Evaluation of Response to Dopamine in Idiopathic Dilated Cardiomyopathy by Echocardiography and Thallium-201 Myocardial Scintigraphy

Kenichi Watanabe, M.D., Hirotaka Oda, M.D., Takashi Tsuda, M.D., and Akira Shibata, M.D.

SUMMARY

Twenty-six patients with idiopathic dilated cardiomyopathy (DCM) underwent thallium-201 myocardial scintigraphy. Nine patients (group A) showed a perfusion defect in the interventricular septum (IVS) and 7 patients (group B) showed a defect in the left ventricular posterior wall (LVPW). Hemodynamic responses and catecholamine levels were compared between 16 patients (DCM group) and 6 control subjects (control group) following dopamine infusion (6 µg/Kg/min). The end-diastolic thickness of the IVS and LVPW, and the percentage wall thickening were assessed by echocardiography.

Plasma dopamine and norepinephrine concentrations in the DCM group were not different from those of the control group at rest. During the dopamine infusion, however, norepinephrine increased only in the control group. There were significant differences in the thickness of the IVS among the 3 groups [7.3±1.4 mm for group A (p<0.001 vs control and p<0.05 vs group B), 8.9±1.5 mm for group B (p<0.01 vs control), 10.2±1.5 mm for the control group]. The percentage thickening of the IVS increased during the dopamine infusion in group B only and the thickening of the LVPW increased in group A only. Thus, in the myocardium of DCM patients with thallium perfusion defects, the degree of thickening did not change during dopamine infusion, but in the myocardium of DCM patients with normal thallium uptake the percentage thickening increased more than in the control group.

Additional Indexing Words:
Idiopathic dilated cardiomyopathy Thallium scintigram Echocardiogram Dopamine Catecholamine

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Received for publication May 21, 1984.
IDIOPATHIC dilated cardiomyopathy (DCM) results in cardiomegaly, impaired left ventricular function and congestive heart failure. Patients with DCM usually have normal coronary arteries and it has been suggested that myocardial damage may be related to an autoimmune mechanism. An altered catecholamine metabolism has been observed in the patients. Other investigators have suggested that cardiomyopathy is closely related to changes in the capillary wall permeability as evidenced by the presence of horseradish peroxidase, a macromolecular tracer which penetrates into the damaged cardiac muscle.

In thallium-201 myocardial perfusion imaging, thallium uptake is affected not only by the coronary flow but also by the myocardial viability. Thallium is believed to be actively transported and concentrated in the myocardial cell. The presence of a reverse redistribution defect or a fixed perfusion defect involving more than 40% of the outer left ventricular perimeter strongly favors a diagnosis of ischemic cardiomyopathy rather than DCM. In another study, however, a focal thallium perfusion defect was studied at autopsy and it did not have a corresponding area of myocardial scarring. Echocardiography has been used to differentiate ischemic cardiomyopathy from DCM by detecting segmental abnormal myocardial wall motion. The combined use of these techniques will be important in the detection and localization of myocardial damage.

The purpose of the present study was to determine whether thallium imaging and echocardiography could be used to distinguish viable muscle in the DCM. The aim of this study was to compare the influence of dopamine on the defect-area with that on the uptake-area of the thallium myocardial scintigram.

SUBJECTS AND METHODS

(1) Patients studied

Sixteen patients were selected from 26 patients with a clinical diagnosis of DCM by thallium myocardial imaging. Ten were males and 6 were females with a mean age of 47 years (range 20–64 years). In the 26 patients, diagnosis was based on the results of cardiac catheterization, including both left ventricular cineangiography and selective coronary arteriography. All subjects had impaired left ventricular function (ejection fraction less than 40%). None of the 26 patients showed any significant narrowing of the coronary artery (more than 50%). The functional class was New York Heart Association class I, II or III.

The control group included 4 healthy persons and 2 patients with small
atrial septal defects (pulmonary flow/systemic flow ratio less than 2.0).

(2) Thallium-201 imaging

Thallium myocardial imaging was performed in all 26 DCM patients. At rest, 3 mCi of thallous chloride was administered intravenously. Images were obtained at 10 min using a gamma camera (Searle, PHO-GAMMA LFOV) fitted with a low energy, high resolution converging collimator. A computer system (Informatek, Simis 3) was interfaced to the gamma camera and images were acquired in static 64×64 word mode. Images were obtained in the antero-posterior, 45° left anterior oblique, 60° left anterior oblique and left lateral projections. A perfusion defect was defined as an area with a count density of less than 70% of the maximum using Goris’ background subtraction method.14)

(3) Dopamine infusion

The 16 DCM and 6 control subjects first rested in a supine position for 30 min. Venous blood samples were then withdrawn for the determination of plasma norepinephrine and dopamine. Catecholamine analysis was made by high performance liquid chromatography.15) During the dopamine infusion at 6 μg/Kg/min, the hemodynamic parameters and plasma levels of norepinephrine and dopamine were determined again at 30 min.

(4) Hemodynamic parameters

The carotid pulse wave and echocardiogram were recorded and the mean blood pressure (systolic+diastolic×2/3) was determined before and

![Diagram](image_url)

Fig. 1. Thicknesses of the interventricular septum and left ventricular posterior wall were measured at end-diastole and end-systole and the percentage thickening (%Th) was determined as shown in the figure.
during the dopamine infusion.

Pre-ejection period / left ventricular ejection time (PEP/LVET) was calculated from the systolic time interval.

The echocardiographic study was performed using a phased array electronic sector scanner (Toshiba, SSH-11A) with a transducer of 2.4 MHz frequency. The end-diastolic thicknesses of the interventricular septum (IVS) and the left ventricular posterior wall (LVPW) were measured at the peak of the R wave on the simultaneously recorded ECG. The end-systolic thickness was measured at the time of the peak posterior movement of the IVS and measurements were made at or just below the tips of the mitral valve. The percentage thickening of the IVS and LVPW were measured as follows: percentage thickening $\left[\frac{\text{end-systolic} - \text{end-diastolic}}{\text{end-diastolic thickness}}\right] \times 100$ (%) (Fig. 1). The ejection fraction was calculated from Teichholz’s formula.16

(5) Statistical analysis

Statistical analysis utilized Student’s t-test. A p value of less than 0.05 was considered to indicate a significant difference.

Results

(1) Thallium myocardial scintigram

The quantitative analysis of the planar images revealed abnormalities in 24 of the 26 patients (92%) with DCM and an absence of abnormality in 2 patients (8%). Diffuse spotty defects of the left ventricular wall were observed in 4 of the 24 patients and 1 patient had a defect in the anterior wall only. The planar imaging correctly identified 9 of 19 patients having defects in the IVS (Fig. 2) and 10 patients with defects in the LVPW (Table I). Three patients were excluded because of poor recording of the cardiac wall in the M-mode echocardiogram. Finally, the group with perfusion defects in the IVS (group A) comprised 9 patients and that with defects in the LVPW 7 patients (group B).

(2) Dopamine and norepinephrine concentrations before and during dopamine administration (Table II)

In the DCM and the control groups, the dopamine concentrations at rest were $5.8 \pm 2.4 \text{ ng/ml}$ (mean values $\pm$ 1 standard deviation) and $5.2 \pm 2.9 \text{ ng/ml}$, respectively. The norepinephrine concentrations were $215 \pm 118 \text{ pg/ml}$ and $130 \pm 39 \text{ pg/ml}$, respectively. These differences were not significant (NS).

During the dopamine infusion, dopamine concentration increased to $70.5 \pm 23.6 \text{ ng/ml}$ in the DCM group and $86.2 \pm 30.8 \text{ ng/ml}$ in the control
Fig. 2. Idiopathic dilated cardiomyopathy in a 56-year-old man. This patient did not have a clear-cut history of myocardial infarction, had no Q waves on ECG and had no coronary arterial stenosis at cardiac catheterization. Left panel: Thallium-201 images in antero-posterior (A-P), 45° left anterior oblique (LAO-45), 60° left anterior oblique (LAO-60) and left lateral (L-LAT) projections showing a defect in the interventricular septum and antero-lateral wall. Right panel: Interventricular thickness and the percentage thickening in this patient measured by M-mode echocardiogram decreased.

<table>
<thead>
<tr>
<th>Table I. Results of Thallium-201 Myocardial Imaging</th>
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<tbody>
<tr>
<td><strong>No. of patients</strong></td>
</tr>
<tr>
<td>total</td>
</tr>
<tr>
<td>abnormality absent</td>
</tr>
<tr>
<td>abnormality present</td>
</tr>
<tr>
<td>diffuse spotty defects</td>
</tr>
<tr>
<td>anterior wall only</td>
</tr>
<tr>
<td>interventricular septum</td>
</tr>
<tr>
<td>left ventricular posterior wall</td>
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</table>

group (before vs during, both p<0.001, and DCM vs control NS). The norepinephrine concentration, however, did not increase in the DCM group (273±134 pg/ml), but did increase to 235±34 pg/ml in the control group (p<0.02)

(3) Hemodynamic changes during the dopamine infusion

Mean values±1SD of heart rate, mean blood pressure and ejection fraction of 16 DCM patients and 6 control subjects before and during the dopamine infusion are listed in Table III.

There were no significant differences in heart rate and mean blood pressure before and during dopamine infusion in the DCM and control groups.
Table II. Serum Dopamine and Norepinephrine Levels before and during Dopamine Infusion

<table>
<thead>
<tr>
<th></th>
<th>serum dopamine (ng/ml)</th>
<th>serum norepinephrine (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before</td>
<td>during</td>
</tr>
<tr>
<td>DCM</td>
<td>5.8±2.4*</td>
<td>70.5±23.6**</td>
</tr>
<tr>
<td>control</td>
<td>5.2±2.9</td>
<td>86.2±30.8*</td>
</tr>
</tbody>
</table>

DCM = idiopathic dilated cardiomyopathy; NS = not significant.
* p<0.001 and ** p<0.02 vs before dopamine infusion.

Table III. Hemodynamic Changes during Dopamine Infusion

<table>
<thead>
<tr>
<th></th>
<th>heart rate (beat/min)</th>
<th>mean blood pressure (mmHg)</th>
<th>PEP/LVET</th>
<th>ejection fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before</td>
<td>during</td>
<td>before</td>
<td>during</td>
</tr>
<tr>
<td>DCM</td>
<td>72±16</td>
<td>73±18</td>
<td>88±16</td>
<td>86±14</td>
</tr>
<tr>
<td>control</td>
<td>70±12</td>
<td>74±16</td>
<td>86±14</td>
<td>87±15</td>
</tr>
</tbody>
</table>

PEP/LVET = pre-ejection period/left ventricular ejection time.
* p<0.02 vs before dopamine infusion.

Table IV. End-diastolic Myocardial Wall Thickness and Thallium-201 Myocardial Perfusion Defect

<table>
<thead>
<tr>
<th></th>
<th>thickness of interventricular septum (mm)</th>
<th>thickness of left ventricular posterior wall (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>group A</td>
<td>7.3±1.4*</td>
<td>8.1±1.2*</td>
</tr>
<tr>
<td>group B</td>
<td>8.9±1.5*</td>
<td>8.8±0.9*</td>
</tr>
<tr>
<td>control</td>
<td>10.2±1.5</td>
<td>10.1±1.3</td>
</tr>
</tbody>
</table>

group A: patients with defect in interventricular septum.
group B: patients with defect in left ventricular posterior wall.
* p<0.01 vs control, ** p<0.05 vs group B.

There were significant differences in PEP/LVET and ejection fraction in the DCM group, but not in the control group.

(4) End-diastolic myocardial thickness and thallium perfusion defect (Table IV)

In group A, the thickness of the IVS was 7.3±1.4 mm, which was less than that of group B (8.9±1.5 mm) (p<0.05) and the control group (10.2±1.5 mm) (p<0.01). The thickness of the IVS of group B was less than that of the control group (p<0.01).

In group A, the thickness of the LVPW was 8.1±1.2 mm and in group B it was 8.8±0.9 mm. The thicknesses of the LVPW of both groups were less than that of the control group (10.1±1.3 mm) (p<0.01). No significant
Table V. Changes of the Percentage Thickening during Dopamine Infusion

<table>
<thead>
<tr>
<th></th>
<th>thickening of interventricular septum (%)</th>
<th>thickening of left ventricular posterior wall (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before</td>
<td>during</td>
</tr>
<tr>
<td>group A</td>
<td>16±10*</td>
<td>20±11*</td>
</tr>
<tr>
<td>group B</td>
<td>35±9</td>
<td>61±15**</td>
</tr>
<tr>
<td>control</td>
<td>47±15</td>
<td>55±16</td>
</tr>
</tbody>
</table>

* p<0.01 vs control and group B in interventricular septum and vs control and group A in left ventricular posterior wall.
** p<0.02 vs before dopamine infusion.
*** p<0.01 vs group A and p<0.05 vs control.

difference was found between the thicknesses of group A and group B.

(5) Percentage thickening of the IVS and LVPW (Table V)

In group A, the percentage thickening of the IVS was 16±10% and in group B, 35±9%. The percentage thickening in group A was smaller than that in group B or the control group (47±15%) (both p<0.01).

In group A, the percentage thickening of the LVPW was 55±23% and in group B, 23±10%. The percentage thickening in group B was smaller than that in group A or the control group (60±27%) (both p<0.01).

(6) Changes in the percentage thickening during the dopamine infusion (Table V)

(i) Percentage thickening of the IVS

No significant changes were found during the dopamine infusion in group A (16±10% vs 20±11%) or the control group (47±15% vs 55±16%). However, in group B the percentage thickening of the IVS increased significantly during the dopamine infusion (35±9% vs 61±15%) (p<0.02). During the dopamine infusion, group B (26±14%) showed a larger change in the percentage thickening of the IVS than did group A (4±8%) (p<0.01) or the control group (8±9%) (p<0.05).

(ii) Percentage thickening of the LVPW

No significant changes were found in group B (23±10% vs 25±9%) or the control group (60±27% vs 80±29%). However, in group A the percentage thickening of the LVPW increased significantly during the dopamine infusion (55±23% vs 94±28%) (p<0.02). During the dopamine infusion, group B showed a smaller increase in the percentage thickening of the LVPW than did group A (2±7% vs 39±24%) (p<0.01) or the control group (20±14%) (p<0.05).
DISCUSSION

The cause and course of DCM are unknown and the response to therapy is generally unsatisfactory. New preventive and therapeutic approaches to this disease are needed.18)

In rheumatic and valvular heart disease not complicated by either congestive failure or angina pectoris, the concentrations of plasma epinephrine and norepinephrine lie within normal limits both before and after exercise. When congestive failure develops, the resting level of plasma norepinephrine is often raised and there is a much greater increase on exercise levels of norepinephrine in these patients than that seen in normal subjects.19) In this study, no significant difference in norepinephrine level from the control group was seen at rest. This may be because we excluded those patients in New York Heart Association class IV.

Some reports indicate that catecholamines reach plateau levels at about 5–10 min after their infusion and the half life in the peripheral blood has been calculated to be less than 20 sec.20,21) There are interrelations among the plasma concentrations of amines when one is infused, and either a fall or increase in the norepinephrine concentration is found after the infusion of epinephrine.22,23) Additionally, in healthy subjects and patients with congestive heart failure, intravenous infusion of dopamine in a small dose (2–5 μg/Kg/min) increases cardiac output without increasing heart rate or blood pressure.24–26) In this study, the norepinephrine concentrations did not change during dopamine infusion in the DCM group, but did increase in the control group. Additionally, dopamine caused no statistically significant change in heart rate and mean blood pressure, but significant alternations of PEP/LVET and ejection fraction were observed in DCM patients. In the control group, PEP/LVET and ejection fraction did not change significantly. These differences may, in part, be caused not only by the impaired left ventricular function, but also by an alternative dopaminergic receptor.19)

Real-time two-dimensional echocardiography and thallium myocardial perfusion scintigraphy have been reported to be useful in detecting the abnormal myocardium.11,27) Bulkley et al performed thallium scintigraphy in 8 patients with DCM.11) All but one of the patients demonstrated either normal perfusion or a defect amounting to less than 20% of the left ventricular circumference. Massie et al compared angiographic wall motion and thallium scintigraphy in patients without evidence of previous myocardial infarction.28) In only two of 100 myocardial segments with normal contraction were perfusion defects found. In addition, they showed that the incidence of perfusion defects was closely related to the degree of coronary artery narrow-
In the present study, 20 of 26 patients with DCM (77%) had localized segmental perfusion defects. Thus, localized segmental perfusion defects are common in patients with DCM.

In the normally functioning ventricle, the systolic wall thickness is thicker than the diastolic. With decreased ventricular function, the degree of thickening decreases and on rare occasions, such as with ischemia, there may actually be a thinning of the ventricular wall during systole. Even if the left ventricular walls move poorly, the wall thickness is within normal limits in some patients. In this study, the IVS thickness in patients who showed thallium myocardial perfusion defects was less than that in either the control group or in patients without a perfusion defect. In addition, the percentage thickening in the thallium perfusion defect area was smaller than that in the thallium uptake area and the control group. The dopamine infusion was effective only in the thallium uptake area in patients with DCM.

The causative mechanism underlying the production of perfusion defects in patients with DCM remains obscure though a number of possibilities exist. Firstly, true myocardial ischemia may be present. In this study, the percentage thickening was reduced in the myocardium with perfusion defects and did not respond to dopamine infusion. Secondly, foci of interstitial or replacement fibrosis are known to occur in DCM and their presence was postulated by Bulkley et al as the possible cause of the defects found in such patients. Furthermore, in our other study in patients with old myocardial infarction, myocardial thickness was less than in the control and the percentage thickening was severely decreased. In addition, the percentage thickening did not change during dopamine infusion. Saltissi et al and Pohost et al found reversible defects to be more common than the fixed ones normally associated with myocardial fibrosis. These data suggest that histological fibrosis of varying degree occurs in DCM and that it tends to produce perfusion defects and decreased response to dopamine of varying degree. Lastly, a primary abnormality at the myocardial cell membrane level may produce perfusion defects. Eckstein et al suggest that an abnormality of the cell membrane may be found not only in the myocardium, but also in other organs, for instance peripheral blood lymphoid cells. In this study, during the dopamine infusion plasma norepinephrine concentration increased in the control group but not in the DCM group.

In conclusion, this study has shown that localized segmental perfusion defects are common in patients with DCM. The percentage thickening and response to dopamine are reduced in the myocardium with perfusion defects. On the other hand, in the myocardium with normal uptake, the percentage thickening and response to dopamine are increased. The thallium perfusion
defect may be related not only to the thickness of the myocardium, but also to its viability.

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