter in heart failure patients compared with placebo treatment. However, there have been no previous reports of a correlation between CSNA and LV volume or regional wall motion parameters in patients with DCM. Accordingly, the present study provided the first evidence of a relationship between CSNA and LV remodelling, as well as between regional adrenergic function and regional wall motion, during the treatment in patients with DCM. Further studies will be needed to confirm these findings in a larger group of patients.

The H/M ratio determined by $^{123}$I-MIBG scintigraphy was higher in our study than in the study of Merlet.\textsuperscript{9} In general, the $^{123}$I-MIBG used in Japan had a higher specific activity (1665–2039 MBq/mg) than that of other MIBG provided by CIS BIO-International,\textsuperscript{37} so the control value of the H/M ratio was significantly higher in this study than in Merlet’s\textsuperscript{5} (2.44 ± 0.26 vs. 1.96 ± 0.33, $P = 0.001$). Although no-carrier-added $^{123}$I-MIBG scintigraphy, with a greater specific activity, has been tested in animal models of heart failure in Europe,\textsuperscript{38} such researches has not been performed in Japan.
Currently, many independent reports from different centers around the world support the concept that 123I-MIBG myocardial scintigraphy provides useful information for assessing patients with heart failure. This modality seems to be valuable for predicting the prognosis and for estimating the long-term efficacy of therapy. However, quantitative 123I-MIBG parameters differ between institutions and between instruments, and this tracer is not widely available. For these reasons, cardiac 123I-MIBG has not yet achieved broad clinical acceptance, and the evidence supporting the clinical value of this imaging technique remains inadequate. We believe that multicenter studies are required to definitively establish the effectiveness of this imaging modality.

The small number of patients included in this study was a limitation. To determine the sample size, we referred to the previous studies in which beta-blocker carvedilol treatment of heart failure was favourable. Three manuscripts, Gerson et al.,13 Agostini et al.,14 and Nakamura et al.,30 enrolled 22, 22, and 23 patients, respectively, and determined that carvedilol improved the outcome of the DCM patients. Based on those studies, we selected this sample size. However, in the future, we need to study the long-term effects of carvedilol on CSNA and LV remodelling in a larger group of patients.

**Conclusions**

The TDS, H/M, and WR determined by 123I-MIBG scintigraphy were all significantly improved by the treatment. LV volume and cardiac function were also improved by the treatment, while the plasma BNP concentration showed a significant decrease. There was a significant correlation between changes of the 123I-MIBG scintigraphic parameters and changes of LV parameters during the treatment. These findings suggest that standard treatment containing carvedilol can improve CSNA and LV remodelling in patients with DCM.

**Conflict of interest:** none declared.

**References**


