Dobutamine Gated Blood Pool Scintigraphy Predicts the Improvement of Cardiac Sympathetic Nerve Activity, Cardiac Function, and Symptoms After Treatment in Patients With Dilated Cardiomyopathy*

Shu Kasama, MD; Takuji Toyama, MD; Hiroshi Hoshizaki, MD; Shigeru Oshima, MD; Koichi Taniguchi, MD; Tadashi Suzuki, MD; and Masahiko Kurabayashi, MD

**Background:** We evaluated whether dobutamine gated blood pool scintigraphy (DOB-GBP) can predict improvement in cardiac sympathetic nerve activity and cardiac function after β-blocker therapy in patients with dilated cardiomyopathy (DCM).

**Methods and results:** Twenty-two patients with DCM underwent DOB-GBP to measure left ventricular ejection fraction (LVEF) at rest, and during 5, 10, and 15 μg/kg/min of dobutamine infusion before therapy. Examinations were performed before and after 1 year of therapy. The heart/mediastinum count (H/M) ratio and total defect score (TDS) were determined for 123I-meta-iodobenzylguanidine images from anterior planar image and single-photon emission CT images. LVEF and left ventricular end-diastolic dimension (LVDd) were determined by echocardiography. After 1 year of treatment, the echocardiographic LVEF improved >5% in 11 patients (group A), but did not improve in the remaining 11 patients (group B). Before treatment, TDS, H/M, LVEF, and LVDd were similar in both groups. However, there was a greater increase in the LVEF during dobutamine infusion in group A than in group B (21 ± 8% vs 9 ± 3%, p < 0.001). If a critical value of 15% for the ΔLVEF was used to predict the improvement in LVEF after treatment, the sensitivity was 91% and specificity was 82%. The TDS, H/M ratio, LVDd, and New York Heart Association functional class improved in group A to a greater extent than in group B.

**Conclusions:** DOB-GBP can be used to predict improved cardiac sympathetic nerve activity, cardiac function, and symptoms after treatment in patients with DCM.

**Key words:** β-adrenergic receptor blockers; cardiomyopathies, dilated; radionuclide imaging

**Abbreviations:** DCM = dilated cardiomyopathy; DOB-GBP = dobutamine gated blood pool scintigraphy; H/M = heart/mediastinum count; LVDd = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; MIBG = meta-iodobenzylguanidine; NYHA = New York Heart Association; SPECT = single-photon emission CT; TDS = total defect score

Since Waagstein et al. reported in 1975 that several patients with decompensated dilated cardiomyopathy (DCM) showed clinical improvement after the administration of β-blockers, various studies have demonstrated that β-blockers can have beneficial effects for selected patients with DCM. However, this treatment may also have adverse effects in patients with heart failure because of its negative inotropic effects.

Dobutamine can increase cardiac contractility and output, improve arterial BP, and reduce total peripheral resistance. Dobutamine gated blood pool scintigraphy (DOB-GBP) has been used to assess myocardial viability and determine prognosis in patients with congestive heart failure. Myocardial imaging with 123I-Meta-iodobenzylguanidine (MIBG), an an-
alog of norepinephrine, is a useful tool for detecting abnormalities of the myocardial adrenergic nervous system in patients with congestive heart failure.\textsuperscript{10–13} Cardiac \textsuperscript{123}I-MIBG uptake is also altered in patients with DCM.\textsuperscript{14–16} Reports\textsuperscript{17–19} have suggested that cardiac \textsuperscript{123}I-MIBG scintigraphy can predict the effects of $\beta$-blocker therapy in patients with DCM. However, it is still difficult to predict what type of patients with DCM will have a beneficial response to $\beta$-blocker therapy. This study was performed to determine whether DOB-GBP can predict the improvement of cardiac sympathetic nerve activity and cardiac function after $\beta$-blocker therapy in patients with DCM.

**Materials and Methods**

**Study Population**

Twenty-two patients, 12 men and 10 women (mean $\pm$ SD age, 56 $\pm$ 12 years; range, 35 to 78 years), with DCM were included in the study. A detailed history and physical were obtained from all of the patients. Chest radiography, standard ECG, echocardiography, \textsuperscript{201}Tl and \textsuperscript{123}I-MIBG scintigraphy, and cardiac catheterization, including coronary angiography and left ventriculography, were performed in all of the patients. Patients with acute or chronic myocarditis, significant coronary artery stenosis, or valvular disease were excluded from the study. Patients were in New York Heart Association (NYHA) functional class II or III and had echocardiographic left ventricular ejection fraction (LVEF) $<50\%$. All of the patients were receiving digitalis, diuretics, and angiotensin-converting enzyme inhibitor therapy. During the follow-up period of 1 year, echocardiographic assessment of the left ventricle was performed in all of the patients. Improvement in the LVEF $>5\%$ compared to before treatment occurred in 11 patients (group A); the others patients had $<5\%$ improvement in the LVEF (group B).

**Study Protocol**

Figure 1 summarizes the study protocol. The initial metoprolol dose was 2.5 to 5 mg/d. Three to 5 months later, the dose was increased to a maintenance dose of 20 to 60 mg/d. We performed a series of examinations before and after 1 year of treatment. In this study, all patients survived and there were no major complications by this treatment.

**DOB-GBP**

Figure 2 summarizes the protocol for DOB-GBP. DOB-GBP was performed in all patients before treatment with $\beta$-blockers. Patients were first injected with pyrophosphate. Twenty minutes later, they received 740 megabecquerel of \textsuperscript{99m}Tc, and the LVEF was calculated at rest and during the infusion of 5, 10, and 15 $\mu$g/kg/min of dobutamine. Data were acquired using an Anger-type gamma camera (ZLC 7500; SIMENS International; Munich, Germany). The percentage of change in LVEF during dobutamine infusion was expressed as the $\Delta$LVEF, which represented the greatest change in LVEF during the infusion of 5, 10, or 15 $\mu$g/kg/min of dobutamine minus the resting LVEF.

**$\textsuperscript{123}I$-MIBG Imagings**

The patients were injected IV with \textsuperscript{123}I-MIBG (111 megabecquerel) while in an upright position. Anterior planar and single-photon emission CT (SPECT) images were acquired 4 h later. SPECT imaging was performed with a dedicated three-headed imaging system (PRISM 3000; Picker International; Cleveland, OH). The energy, uniformity, and linearity were constantly corrected. Images were acquired for 20-s each at 3° steps over a 360° orbit and were recorded at a digital resolution of 64×64 from the anterior planar \textsuperscript{123}I-MIBG image. The heart/mediastinum count (H/M) ratio was determined (Fig 3).

The myocardial SPECT images for each patient were divided into 20 segments (Fig 4). The short-axis images at the basal, middle, and apical ventricular levels were divided into six segments. The apical segment of the vertical long-axis image was divided into two segments. Regional tracer uptake was assessed semiquantitatively using a 4-point scoring system (0, normal uptake; 1, mildly reduced uptake; 2, moderately reduced uptake; and 3, severely reduced uptake). The total defect score (TDS) was calculated as the sum of the scores for all 20 segments.

**M-Mode Echocardiography**

Echocardiographic measurement was performed using standard methods.\textsuperscript{20} Left ventricular end-diastolic dimension (LVDd) and left ventricular end-systolic dimension were obtained, and the LVEF was calculated using the Teichholz method.\textsuperscript{21}
Data Analysis and Statistics

Statistical analysis was performed using Statview for Macintosh (Abacus Concepts; Berkeley, CA). Unpaired t tests and χ² tests were used to compare the two groups. All values are reported as the mean ± SD. A value for p < 0.05 was considered statistically significant.

RESULTS

There were no significant differences in the hemodynamic characteristics of the two groups. Before treatment, TDS, H/M ratio, LVEF, and LVDd were similar in both groups. ΔLVEF is shown in Figure 5. ΔLVEF in group A was 21 ± 8%, which was significantly higher than the ΔLVEF in group B (9 ± 3%, p < 0.001). The correlation was recognized between LVEF measured by echocardiography and LVEF measured by scintigraphy at rest (Fig 6). Using a critical value of 15% for the ΔLVEF to predict an improvement in LVEF after 1 year, the sensitivity was 91% and specificity was 82% (Fig 7).

The TDSs are reported in Table 1. In group A, the TDS decreased significantly after 1 year (18 ± 12) compared to the baseline value (29 ± 10; p < 0.0005). In contrast, in group B, there was no significant difference between the baseline value and the value after 1 year of treatment. Furthermore, after 1 year of treatment, the TDS in group A was significantly lower than in group B (p < 0.05). The H/M ratios are reported in Table 1. In group A, the

![Figure 3. Cardiac ¹²³I-MIBG uptake was quantified as the H/M ratio 4 h after ¹²³I-MIBG injection, using regions of interest positioned over the heart (H) and upper mediastinum (M).](#)

![Figure 5. ΔLVEF before treatment. Filled circles represent group A; unfilled circles represent group B.](#)

![Figure 6. Relationship between LVEF measured by echocardiography and LVEF measured by scintigraphy at rest.](#)
H/M ratio increased significantly after 1 year (1.97 ± 0.39), compared to the baseline value (1.69 ± 0.20; p < 0.01). In group B, there was no significant difference between the baseline value and the value after 1 year of treatment. Furthermore, after 1 year of treatment, the LVDd in group A was significantly lower than in group B (p < 0.0005). The LVEFs are reported in Table 2. In group A, the LVEF increased significantly after 1 year (51 ± 7%), compared to the baseline value (28 ± 7%; p < 0.0001). In the group B, there was no significant difference between the values at baseline and after 1 year of treatment. Furthermore, after 1 year of treatment, the LVEF of patients in group A was significantly higher than in group B (p < 0.0001).

The NYHA functional class of the patients are shown in Table 2 and Figure 8. Patients in group A and group B showed improvement after 1 year of treatment compared to baseline (group A, from 2.9 ± 0.3 to 1.5 ± 0.5, p < 0.0001; group B, from 3.0 ± 0.0 to 2.5 ± 0.7, p < 0.05). Furthermore, after 1 year of treatment, the NYHA functional class of patients in group A was better than that of patients in group B (p < 0.005).

Table 1—Changes in TDS and H/R Ratio for 123I-MIBG Imaging in Patients With DCM

<table>
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<th>Patient No.</th>
<th>Gender</th>
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<th>TDS 1 yr</th>
<th>H/M Ratio Baseline</th>
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<td>Mean ± SD</td>
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<td>29 ± 10</td>
<td>18 ± 12†</td>
<td>1.69 ± 0.20</td>
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<td>Mean ± SD</td>
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<td>60 ± 14</td>
<td>32 ± 12</td>
<td>35 ± 14</td>
<td>1.66 ± 0.30</td>
<td>1.61 ± 0.31†</td>
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*p < 0.0005 vs baseline.
†p < 0.05 vs group B.
‡p < 0.01 vs baseline.
Idiopathic DCM, which is characterized by dilated ventricles and decreased systolic function, is generally regarded as having a poor prognosis. In early reports, the survival rate for patients with DCM was 70 to 75% at 1 year and 50% at 5 years. However, in later reports, the prognosis has improved, with a 5-year survival rate of 60 to 80%.

Earlier detection of the disease, as well as the introduction of treatments with β-blockers, may be related to this improvement in prognosis. The mechanisms responsible for the beneficial action of β-blockers, in the setting of DCM include the following: (1) increased myocardial energy for synthetic and reparative processes; (2) improved diastolic relaxation, filling, and compliance; (3) inhibition of sympathetically mediated vasoconstriction by prostaglandins and renin release through the up-regulation of β-adrenergic receptors; (4) protection against catecholamine-induced myocardial damage and necrosis; and (5) restoration of catecholamine responsiveness.

However, β-blockers have negative inotropic effects. Reports suggest that cardiac 123I-MIBG...
scintigraphy can be used to predict the effects of β-blocker therapy in patients with DCM. However, it is still difficult to predict whether patients with DCM will respond favorably to treatment with β-blockers. In this study, we administered β-blockers to the 22 patients with DCM. The overall improvement in LVEF, LVDd, and NYHA functional class in all patients was accepted as well as previous reports2.4–7 (LVEF, from 28 ± 8% to 38 ± 15%, p < 0.005; LVDd, from 67 ± 6 to 62 ± 9 mm, p < 0.01; and NYHA, from 3.0 ± 0.2 to 2.0 ± 0.8, p < 0.0001). However, there were some cases that accepted the deterioration of these parameters. Therefore, we examined it using DOB-GBP.

DOB-GBP has potent inotropic activity but minimal chronotropic, arrhythmogenic, or vascular effects.8,29–34 Furthermore, dobutamine causes relatively greater increases in coronary blood flow than other inotropic agents when myocardial oxygen consumption increased.35 Myocardial viability can be assessed using low-dose dobutamine infusions to identify functional improvement in regions with resting dyssynergy. The wall motion response during dobutamine infusion can be used to predict the functional recovery of stunned and hibernating myocardium in patients with ischemic heart disease.36,37 There have also been several reports38,39 on the prediction of functional recovery by dobutamine stress echocardiography in patients with DCM.

DOB-GBP has been used to assess myocardial viability and prognosis in patients with congestive heart failure.9 However, there are no reports concerning the use of DOB-GBP in patients with DCM. In this study, DOB-GBP identified patients that benefited from β-blocker therapy. The exact mechanism responsible for the recovery of systolic function during dobutamine infusion is unclear. Although differences in the degree of down-regulation of the myocardial β-adrenergic system may play a role, this has been reported in association with progressive left ventricular deterioration. Furthermore, diminished β-adrenergic contractile reserve predicts the clinical outcome in patients with DCM.40 Therefore, this study suggested that contractile reserve-related β-adrenergic stimulation may be the predominant factor in the improvement in ΔLVEF.

**Conclusion**

DOB-GBP can be used to predict improvement in cardiac sympathetic nerve activity, cardiac function, and symptoms after treatment with β-blocker in patients with DCM.

**References**

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