CLINICAL SIGNIFICANCE OF DIPYRIDAMOLE TI-201 EMISSION COMPUTED
TOMOGRAPHY PERFUSION ABNORMAlITY FOR EVALUATING
PATHOPHYSIOLOGICAL AND PATHOLOGICAL ASPECTS
IN HYPERTROPHIC CARDIOMYOPATHY

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A dipyridamole-induced TI-201 perfusion abnormality was evaluated from its
clinical features, echocardiography and myocardial histopathology in 39
patients with hypertrophic cardiomyopathy (HCM). From the findings of
TI-201 emission computed tomography (ECT), subjects were divided into
three groups: group 1 (n = 16) which did not show a perfusion abnormality
in the hypertrophic region; group 2 (n = 12) which showed a perfusion defect
on the initial image with complete redistribution on the delayed image; and
group 3 (n = 11) which showed a persistent perfusion defect—this group in-
cluded most patients who revealed partial and/or incomplete redistribution.
Echocardiography revealed that group 2 showed a marked asymmetrical septal
hypertrophy and an incidental obstructive pattern, and that group 3 had a
significantly dilated left ventricular diastolic dimension and a decreased
percentage of fractional shortening. Group 3 also showed frequent ventricular
tachycardia and a familial history of cardiomyopathy. As for the myocardial
biopsy findings, group 3 had significantly advanced myocardial fibrosis, the
percentage being 6.0 ± 3.1% in group 1; 5.5 ± 2.5% in group 2; and 11.9 ±
3.4% in group 3. Thus, it was concluded that the persistent perfusion defect
on dipyridamole stress TI-201 ECT testing is an important finding corre-
spending to the advanced clinical and pathological aspects of HCM.

ABNORMAL thallium-201 (TI-201) myocardial
perfusion detected by stress test has been
reported in hypertrophic cardiomyopathy
(HCM). The mechanism of this phenomenon
has been postulated to arise from transient myo-
cardial ischemia, myocardial damage or marked
myocardial hypertrophy itself. However, the
clinical significance of this finding still remains
uncertain. In this study, we examined the
dipyridamole-induced TI-201 perfusion abnor-
mality by using ECT, and assessed the relation-
ship between the perfusion abnormality and the
histopathological characteristics of HCM.

METHOD

Patients: Thirty-nine HCM patients with asym-
metrical septal hypertrophy were studied. The
diagnosis was made according to the criteria laid
down by the Committee for Investigation of
Idiopathic Cardiomyopathy. Twenty-nine were
male and 10 were female. The mean age was 51
years (range 26–74 years). Nine of the 39

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patients revealed an obstructive pattern indicated by a marked systolic anterior movement of the anterior mitral leaflet reaching the interventricular septum in mid-systole on echocardiography; the remaining 30 patients revealed a non-obstructive pattern. No patients showed evidence of coronary artery lesions on angiography.

**Classification of the patients:** On the basis of the findings of dipyridamole TI-201 ECT testing, we classified subjects into 3 groups. Group 1 consisted of 16 cases who did not show a TI-201 perfusion defect in the hypertrophic regions when examined by echocardiography. Group 2 consisted of 12 cases whose initial TI-201 image showed a perfusion defect in the hypertrophic regions, which completely disappeared on the delayed image, i.e. "complete redistribution". Group 3 consisted of 11 cases whose initial TI-201 perfusion defect in the hypertrophic regions remained on the delayed image, i.e. a "persistent defect". However, in 9 cases in group 3, partial or incomplete redistribution was recognized by initial TI-201 perfusion defect segments on the delayed image.

**Dipyridamole TI-201 ECT:** A rotating gamma camera (Shimazu LFOV) and an analyzing system (Scintipac 2400) were used for ECT. With monitoring of the electrocardiogram, heart rate and blood pressure, 0.56 mg/kg dipyridamole was intravenously injected for 4 min. Then, 2 mCi of TI-201 was injected as a bolus 3 min after dipyridamole injection. TI-201 ECT was started 5 min later. This was designated the "initial image". After a period of 3 h, TI-201 ECT was repeated in the same position, which was designated the "delayed image". The range of rotation of the gamma camera was 180° (from 60° left posterior oblique to 60° right anterior oblique). The left ventricular image of TI-201 ECT was reconstructed using a convolution algorithm without attenuation correction. Four sectional images were recorded along the long axis, two levels of short axis and a four chamber section. The left ventricular wall on these images was divided into nine segments, based on the angiographic ventricular segmentation of the American Heart Association (Fig. 1). The regions of interest (ROIs) were situated in these nine segments. The relative activity was assessed for TI-201 perfusion defect and redistribution. This was calculated as the ratio of TI-201 activity of each segment to the maximal TI-201 activity among segments of a section. The normal lower limit of relative activity was determined from 12 normal subjects as mean−2 SD (standard deviation). A "TI-201 perfusion defect" was taken to be present when the relative activity was below the normal lower limit. "Complete redistribution" was taken to be present when the relative activity on the defect segment attained the normal range on the delayed image and all evidence of a TI-201 perfusion defect disappeared. "Partial redistribution" was taken to be present when the relative activity on part of the defect segment attained the normal range on the delayed image but the TI-201 perfusion defect remained partially on the delayed image. "Incomplete redistribution" was taken to be present when the value of the relative activity of the defect segment improved by more than 2 SD, but remained below the normal limit on the delayed image. A "persistent defect" was taken to be present when the relative activity remained below the normal lower limit on the delayed image. All group 2 patients exhibited complete redistribution only, while group 3 patients revealed persistent defects with or without partial and/or incomplete redistribution. In this study, the TI-201 perfusion defect was evaluated only in hypertrophic regions as confirmed by echocardiography.
### TABLE 1 COMPARISON OF HEMODYNAMICS AT REST AND AFTER DIPYRIDAMOLE BETWEEN GROUPS 1, 2 AND 3

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (l/min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>65.1 ± 7.6</td>
<td>62.0 ± 6.6</td>
<td>69.0 ± 15.6</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>82.9 ± 13.0</td>
<td>80.0 ± 12.4</td>
<td>82.5 ± 14.1</td>
</tr>
<tr>
<td><strong>Systolic pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>124.6 ± 16.8</td>
<td>121.0 ± 17.4</td>
<td>127.5 ± 21.5</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>116.3 ± 15.9</td>
<td>108.5 ± 17.9</td>
<td>113.3 ± 17.5</td>
</tr>
<tr>
<td><strong>Diastolic pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>78.8 ± 11.7</td>
<td>74.8 ± 8.9</td>
<td>77.5 ± 15.4</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>71.8 ± 11.7</td>
<td>66.6 ± 11.0</td>
<td>68.4 ± 14.3</td>
</tr>
</tbody>
</table>

The response of heart rate and blood pressure to dipyridamole administration was similar in all three groups.

### TABLE II CLINICAL FEATURES OF GROUPS 1, 2 AND 3

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>16</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52 ± 13</td>
<td>55 ± 12</td>
<td>54 ± 16</td>
</tr>
<tr>
<td>Sex</td>
<td>F 3 M 3</td>
<td>F 3 M 9</td>
<td>F 4 M 7</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cases)</td>
<td>0/16</td>
<td>3/12</td>
<td>5/11*</td>
</tr>
<tr>
<td>Exertional dyspnea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cases)</td>
<td>1/16</td>
<td>2/12</td>
<td>5/11*</td>
</tr>
<tr>
<td>Chest X-p CTR</td>
<td>49.0 ± 5.7</td>
<td>52.5 ± 5.0</td>
<td>55.0 ± 5.1*</td>
</tr>
<tr>
<td>ECG abnormal Q-wave</td>
<td>2/16</td>
<td>2/12</td>
<td>5/11*</td>
</tr>
<tr>
<td>(cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>So1 + Rs5 (mm)</td>
<td>29 ± 13</td>
<td>45 ± 21*</td>
<td>47 ± 21*</td>
</tr>
<tr>
<td>Holter ECG VT</td>
<td>1/14</td>
<td>2/10</td>
<td>4/18*</td>
</tr>
<tr>
<td>(cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCG IVST (mm)</td>
<td>16.4 ± 2.7</td>
<td>19.2 ± 2.6*</td>
<td>17.9 ± 3.0</td>
</tr>
<tr>
<td>LVPWT (mm)</td>
<td>11.1 ± 1.9</td>
<td>11.5 ± 1.6</td>
<td>11.3 ± 1.9</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>42.7 ± 4.1</td>
<td>40.8 ± 5.2</td>
<td>51.1 ± 2.9*</td>
</tr>
<tr>
<td>%FS (%)</td>
<td>41.6 ± 7.0</td>
<td>46.3 ± 6.4</td>
<td>33.8 ± 7.0*</td>
</tr>
<tr>
<td>Obstructive type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cases)</td>
<td>3/16</td>
<td>6/12</td>
<td>0/11</td>
</tr>
<tr>
<td>Biopsy %fibrosis (%)</td>
<td>6.0 ± 3.1 (n = 11)</td>
<td>5.5 ± 2.5 (n = 6)</td>
<td>11.9 ± 3.4 (n = 5)*</td>
</tr>
</tbody>
</table>

Each value in groups 2 and 3 was compared with that of group 1 as control value (*p < 0.05, **p < 0.01). VT = ventricular tachycardia; IVST = interventricular septal thickness; LVPWT = left ventricular posterior wall thickness; LVDD = left ventricular diastolic dimension; %FS = percentage fractional shortening.

Graphy, because non-hypertrophic segments were often recognized as showing hypoperfusion compared with asymmetrical hypertrophic segments.

**Echocardiography:** All patients underwent echocardiography using a Toshiba Ultrasound SSH-40A. The measurement of interventricular septal thickness, left ventricular posterior wall thickness, left ventricular end-diastolic dimension (LVDD) and end-systolic dimension (LVDs) was carried out using a strip chart M-mode record, and averaging serial five beats. The percentage fractional shortening (%FS) was calculated as LVDD - Ds/Dd x 100 (%).

**Myocardial biopsy:** Right sided interventricular septum endomyocardial biopsy was performed in 22 cases. The position of the hypertrophic region of the interventricular septum for biopsy was confirmed by biplane left ventriculography
and right ventriculography. The biopsy specimens obtained from the hypertrophic regions were stained with Azan stains. The percentage of fibrosis was measured by a point counting method using a light microscope, i.e., the number of cross-points lying on fibrotic areas divided by the total number of cross-points.

**Statistical analysis:** Mean value ± standard deviation was calculated for each variable. A non-paired student t-test and χ²-test was used to compare the two groups. A probability (p) value of less than 0.05 was considered to be significant.

**RESULTS**

**Dipyridamole TI-201ECT:** On initial image, a TI-201 perfusion defect in the hypertrophic region was observed in 23 out of the 39 cases (59.0%). As described in the patients' classification, the TI-201 perfusion defect completely disappeared on the delayed image in 12 of the 23 cases groups. It remained on the delayed image in 11 of the 23 cases (group 3). In the total of 49 hypertrophic segments detected in group 2, 13 (26%) showed a TI-201 perfusion defect on the initial image only. Of the total of 44 hypertrophic segments detected in group 3, 19 showed a TI-201 perfusion defect on the initial image, of which 6 revealed partial redistribution, while 13 remained as a persistent defect on the delayed image. Nine of these 13 segments were associated with incomplete redistribution.

The response of heart rate, blood pressure and rate pressure product to dipyridamole administration was similar in all 3 groups (Table I). Chest oppression occurred in 12.5% of group 1, 33% of group 2 and 9.1% of group 3. ST depression was not found in any of the cases.

**Clinical features** (Table II): Age and male-female ratio were similar in all 3 groups. A family history of cardiomyopathy was frequently recorded in group 3. The cardiothoracic ratio was greatest in group 3, and the ratio significantly different from that of group 1. An abnormal Q-wave was frequently found in group 3 on electrocardiography. The electrocardiographic left ventricular voltage was markedly elevated in groups 2 and 3. Ventricular tachycardia as detected by Holter monitoring was most frequent.
Fig. 4. Comparison of percentage fractional shortening (%FS) between groups 1, 2 and 3.

Fig. 5. Comparison of percentage fibrosis on endomyocardial biopsy specimens between groups 1, 2 and 3.

Fig. 6. Representative case of group 3. The upper part shows the initial images after dipyridamole administration, which indicate the presence of a perfusion defect in septum, anterior and apex. Delayed images shown in the lower part indicate the persistent perfusion defect in the septum with incomplete redistribution.

in group 3.

Echocardiographic findings: Left ventricular outflow tract obstruction was frequently found in group 2 (50%). The interventricular septum was thickest in group 2, which was significantly different from group 1 (Fig. 2). However, the left ventricular posterior wall thickness was similar in all 3 groups. LVDd was significantly
larger in group 3 compared with groups 1 and 2 (Fig. 3). %FS was significantly decreased in group 3 compared with groups 1 and 2 (Fig. 4). Thus, from echocardiographic findings, group 2 was characterized by marked interventricular septal hypertrophy and group 3 had decreased left ventricular function; group 1 did not exhibit such findings.

Myocardial biopsy: Myocardial fibrosis determined by biopsy was extensive in group 3. The percentage of fibrosis was significantly higher in group 3 compared with groups 1 and 2 (Fig. 5).

Representative case: A 34 year old man. Echocardiographically, hypertrophy was observed in the interventricular septum, anterior wall and apex. On Ti-201 ECT testing, a perfusion defect was observed in the anterior and septal wall on the initial image (upper part Fig. 6), and incomplete redistribution occurred in the same region on the delayed image, i.e. a persistent perfusion defect was present (lower part of Fig. 6). Thus, this case was included in group 3. The percentage of fibrosis on myocardial biopsy was 12.1%.

DISCUSSION

In patients with HCM, the appearance of a Ti-201 perfusion defect and redistribution phenomenon on stress Ti-201 myocardial scintigraphy has been recognized. Disturbed coronary blood flow reserve has been hypothesized to be one of the factors giving rise to this phenomenon. On the other hand, a Ti-201 persistent perfusion defect is known to indicate myocardial necrosis or fibrosis. However, in patients with HCM the histopathological characteristic corresponding to the Ti-201 perfusion image have not yet been reported. This investigation was designed to examine the mechanisms and significance of a dipyridamole-induced Ti-201 perfusion abnormality from the viewpoint of clinical features, echocardiography and myocardial histopathology obtained from a biopsied specimen.

In general, an initial Ti-201 perfusion defect is caused by myocardial blood flow disparity in the different myocardial regions while the redistribution phenomenon on the delayed image is considered to indicate the presence of viable muscle in that region. Therefore, in this study an initial Ti-201 perfusion defect in the hypertrophic region caused by dipyridamole indicates insufficient coronary blood flow augmentation in that hypertrophic region during its vasodilator action. The persistent perfusion defect indicates myocardial cell damage, while the redistribution reflects the presence of viable...
myocardium with a decreased perfusion reserve.

Several possible mechanisms are speculated to contribute to the decreased coronary blood flow reserve in HCM, namely intramyocardial small vessel disease,13–15 inadequate capillary density in proportion to the increased myocardial mass,16,17 brief hypotension due to increased left ventricular outflow obstruction during stress,18 septal perforator compression and coronary microvascular spasm.19 However, the dominant mechanism for TI-201 perfusion abnormality is still unknown. Our study shed light on the fact that dipyridamole-induced vasodilation causes two types of TI-201 perfusion abnormality in HCM. The first is an initial perfusion defect with complete redistribution and the second is persistent perfusion defect with or without partial and/or incomplete redistribution. From the echocardiographic findings, group 2 patients who showed an initial TI-201 perfusion defect with complete redistribution were characterized by marked asymmetrical septal hypertrophy. This may suggest that relatively less capillary density against the marked hypertrophy is the important mechanism for complete redistribution in HCM. In addition, incidental left ventricular outflow tract obstruction may contribute to decreased myocardial perfusion during dipyridamole action. On the other hand, group 3 patients with persistent perfusion defects were characterized by advanced myocardial fibrosis. This may suggest that advanced myocardial cell damage resulting in increased fibrosis is the direct cause of persistent perfusion defect on the delayed image. The advanced myocardial damage in group 3 may be associated with worse clinical signs, such as left ventricular dilation with decreased fractional shortening and a high incidence of ventricular tachycardia and a family history of cardiomyopathy. These clinical signs are known to be indicators of a poor prognosis in HCM.20,21 Thus the finding of a TI-201 persistent perfusion defect with or without partial and/or incomplete redistribution may be important for the prognosis. Recently, it has been reported that some patients with HCM have some features similar to dilated cardiomyopathy.22,24 Those cases have a markedly dilated left ventricle with severe dysfunction and a TI-201 persistent perfusion defect, which may be a progressed feature of our group 3 patients. The histopathological basis in these patients is reported to be advanced myocardial fibrosis.13,14,22,24 This similarity between our group 3 patients and those with reported dilated cardiomyopathy-like HCM suggests that there may be a subgroup of HCM whose myocardial involvement progresses by fibrosis, and the presence of a TI-201 persistent perfusion defect may be one of the important signs to differentiate this subgroup. Maron et al. reported that intramural small coronary artery disease might be an important cause of myocardial fibrosis in HCM.15 Our endomyocardial biopsy results failed to detect such small coronary artery lesions, because the small biopsy specimens seldom included arterioles. However, the partial and/or incomplete redistribution observed in the persistent perfusion defect segments in most group 3 patients suggests that small coronary artery lesions might decrease myocardial perfusion and induce myocardial fibrosis simultaneously. As supporting evidence, one autopsied case in group 3 revealed medial hypertrophy and luminal narrowing of the arterioles in the hypertrophic region (Fig. 7). Advanced myocardial damage, resulting from extensive fibrosis and possibly from small coronary artery lesions, is considered to contribute to the worse clinical signs in group 3 HCM patients.

It is concluded that dipyridamole stress TI-201 myocardial scintigraphy is of great use for differentiating the two types of perfusion abnormality. The complete redistribution is associated with marked hypertrophy, while a persistent perfusion defect corresponds to advanced myocardial damage which contributes to the occurrence of the worse clinical aspects of HCM.

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