EFFECT OF DILTIAZEM ON LEFT VENTRICULAR
ISOVOLUMIC RELAXATION TIME IN PATIENTS
WITH HYPERTROPHIC CARDIOMYOPATHY

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The effect of diltiazem on left ventricular isovolumic relaxation time was
examined in 11 patients with hypertrophic obstructive and non-obstructive
cardiomyopathy in a combined study using phonocardiograms and echocar-
diograms. Five to 10 min after intravenous injection of diltiazem (0.2 mg/kg,
body weight), a prolonged isovolumic left ventricular relaxation time, which
was measured from aortic component of the second heart sound to the mitral
opening on the echocardiogram, decreased from 63.1 ± 26.0 to 46.9 ± 28.0
msec (p < 0.01).

This study suggests that diltiazem, one of the calcium blocking agents,
may ameliorate the impaired left ventricular diastolic function in patients
with hypertrophic cardiomyopathy.

HYPERTROPHIC cardiomyopathy is often
associated with an abnormally prolonged
left ventricular isovolumic relaxation time and a
deteriorated left ventricular diastolic function.1–4
It has been recently reported that calcium
blocking agents such as verapamil3–5 and
nifedipine6 improve left ventricular diastolic
function in patients with hypertrophic cardiomyopathy. To the best of our knowledge,
however, the effect of diltiazem, another calcium
blocking agent, on hypertrophic cardiomyopathy
has not been reported. We examined the effect
of diltiazem7 on left ventricular isovolumic
relaxation time in patients with hypertrophic
cardiomyopathy.

MATERIALS AND METHODS

Patients

Key Words:
Diltiazem
Isovolumic relaxation time
Hypertrophic cardiomyopathy

Eleven patients with hypertrophic cardiomyo-
pathy (10 males and one female, ranging in age
from 15 to 63 years with an average of 44.2)
were studied. Their clinical and angiographic
data are shown in Table I. In all patients the
diagnosis of hypertrophic cardiomyopathy was
based on the typical angiographic, hemodynamic
and echocardiographic criteria described below. Patients with arrhythmia were excluded from the
study.

All patients had echocardiographic evidence of
asymmetric septal hypertrophy (a septal to
posterobasal left ventricular free wall thickness
ratio of 1.3 or more with or without SAM)
without any other type of acquired or congenital
heart diseases. The criterion for the obstructive
form of hypertrophic cardiomyopathy was the
presence of at least a 30 mmHg subaortic peak
systolic pressure gradient in the basal state or
during isoproterenol infusion. The criterion for
the non-obstructive form of hypertrophic cardio-
myopathy was the absence of such a pressure
gradient. According to this criterion, 5 patients

(Received December 2, 1981; accepted August 3, 1982)
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<table>
<thead>
<tr>
<th>Case</th>
<th>Sex &amp; Age</th>
<th>ECG Type</th>
<th>Location</th>
<th>IVS (mm)</th>
<th>IVS/PW</th>
<th>SAM</th>
<th>LVESD (mm)</th>
<th>LVEDD (mm)</th>
<th>Coronary arteriogram (% Stenosis)</th>
<th>Catheterization Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. SO</td>
<td>M 63</td>
<td>Giant neg. T</td>
<td>I-aVL, V4-6</td>
<td>22</td>
<td>1.3</td>
<td>-</td>
<td>24</td>
<td>38</td>
<td>normal</td>
<td>22</td>
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<tr>
<td>2. CE</td>
<td>M 37</td>
<td>q Peaked T</td>
<td>II-III-aVF, V5-7</td>
<td>22</td>
<td>1.8</td>
<td>-</td>
<td>15</td>
<td>28</td>
<td>normal</td>
<td>8</td>
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<tr>
<td>3. FS</td>
<td>F 54</td>
<td>ST1 and neg. T</td>
<td>V4-7</td>
<td>20</td>
<td>1.3</td>
<td>-</td>
<td>16</td>
<td>26</td>
<td>normal</td>
<td>13</td>
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<tr>
<td>4. MM</td>
<td>M 15</td>
<td>Giant neg. T</td>
<td>V2-3</td>
<td>18</td>
<td>2.0</td>
<td>-</td>
<td>26</td>
<td>35</td>
<td>normal</td>
<td>5</td>
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<td>5. SI</td>
<td>M 39</td>
<td>neg. T</td>
<td>V3-7</td>
<td>24</td>
<td>1.6</td>
<td>-</td>
<td>10</td>
<td>40</td>
<td>normal</td>
<td>15</td>
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<tr>
<td>6. KC</td>
<td>M 29</td>
<td>Q</td>
<td>II-III-aVF</td>
<td>16</td>
<td>1.3</td>
<td>-</td>
<td>23</td>
<td>40</td>
<td>normal</td>
<td>8</td>
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<td>7. SN</td>
<td>M 51</td>
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<td></td>
<td>18</td>
<td>1.3</td>
<td>-</td>
<td>25</td>
<td>40</td>
<td>normal</td>
<td>18</td>
</tr>
<tr>
<td>8. ME</td>
<td>M 46</td>
<td>ST1 and neg. T</td>
<td>V2-6</td>
<td>18</td>
<td>2.0</td>
<td>-</td>
<td>26</td>
<td>40</td>
<td>normal</td>
<td>12</td>
</tr>
<tr>
<td>9. AH</td>
<td>M 48</td>
<td>ST1 and neg. T</td>
<td>V2-7</td>
<td>25</td>
<td>2.1</td>
<td>+</td>
<td>18</td>
<td>35</td>
<td>normal</td>
<td>24</td>
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<tr>
<td>10. HM</td>
<td>M 58</td>
<td>neg. T</td>
<td>I-II-III-aVL, aVF, V4-7</td>
<td>20</td>
<td>1.7</td>
<td>-</td>
<td>22</td>
<td>33</td>
<td>RCA 50%</td>
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<tr>
<td>11. TS</td>
<td>M 46</td>
<td>neg. T</td>
<td>aVL, V5-7</td>
<td>22</td>
<td>1.5</td>
<td>-</td>
<td>20</td>
<td>35</td>
<td>normal</td>
<td>14</td>
</tr>
</tbody>
</table>

Abbreviations: IVS = interventricular septum, PW = left ventricular posterior wall, SAM = systolic anterior motion, LVESD = left ventricular end-systolic dimension, LVEDD = left ventricular end-diastolic dimension, neg. = negative, ST1 = ST depression
had left ventricular outflow obstruction and 6 had no left ventricular outflow obstruction. All patients had no medication for at least 3 days before the study. In all patients selective coronary angiography according to Judkins technique revealed no significant organic stenosis of the coronary arteries except in Case 10 who had a 50% stenosis of the right coronary artery (Table I). Each patient gave informed consent for all procedures.

**Echocardiographic and Phonocardiographic Studies**

Echocardiograms were recorded by a Toshiba Sonocardiograph UCG-O1A using a 1.0 cm diameter, 2.25 Mega Hz transducer with a pulse repetition rate of 1000 cycles/sec. They were recorded using a multichannel Honeywell LS-8 linescan recorder at a paper speed of 50 mm/sec together with an electrocardiogram and phonocardiogram. The phonocardiogram (Nihon Kohden microphone TA-501T) was recorded to define aortic valve closure (A2). Echocardiograms were obtained from all patients in a supine position. During the examinations the transducer was kept constant in the intercostal space near

**TABLE II ECHOCARDIOGRAPHIC DATA OF ELEVEN PATIENTS WITH HCM**

<table>
<thead>
<tr>
<th>Index</th>
<th>Before diltiazem</th>
<th>After diltiazem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isovolumic relaxation time (msec)</td>
<td>63 ± 26</td>
<td>46 ± 28*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>127 ± 15</td>
<td>123 ± 17†</td>
</tr>
<tr>
<td>Cardiac cycle length (msec)</td>
<td>785 ± 133</td>
<td>810 ± 133†</td>
</tr>
<tr>
<td>LV end-systolic dimension (mm)</td>
<td>20.8 ± 6.2</td>
<td>20.3 ± 4.5†</td>
</tr>
</tbody>
</table>

* = p < 0.01 for after diltiazem as compared to before diltiazem.
† = not significant
Statistical significance of differences was evaluated by the Wilcoxon signed rank test.

Fig. 1. Simultaneous recording of an echocardiogram and a phonocardiogram in a patient with hypertrophic cardiomyopathy. A2 = aortic valve closure; MVO = mitral valve opening.
RESULTS

After the diltiazem injection, isovolumic relaxation time decreased significantly from 63 ± 26 to 46 ± 28 msec by an average of 30 ± 19% (p < 0.01, Fig. 2). Mean systolic blood pressure, mean cardiac cycle length and left ventricular end-systolic dimension did not differ significantly before and after the diltiazem injection (Table II). There was no difference in the response to diltiazem between patients with left ventricular outflow obstruction and those without.

DISCUSSION

Left ventricular isovolumic relaxation time is one of the indicators of left ventricular diastolic function and it has been shown that this parameter is often abnormally prolonged in patients with hypertrophic cardiomyopathy. In the present study isovolumic relaxation time is defined as the time interval between the first high frequency component of the second heart sound measured phonocardiographically and the onset of mitral valve separation measured echocardiographically. It has been reported that the changes of left ventricular end-diastolic pressure or left atrial pressure have an influence on the onset of mitral valve opening and so isovolumic relaxation time measured with non-invasive techniques is not reliable as compared to that with invasive techniques. However, since intravenous administration of diltiazem does not change left ventricular end-diastolic pressure or pulmonary arterial diastolic pressure at rest as reported previously by our group the measurement of isovolumic relaxation time in the present study is reliable.

The present study shows that the intravenous administration of diltiazem decreased left ventricular isovolumic relaxation time without any change in heart rate, systolic arterial blood pressure and left ventricular end-systolic dimension in patients with hypertrophic cardiomyopathy. We have recently reported that intravenous administration of diltiazem suppresses an exercise-induced elevation of pulmonary arterial diastolic pressure, which reflects left ventricular filling pressure, without changing the left ventricular systolic function. Furthermore, Toshima et al have reported that diltiazem improves peak negative dp/dt in patients with hypertrophic cardiomyopathy. These facts suggest that diltiazem improves left ventricular diastolic func-

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*Japanese Circulation Journal Vol. 47, January 1983*
tion in this disorder. Such an impaired left ventricular relaxation is thought to be caused by subendocardial ischemia due to an imbalance between the oxygen demand of the excessively hypertrophied myocardium and the oxygen delivery. A recent in vitro study by Nayler and Williams strongly supports the view that impaired relaxation of the heart muscle is primarily caused by a sudden depletion of the high energy phosphate reserves in the heart muscle due to hypoxia, followed by a subsequent disturbance of the intracellular calcium metabolism. The beneficial effect of diltiazem on left ventricular isovolumic relaxation time seems to be related to an improvement of an ischemic myocardium as reported by Weishaar and his coworkers. However, further studies are needed to elucidate the mechanism(s) by which diltiazem improves left ventricular diastolic function in patients with hypertrophic cardiomyopathy.

REFERENCES
2. HANRATH P, MATHEY DG, SIEGERT R, BLEIFELD W: Left ventricular relaxation and filling pattern in different forms of left ventricular hypertrophy: An echocardiographic study. Am J Cardiol 45: 15, 1980