Relation between myocardial response to dobutamine stress and sympathetic nerve activation in patients with idiopathic dilated cardiomyopathy: A comparison of $^{123}$I-MIBG scintigraphic and echocardiographic data

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It is likely that a close association exists between findings obtained by two methods: dobutamine stress echocardiography and $^{123}$I-MIBG scintigraphy. Both of these methods are associated with $\beta$-adrenergic receptor mechanisms. This study was conducted to demonstrate the relation between myocardial response to dobutamine stress and sympathetic nerve release of norepinephrine in the failing heart. In 12 patients with heart failure due to idiopathic dilated cardiomyopathy, the myocardial effects of dobutamine stress were evaluated by low-dose dobutamine stress echocardiography; and sympathetic nerve function was evaluated by scintigraphic imaging with iodine-123 $^{[123]}$I-meta-iodobenzylguanidine (MIBG), an analogue of norepinephrine. Echocardiography provided quantitative assessment of wall motion and left ventricular dilatation; radiotracer studies with $^{123}$I-MIBG provided quantitative assessment of the heart-to-mediastium (H/M) uptake ratio and washout rate. Results showed that H/M correlated with baseline wall motion ($r = 0.682$, $p = 0.0146$), wall motion after dobutamine stress ($r = 0.758$, $p = 0.0043$), the change in wall motion ($r = 0.667$, $p = 0.0178$), and with left ventricular diastolic diameter ($r = 0.837$, $p = 0.0007$). In addition, the $^{123}$I-MIBG washout rate correlated with baseline wall motion ($r = 0.608$, $p = 0.0360$), wall motion after dobutamine stress ($r = 0.703$, $p = 0.0107$), and with the change in wall motion ($r = 0.664$, $p = 0.0185$). Wall motion, especially in the myocardial response to dobutamine stress, is related to sympathetic nerve activity in heart failure.

Key words: $^{123}$I-MIBG scintigraphy, dobutamine stress echocardiography, idiopathic dilated cardiomyopathy

INTRODUCTION

DECREASED catecholamine sensitivity due to a reduction in $\beta$-adrenergic receptors is considered to be one of the mechanisms leading to systolic dysfunction in heart failure.$^{1,2}$ In such myocardium, norepinephrine content is reduced and sympathetic nerve terminals augment its release. The reduction in $\beta$-receptors has been assessed from their response to inotropic stimulation with $\beta$-agonists.$^3$ From this point of view, assessing contractile reserve with dobutamine stress echocardiography$^{4,5}$ can be a suitable approach for evaluating $\beta$-receptor reduction.

Myocardial imaging with $^{123}$I-meta-iodobenzylguanidine (MIBG) has been used for noninvasive assessment of myocardial sympathetic nerve activity.$^6$ MIBG is an analogue of norepinephrine, and the myocardial uptake and washout of $^{123}$I-MIBG generally parallel the kinetics of cardiac norepinephrine. This radiotracer method provides quantitative indices such as the heart-to-mediastinum (H/M) uptake ratio and myocardial washout rate. In heart failure, $^{123}$I-MIBG studies have shown decreased H/M and increased washout rate.$^7$
Table 1 Patient characteristics and myocardial assessment data

<table>
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<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>NYHA class</th>
<th>H/M ratio</th>
<th>WR (%)</th>
<th>WM&lt;sub&gt;base&lt;/sub&gt; score</th>
<th>WM&lt;sub&gt;ab&lt;/sub&gt; score</th>
<th>ΔWM score</th>
<th>LVDd (mm)</th>
<th>Administration of β blocker</th>
<th>Myocardial biopsy</th>
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NYHA = New York Heart Association functional class of severity of heart failure, H/M = heart-to-mediastinum ratio of 123<sup>i</sup>-MBG uptake, WR = washout rate, WM<sub>base</sub> = wall motion at baseline, WM<sub>ab</sub> = wall motion after dobutamine stress, ΔWM = change in wall motion (WM<sub>ab</sub> - WM<sub>base</sub>), LVDd = left ventricular diastolic diameter, F = fibrosis, I = infiltration of white blood cell, H = hypertrophy of myocyte.

It is likely that a close association exists between findings obtained with two methods: dobutamine stress echocardiography and 123<sup>i</sup>-MBG scintigraphy. Both of these methods are associated with β-adrenergic receptor mechanisms. To date, however, no comparison of these methods has been reported. To elucidate the relation between contractile reserve and sympathetic nerve activity in the failing heart, we compared myocardial wall motion in low-dose dobutamine stress echocardiography with H/M and the washout rate by means of 123<sup>i</sup>-MBG myocardial imaging in patients with idiopathic dilated cardiomyopathy, typically associated with heart failure.

MATERIALS AND METHODS

Study Population

The study population included 12 patients with idiopathic dilated cardiomyopathy (9 males, 3 females, mean age 56 ± 11 years). Criteria for inclusion were symptoms of heart failure, defined as New York Heart Association (NYHA) functional class II or III for > 1 year, and no recognized cause of heart failure other than idiopathic dilated cardiomyopathy. In all patients, valvular heart disease and coronary artery disease (arterial stenosis >50%) were ruled out. Patients with diabetes mellitus were excluded. All medication, including digitalis preparation, diuretic drugs, β-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, and calcium-channel blockers, were continued through the study. The age, gender, and NYHA class of all patients are shown in Table 1.

Myocardial Assessment Studies

Valvular disease and coronary artery disease were ruled out in all patients by means of coronary angiography and 2-dimensional echocardiography. Left ventricular diastolic diameter (LVDd), a measure of left ventricular dilation, was obtained by M-mode echocardiography.

Low-dose dobutamine stress echocardiography

Data acquisition. Low-dose dobutamine stress echocardiography was performed with the Toshiba Model SSH-60A or SSH-160A ultrasound diagnostic system (Toshiba Corp., Tokyo, Japan). Parasternal short-axis views on expiration in the left semicircumference position were recorded on videotape.

Data analysis. Quantitative computer analysis was obtained with the Mipron (Kontron Elektronik; München, Germany) medical image processing system by the centerline method described by Sheehan et al. In short axial slices at the level of the papillary muscle, the computer constructed end-diastolic and end-systolic left ventricular contours and centerlines between these contours. Regional wall motion, measured along 100 chords constructed perpendicular to the centerline, was normalized at each chord by the end-diastolic perimeter to yield a shortening fraction. Normalized wall motion was then obtained with the following equation: normalized wall motion = length of wall motion + length of end-diastolic perimeter. Normalized wall motion was compared with normal values obtained from 20 control subjects, then a standard deviation (SD) was obtained in each chord. Quantitative index of wall motion (WM) was a summation of the SD values for all chords. This value represented the global function of the left ventricle. Then 10 μg/kg/min of dobutamine hydrochloride was administered intravenously for inotropic stimulation. Values for wall motion at baseline (WM<sub>base</sub>) and after dobutamine stress (WM<sub>ab</sub>) were obtained. Change in wall motion (ΔWM) was the marker of contractile reserve in the present study. ΔWM = WM<sub>ab</sub> - WM<sub>base</sub> (Fig. 1).
H/M = $H_{\text{delayed}} / M_{\text{delayed}}$

Washout rate (%) = $(H_{\text{initial}} - H_{\text{delayed}}) / H_{\text{initial}} \times 100$

Fig. 2 Initial and delayed $^{123}$I-MIBG planar images showing regions of interest for the heart (H) and mediastinum (M) from where counts/pixel are obtained to calculate H/M values. $H/M = H_{\text{delayed}} / M_{\text{delayed}}$ where $H =$ mean counts/pixel in the left ventricle and $M =$ mean counts/pixel in the upper mediastinum. The myocardial washout rate of $^{123}$I-MIBG was defined as $(H_{\text{initial}} - H_{\text{delayed}}) / H_{\text{initial}} \times 100\%$.

$^{123}$I-MIBG myocardial imaging

Data acquisition. Patients were placed in the supine position and 111 MBq (3 mCi) of $^{123}$I-MIBG (Daichi Radioisotope Laboratory, Tokyo, Japan) was injected. Myocardial images were acquired by means of a standard field gamma camera equipped with a low-energy, parallel-hole collimator (Starcam 3000 XCT, General Electric, Milwaukee, USA), with a 20% window centered at an energy peak of 159 keV. Planar imaging was performed for 3 min in the anterior view. The first acquisition began 15 min after radiotracer injection (initial image). An identical acquisition was performed 3 hours after injection (delayed image).

Data analysis. Left ventricular $^{123}$I-MIBG activity was measured in a manually drawn region of interest around the left ventricular myocardium. A 20-× 20-pixel region of interest was placed over the upper mediastinal area. Background subtraction was performed with the upper mediastinal region of interest. To evaluate myocardial uptake of $^{123}$I-MIBG, the heart-to mediastinal (H/M) activity ratio was calculated with data from the delayed image (Fig. 2): $H/M = H_{\text{delayed}} / M_{\text{delayed}}$ where $H =$ mean counts/pixel in the left ventricle and $M =$ mean counts/pixel in the upper mediastinum. The myocardial washout rate of $^{123}$I-MIBG was defined as $(H_{\text{initial}} - H_{\text{delayed}}) / H_{\text{initial}} \times 100\%$.

Statistics

$WM_{\text{base}}$ was compared with $WM_{\text{dub}}$ by means of a paired t test, and all other indices were compared by linear correlation with statistical significance defined as $p < 0.05$.

RESULTS

Raw data for each patient are shown in Table 1. Mean LVEF was $34 \pm 8\%$. $WM_{\text{base}}$ was greatly decreased by an average of $185.0 \pm 73.7$. All cases showed improved wall...
motion (Fig. 3) with a mean $W_{Mob}$ of 117.8 ± 102.6 (p = 0.0001). Mean LVDD 62.5 ± 10.7 mm. Six patients had abnormally high LVDD and six patients had slightly higher than normal LVDD (55%).

**H/M vs. washout rate.** H/M tended to be inversely proportional to washout rate, although the correlation coefficient was not significant ($r = 0.563$, $p = 0.0568$). The reason for the poor correlation was that patients who showed decreased uptake (i.e., low H/M) had considerable variation in the washout rate, as shown in Figure 4.

**H/M vs. echocardiographic data.** As shown in Figure 5, H/M correlated with $W_{Mbase}$ ($r = 0.682$, $p = 0.0146$), $W_{M Dob}$ ($r = 0.758$, $p = 0.0043$), $\Delta W_{M}$ ($r = 0.667$, $p = 0.0178$) and LVDD ($r = 0.837$, $p = 0.0007$).

**Washout rate vs. echocardiographic data.** As shown in Figure 6, the washout rate correlated with $W_{Mbase}$ ($r = 0.608$, $p = 0.0360$), $W_{M Dob}$ ($r = 0.703$, $p = 0.0107$) and $\Delta W_{M}$ ($r = 0.664$, $p = 0.0185$), although the washout rate did not correlate with LVDD ($r = 0.492$, $p = 0.1044$)

**DISCUSSION**

A considerable number of studies have evaluated heart failure by means of $^{123}$I-MIBG myocardial imaging. Reduced norepinephrine levels are demonstrated as decreased H/M and augmented norepinephrine release at the sympathetic nerve terminal is demonstrated by increased washout rate. Both H/M and the washout rate have been reported to correlate with the degree of heart failure, with H/M inversely proportional to the washout rate.

The findings of the present study, however, differ from those of previous reports in that patients with decreased H/M had various washout rates. Such results were demonstrated in cases 1 and 4 (Table 1, Fig. 4), both of which showed large LVDD and marked asynergy. In patients with advanced heart failure, viable myocardium converts
to fibrous tissue with resulting remodeling and cardiomegaly. The amount of viable myocardium has an impact on H/M, but the washout rate is standardized by the initial myocardial uptake of $^{123}$I-MIBG, regardless of the amount of viable myocardium. It is likely that this difference causes a poor correlation between H/M and the washout rate. Since the washout rate is independent of the amount of viable myocardium, this measurement could more accurately represent the sympathetic nerve activity than H/M. The discordance between these two measurements was shown by the fact that LVDd correlated well with H/M but just tended to correlate with the washout rate. Therefore, H/M and the washout rate were considered to be independent indices.

High dose dobutamine stress echocardiography has been applied to detect myocardial ischemia in the patients with coronary artery disease, but asynergy was not induced by high-dose dobutamine stress in the present study. And we could evaluate contractile reserve without induced ischemia because all cases showed improved wall motion after low-dose dobutamine stress. Baseline wall motion correlated with sympathetic nerve activity represented by $^{123}$I-MIBG uptake in myocardial images, and this finding supports previous reports. H/M showed better correlation with WM_base than did the washout rate. One explanation for this result could be that the WM_base depends upon the amount of viable myocardium.

The mechanism that relates myocardial contractile reserve to dobutamine stress is probably multifactorial. One of the major factors is myocardial blood flow, and another important determinant is believed to be the β-receptor density represented by contractile reserve in dobutamine stress. The norepinephrine reserve (represented by H/M) seems to be decreased, and the norepinephrine release (represented by the washout rate) seems to be augmented in the down-regulated myocardium. These factors help explain why dobutamine stress improves the coefficient of correlation between wall motion and indices of $^{123}$I-MIBG imaging. The findings obtained with two methods, dobutamine stress echocardiography and $^{123}$I-MIBG scintigraphy, showed good correlation although among the indices the clinical implications were slightly different. Both ΔWM and H/M were indices depending on the viable myocardium. On the other hand, the washout rate was the index of sympathetic nerve activity per viable myocardium. Such a detailed evaluation was considered to be useful, for example, in deciding on the β-blocker treatment strategy. The limitation of the study was that MIBG did not represent receptor function directly, but catecholamine kinetics at the end of sympathetic nerves.

Therefore, we conclude that wall motion, especially in the myocardial response to dobutamine stress, in patients with heart failure is related to sympathetic nerve activity.
REFERENCES


