Using Isoproterenol Stress Echocardiography to Predict the Response to Carvedilol in Patients With Dilated Cardiomyopathy

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Trials have demonstrated that carvedilol can produce hemodynamic, symptomatic, and prognostic improvements in dilated cardiomyopathy (DCM), but some DCM patients have deteriorated after carvedilol, developing congestive heart failure. The present study investigated the use of isoproterenol (ISP) stress echocardiography to select those patients with DCM who would respond to carvedilol. ISP was infused intravenously in 22 patients with DCM and they were classified into 2 groups based on the left ventricular systolic response: good response to ISP [change in fractional shortening (FS) with ISP >0.05, n=13] and poor response to ISP (change ≤0.05, n=9). In the good response group, FS significantly increased from 0.12±0.04 to 0.17±0.08 (mean±SD, p<0.05) with carvedilol, and 7 patients improved symptomatically (New York Heart Association class). However, in the poor response group, no significant difference was observed between FS at baseline and that at the end of follow-up. Moreover, only 1 patient in the poor response group improved symptomatically. ISP stress echocardiography can assist in selecting patients with DCM who will respond positively to carvedilol. (Jpn Circ J 2001; 65: 514–518)

Key Words: Carvedilol; Dilated cardiomyopathy; Echocardiography; Isoproterenol

Dilated cardiomyopathy (DCM) is manifested by marked chamber dilation, diffusely reduced wall motion of the left ventricle, and congestive heart failure; it has a poor prognosis. However, recent clinical trials have demonstrated that β-blocker therapy can produce hemodynamic, symptomatic, and prognostic improvements in patients with DCM, although there was a subgroup that did not improve. Only a few reports have investigated the characteristics of patients with DCM who are likely to respond to β-blocker therapy, so it remains unclear which subgroup of patients with DCM is likely to benefit from such treatment. Moreover, β-blocker therapy must be initiated with small doses to prevent aggravation of heart failure, so although full doses of β-blocker could be administered, it would take several months to confirm which patients responded. It would be very useful to predict which patients will respond to β-blocker therapy before its administration.

Isoproterenol (ISP) stress echocardiography has been used to assess prognosis in patients with DCM; a reduced response to ISP may be due to myocardial damage caused by fibrosis, degeneration, or other factors. In the present study, to assess the relationship between the capacity of the left ventricle to respond to ISP and the functional changes of the left ventricle to β-blocker (carvedilol), we used ISP stress echocardiography to monitor 22 patients with DCM and assessed whether it could predict those patients who would improve with carvedilol treatment.

Methods

Patients

We enrolled 22 patients with DCM admitted to Tsukuba University Hospital (12 men, 10 women; age range, 35–75 years [mean: 57±11]). The diagnosis of DCM was based on findings obtained at echocardiography or cardiac catheterization using the following criteria: (1) left ventricular dilation (left ventricular end-diastolic dimension ≥55 mm or ≥36 mm/m²); (2) impaired systolic function defined as a fractional shortening <0.25; and (3) absence of severe valvular heart disease, severe systemic hypertension, cor pulmonale, chronic systemic disease involving the heart muscle, or increased alcohol intake. In 19 of the 22 patients, coronary angiography was performed, and significant coronary lesions were only detected in 1 patient whose right coronary artery segment 1 demonstrated 90% luminal narrowing. However, that patient's right coronary artery was hypoplastic, and the left circumflex artery was dominant. The remaining 3 patients who did not undergo coronary angiography had no clinical history to suggest ischemic heart disease. Fifteen patients were in New York Heart Association (NYHA) functional class II and 7 were in class III. The cardiac symptoms were also assessed using the specific activity scale score. Among the 22 patients, 16 were in sinus rhythm, 5 had atrial fibrillation, and 1 was in a pacemaker rhythm. Diuretics were prescribed for 19 patients, digitalis was prescribed for 5, and angiotensin-converting enzyme (ACE) inhibitors were prescribed for 11 patients. The remaining 11 patients did not receive ACE inhibitors because their blood pressure was low (systolic blood pressure (SBP) <110mmHg), the SBP decreased by 20mmHg after an initial trial of ACE inhibitors, or they...
developed a dry cough. None of the patients had received β-blockers or ß-agonists within 1 month of the ISP stress test. The study was explained to each patient, and informed consent was obtained.

Administration of Carvedilol

Carvedilol therapy began after ISP stress echocardiography was performed. Each patient was monitored in the hospital until the maximal dose was achieved and the patient’s condition stabilized. The initial dose was 1–2.5 mg/day, in addition to conventional therapy, and gradually increased over a 4-week period to the final dose of 20 mg/day, unless severe hypotension (<80 mmHg), bradycardia (<40 beats/min), or any signs of clinical decompensation appeared.

Echocardiographic Studies

All 22 patients underwent echocardiography using a Toshiba SSH-160A, SSA-370A, SSA-380A, or SSA-390A ultrasonoscope (Toshiba Co, Tokyo, Japan) equipped with a 2.5- or 3.75-MHz transducer. An electrocardiogram and a phonocardiogram were recorded simultaneously with the echocardiogram. Fractional shortening (FS) was calculated as (left ventricular end-diastolic dimension (mm) – left ventricular end-systolic dimension (mm)) / left ventricular end-diastolic dimension (mm). The left ventricular ejection fraction (LVEF) was calculated with the Teichholz method.

ISP Echocardiography  The ISP test was performed in the afternoon in all 22 patients using a previously described technique.11–15 Briefly, the patient lay in the supine position in a darkened room, and ISP was infused for 5 min through an antecubital vein at doses of 0.01 and 0.02 μg·kg⁻¹·min⁻¹ using a calibrated infusion pump. During ISP infusion, the electrocardiogram was monitored continuously. Blood pressure was also measured with a mercury column sphygmomanometer at rest and every minute during ISP infusion. M-mode echocardiography was performed before and immediately after ISP infusion and was recorded on a line scan recorder at 50 mm/s. The change in the FS with ISP infusion (FS immediately after ISP infusion at a dose of 0.02 μg·kg⁻¹·min⁻¹) was determined and ranged from −0.03 to 0.12. We had previously demonstrated that at a dose of 0.02 μg·kg⁻¹·min⁻¹, the change in FS in healthy individuals was 0.14±0.0312 and in the present study, the criterion of poor response to ISP was defined as ≤0.05 (mean value of healthy individuals –3SD). The patients were classified into 2 groups: good response (change in FS ≥0.05; n=13) and poor response (change <0.05; n=9) (Table 1).

Follow-up Studies

After initial evaluation by ISP stress echocardiography, all patients were followed at Tsukuba University Hospital for at least 6 months. The effectiveness of carvedilol therapy was reassessed by echocardiography at 6 or more months after beginning carvedilol; the β-blocker effect was expected to be manifest after more than 2 months and in most cases, at about 6 months, as noted in previous studies.1–4,7–10,16–23 Clinical findings, NYHA functional class and specific activity scale score were repeated at the end of follow-up. The left ventricular end-diastolic and end-systolic dimensions, FS, and LVEF were evaluated by

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Table 1  Clinical Characteristics of the Good and Poor Response Groups at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Good response (n=13)</th>
<th>Poor response (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59±11</td>
<td>55±12</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>7/6</td>
<td>5/4</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>104±14</td>
<td>105±25</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>59±11</td>
<td>61±17</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>70±15</td>
<td>69±17</td>
</tr>
<tr>
<td>NYHA class (II/III)</td>
<td>10/3</td>
<td>5/4</td>
</tr>
<tr>
<td>Specific activity scale (Mets)</td>
<td>4.8±0.9</td>
<td>4.5±0.8</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Diuretics</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Digitalis</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>65±7</td>
<td>66±6</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>57±7</td>
<td>59±7</td>
</tr>
<tr>
<td>FSH</td>
<td>0.12±0.04</td>
<td>0.11±0.05</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.25±0.08</td>
<td>0.24±0.10</td>
</tr>
<tr>
<td>ΔFS</td>
<td>0.09±0.02*</td>
<td>0.03±0.02</td>
</tr>
</tbody>
</table>

*p<0.01 vs poor response group. Values are expressed as mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; FS, fractional shortening; LVEF, left ventricular ejection fraction; ΔFS, change in fractional shortening with isoproterenol.

Table 2  Hemodynamic Data Before and After Isoproterenol (ISP) Infusion

<table>
<thead>
<tr>
<th></th>
<th>Good response group</th>
<th>Poor response group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After ISP</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>70±15</td>
<td>105±18*</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>104±14</td>
<td>105±12</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>59±11</td>
<td>52±9*</td>
</tr>
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</table>

Before vs After ISP *p<0.01, 'p<0.05. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.
echocardiography before and at least 6 months after carvedilol was started.

Statistical Analysis

Data are presented as the mean±SD. Significant differences were determined with the paired or unpaired t-test where appropriate. Differences in frequencies were analyzed with the Fisher exact probability test or the chi-square test. Statistical calculations were performed using Statview software. A p value less than 0.05 was considered statistically significant.

Results

Clinical Findings

Table 1 summarizes the clinical characteristics and medications of the 2 groups of patients at baseline. There were no differences between the 2 groups in any variable examined except the change in FS with ISP infusion. There were also no differences between the groups for therapeutic agents at baseline.

Hemodynamic Data

There was no difference in heart rate (HR), SBP, or diastolic blood pressure (DBP) either at rest or immediately after ISP infusion in the 2 groups (Table 2). In response to ISP infusion, the HR increased, and DBP decreased significantly, but the SBP did not change (Table 2).

Response to Carvedilol

Three patients in the poor response group showed exacerbation of congestive heart failure as a result of initial carvedilol administration. All 13 patients in the good response group and 5 of the 9 patients in the poor response group achieved a final dose of 20 mg/day; 3 patients in the poor response group received a dose of 15 mg/day and the remaining patient developed uncontrollable congestive heart failure at a dose of 7.5 mg/day and died after 7 months, despite the implantation of a left ventricular assist device. Carvedilol was discontinued after almost 1 year in 2 patients in the poor response group because of uncontrollable heart failure and both patients died despite implantation of either a left ventricular assist device or intraaortic balloon pump.

One patient in the poor response group discontinued carvedilol because of heart failure 3 months after the start of therapy. The statistical analysis in the poor response group was limited to 8 patients after excluding this patient. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; FS, fractional shortening; LVEF, left ventricular ejection fraction.

Follow-up period (month) 8±2 8±1

Table 3 Hemodynamic and Echocardiographic Findings at Baseline and End of Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Good response group (n=13)</th>
<th>Poor response group (n=8)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>104±14</td>
<td>111±13</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>59±11</td>
<td>65±11</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>70±15</td>
<td>64±12</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>65±7</td>
<td>61±5*</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>57±7</td>
<td>51±10*</td>
</tr>
<tr>
<td>FS</td>
<td>0.12±0.04</td>
<td>0.17±0.08*</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.25±0.08</td>
<td>0.34±0.15*</td>
</tr>
</tbody>
</table>

*p<0.05 vs baseline value. One patient in the poor response group discontinued carvedilol because of heart failure 3 months after the start of therapy. The statistical analysis in the poor response group was limited to 8 patients after excluding this patient. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; FS, fractional shortening; LVEF, left ventricular ejection fraction.

Fig. 1. New York Heart Association (NYHA) functional class at baseline and at the end of follow-up in the good (left) and poor (right) response groups.

Fig. 2. Specific activity scale score at baseline and at the end of follow-up in the good (left) and poor (right) response groups.
ISP Predicts Response to Carvedilol in DCM

A significant difference was observed between BP or HR at baseline and the values at the end of follow-up in the 2 groups (Table 3). In the poor response group, the HR did not even tend to decrease (Table 3), but in the good response group, the HR at the end of follow-up (64±12 beats/min) tended to be lower than that at baseline (70±15 beats/min, p=0.072, Table 3).

Serial Echocardiographic Follow-up Study (Table 3)

Fig 3 shows the left ventricular end-diastolic dimension at baseline evaluation and at the end of follow-up in the 2 groups. In the good response group, there was a significant decrease from 65±7 mm to 61±9 mm (p<0.05), but in the poor response group, there was no significant difference in the left ventricular end-diastolic dimension between at baseline and at the end of follow-up. Fig 4 illustrates the FS, which in the good response group significantly increased from 0.12±0.04 to 0.17±0.08 (p<0.05), but did not in the poor response group. The LVEF also significantly increased in the good response group, from 0.25±0.08 to 0.34±0.15 (p<0.05), but not in the poor response group. Thus, both a decrease in left ventricular end-diastolic dimension and an increase in left ventricular systolic function were observed in the good response group.

The mean follow-up period was 8±2 months in the good response group and 8±1 months in the poor response group (p=NS, Table 3).

Discussion

We investigated whether ISP stress echocardiography could predict those patients with DCM who will improve after treatment with carvedilol. There were no differences between the good and poor response groups in any variable examined except the change in FS with ISP infusion at baseline. Improvements of cardiac performance, NYHA class, or activity scale were observed with carvedilol in the greater part of patients in the good response group. But in the poor response group, no improvement of cardiac performance was observed with carvedilol, and 3 patients died during or after the follow-up period. Therefore, ISP stress echocardiography can be used to predict those patients with DCM who will improve after treatment with carvedilol.

Some patients showing an increased HR before administration have responded to ß-blocker therapy, but other investigators have found that the HR before administration was not related to treatment response. Eichhorn et al reported that patients with increased SBP respond to ß-blocker therapy, but others have reported that this variable was not related to treatment response. Thus, the clinical significance of hemodynamic variables at rest for predicting the effectiveness of ß-blocker therapy remains controversial in patients with DCM.

Yamada et al demonstrated that patients with mild fibrinogenesis on myocardial biopsy responded to ß-blocker therapy, but those with severe fibrinogenesis did not. However, it is difficult to perform myocardial biopsy in all DCM patients before the start of ß-blocker therapy. In an experimental model of DCM with an attenuated contractile response to ISP infusion, interstitial fibrosis was observed in the heart tissue. Taken together, these results suggest that patients with a good response to ISP infusion are likely to improve with ß-blocker treatment.

It has been suggested that the effects of ß-blocker therapy on DCM patients can be predicted by means of 123I-I-15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid myocardial scintigraphy, which reflects abnormalities in myocardial metabolism or 123I-metaiodobenzylguanidine imaging. However, the advantages of stress echocardiography are the absence of radiation exposure, portability, limited time requirement, relatively low cost, versatility, and efficiency. In addition, ß-adrenergic stress echocardiography can detect ‘hypocontractile but reversible’ myocardium and assess clinical outcome in patients with DCM.

Although the exact mechanisms by which ß-blockers improve the status of patients with DCM are not known, it has been established that they have effects on myocardial metabolism, diastolic function, neurohormones and myocardial norepinephrine depletion. Free radicals and cytokines play an important role in hypocontractile myo-
cardium, so β-blockers, which activate free radical scavenging and attenuate production of cytokines, restore myocardial contraction. We speculate that these mechanisms were involved in the improvement after β-blocker therapy in patients with a good response to ISP and that the severely reduced response to ISP might be due to myocardial damage caused by fibrosis or irreversible degeneration.

Most previous studies of β-blocker therapy have found a decrease in the HR with this treatment, but the present study found no significant difference between HR at baseline and that at the end of follow-up; in the good response group, HR tended to decrease whereas in the poor response group, it did not. Because the final dose of carvedilol in the poor response group was smaller than in the good response group, occult heart failure in the former may have activated sympathetic activity that antagonized the effects of the β-blocker.

Study Limitation

The number of patients was small, so this can only be considered as a pilot study and the findings need to be confirmed in a larger cohort of patients.

Conclusions

ISP stress echocardiography is useful for selecting patients with DCM who will improve with carvedilol therapy.

Acknowledgment

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References


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