Increased Cardiovascular Response to Epinephrine in Hypertrophic Cardiomyopathy

Yoshinori Koga, M.D., Morio Itaya, M.D., and Hironori Toshima, M.D.

Summary

To study the role of catecholamines in the pathogenesis of hypertrophic cardiomyopathy (HCM), hemodynamic responses to low and high dose infusions of epinephrine (0.037 and 0.074 μg/Kg/min) were compared between 21 patients with nonobstructive HCM and 21 healthy controls, matched for age and sex. During low dose infusion, patients with HCM showed significantly greater responses (p<0.05) than controls in echocardiographic left ventricular (LV) end-systolic dimension (−8±1% vs −4±1%, mean ±SEM), fractional shortening (12±2% vs 7±1%) and peak systolic velocity of the LV posterior wall (32±5% vs 15±4%), but the differences disappeared during high dose infusion. Thus, patients with HCM started to respond to epinephrine earlier than controls and seemed to have an increased sensitivity of β-adrenergic receptors in the cardiovascular system. As the augmented responses were more evident in younger patients (<35 years) who manifested frequent familial occurrences of HCM, the increased sensitivity to catecholamine was postulated to be genetically determined and to be related to the abnormal myocardial hypertrophy of HCM.

Additional Indexing Words:
Echocardiography  Systolic function of the left ventricle  β-adrenergic receptor

Hypertrophic cardiomyopathy (HCM) is a disease characterized by massive hypertrophy of the ventricular muscle. Although the disorder is generally accepted to be transmitted genetically,11,31 the exact mechanism which causes massive hypertrophy is not well understood.

There is substantial evidence which suggests a link between abnormal
catecholamine metabolism and HCM.\textsuperscript{3} Clinically, HCM has been reported in association with disorders of catecholamines and neural crest tissue, such as neurofibromatosis,\textsuperscript{4} pheochromocytoma,\textsuperscript{5} and lentiginosis.\textsuperscript{6-8} In experimental studies, Laks et al\textsuperscript{9} and Blaufuss et al\textsuperscript{10} demonstrated that a subhypertensive dose of norepinephrine caused HCM in dogs. Administration of nerve growth factor\textsuperscript{11} was shown to increase the amount of catecholamine in the base of the heart and to produce hypertrophy, gradient and myocardial fiber disarray in dogs. However, considerable controversy exists concerning catecholamine levels in patients with HCM. In 1964, Pearse\textsuperscript{12} reported that norepinephrine content and sympathetic innervation were increased in septal muscle obtained by myectomy. Subsequent studies by McCallister and Brown,\textsuperscript{13} Van Noorden et al\textsuperscript{14} and Kawai et al,\textsuperscript{15} however, failed to confirm this observation. In work on catecholamines in the peripheral blood, Dargie et al\textsuperscript{16} described an increase in norepinephrine levels in patients with HCM. On the other hand, Sugishita et al\textsuperscript{17} showed a depressed increase of norepinephrine during exercise in patients with this condition. Norepinephrine levels in coronary sinus blood were also reported by Haneda et al\textsuperscript{18} to be lower in HCM.

The recent study by Nomura et al\textsuperscript{19} in our laboratory showed significantly lower 24 hour urinary excretion of norepinephrine in hypertensive patients with asymmetric hypertrophy as compared to those with concentric hypertrophy. As those with asymmetric hypertrophy showed enhanced left ventricular function despite lower norepinephrine, it was postulated that increased sensitivity of adrenergic receptors might be a possible mechanism responsible for the massive hypertrophy in these patients. To investigate further this hypothesis, we studied the response of left ventricular function to epinephrine in patients with HCM.

**Materials and Methods**

**Study subjects:** Twenty-one patients with nonobstructive hypertrophic cardiomyopathy (HCM), 16 men and 5 women, were included in this study. Their mean age was $37 \pm 3$ years (range 15 to 60). The diagnosis of HCM was established with M-mode and two-dimensional echocardiography and left ventricular angiography by the demonstration of a nondilated, hypertrophied left ventricle in the absence of other cardiac or systemic disease which itself could produce left ventricular hypertrophy. Four patients had a history of mild hypertension, but were included because they also demonstrated clinical and hemodynamic features consistent with HCM and/or because the extent of left ventricular hypertrophy clearly exceeded that which would have been
expected to result from hypertension alone. Echocardiographic and angiographic examination revealed asymmetric septal hypertrophy in 17 patients and apical hypertrophy in 4 patients. We excluded from the study obstructive patients with a resting pressure gradient in the left ventricle of 20 mmHg or more, because outflow obstruction may alter the left ventricular response to epinephrine. However, 4 patients with a small systolic anterior movement of the mitral valve were included in the study.

Family surveys were conducted on 51 first degree relatives of 18 patients using electrocardiography. Familial occurrence was taken as positive when T wave inversion or an abnormal Q wave of unexplained cause was detected.

Control subjects were 21 healthy volunteers matched for sex and age within 5 years. They included 6 hospital staff, 4 students and 11 non-medical volunteers. All of them were sedentary and had no known clinical heart disease.

All subjects had a normal sinus rhythm and took no cardiac medication for at least 5 days before the study.

**Echocardiographic examination:** Echocardiography was performed using a phased-array 78° sector scanner with a 2.4 MHz transducer (Toshiba Sonolayergraph model SSH 11A). Patients were studied in the left lateral position with the transducer placed in the third or fourth interspace at the left sternal edge. Care was taken to avoid alterations in transducer position during the study. A short-axis view of the left ventricle at the level of the chordae tendineae was obtained and the M-mode cursor was positioned centrally in the two-dimensional image. The derived M-mode image was recorded on photographic paper with a strip-chart recorder at a paper speed of 50 mm/sec.

Left ventricular end-diastolic dimension (EDD) was measured at the peak of the R wave of the simultaneously recorded electrocardiogram. End-systolic dimension (ESD) was taken as the smallest dimension between the left septal and posterior wall endocardium during systole. Fractional shortening was calculated as $100 \times (\frac{[\text{EDD} - \text{ESD}]}{\text{EDD}})$. Peak systolic velocity of the posterior left ventricular wall was determined by drawing a tangent to the steepest point of the systolic limb of the curve and measuring in millimeters per second.

**Study protocol (Fig. 1):** After baseline echocardiographic and electrocardiographic recordings and blood pressure measurements by cuff, epinephrine was infused intravenously using a Truth infusion pump (Type B-1) by Nakagawa Seikodo Co., Ltd. (Hongo, Tokyo). The dose of epinephrine was doubled every 6 min from an initial dose of 0.0185 μg/Kg/min to
Fig. 1. Study protocol (top). Dose of epinephrine was doubled every 6 min. An average of the readings before and 6 min after the initial dose infusion (0.0185 µg/Kg/min) was taken as the baseline value. Readings during low (0.037 µg/Kg/min) and high dose (0.074 µg/Kg/min) infusion were obtained by averaging measurements at 3 and 6 min in each stage. Echocardiograms from a patient with hypertrophic cardiomyopathy (bottom) show augmentation of left ventricular wall motion during epinephrine infusion.

0.037 µg/Kg/min and then to 0.074 µg/Kg/min. Blood pressure, electrocardiogram and echocardiogram were recorded every 3 min in each stage. As the initial dose (0.0185 µg/Kg/min) of epinephrine infusion did not alter the hemodynamic measurements, the average of the readings before and 6 min after the initial infusion of epinephrine was taken as the baseline value. Readings during lower (0.037 µg/Kg/min) and higher (0.074 µg/Kg/min) dose infusions were obtained by averaging the measurements at 3 and 6 min in each stage. The effect of epinephrine was evaluated by deriving percent change from the baseline measurements.

**Statistical analysis:** All data were expressed as mean ± standard error of the mean. The unpaired Student's t-test was used for comparison of the effects of epinephrine between HCM patients and controls. Differences were considered significant if p<0.05.
RESULTS

Table I shows baseline characteristics in patients with hypertrophic cardiomyopathy (HCM) and control subjects. Of 21 patients with HCM, 9 were younger than 35 years old (younger group) and 12 were 35 years or older (older group). Fourteen of 51 first degree relatives studied demonstrated abnormal electrocardiograms of unexplained cause and familial occurrence was considered as positive in 11 patients, 6 in the younger and 5 in the older group. A history of hypertension was reported in 4 of 12 in the older HCM group and of the remaining 8 patients in the older group, 3 were performing regular sports activity. Echocardiographic examination of patients with HCM showed significantly greater ventricular septal and posterior wall thickness than controls, while the septum was significantly thicker than the posterior

<table>
<thead>
<tr>
<th></th>
<th>Hypertrophic cardiomyopathy</th>
<th>Control (n=21)</th>
<th>P value</th>
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<tbody>
<tr>
<td></td>
<td>Total (n=21)</td>
<td>Younger (n=9)</td>
<td>Older (n=12)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37±3</td>
<td>23±3</td>
<td>47±2</td>
</tr>
<tr>
<td>Sex (male: female)</td>
<td>16:5</td>
<td>8:1</td>
<td>8:4</td>
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<tr>
<td>Familial occurrence†</td>
<td>11 (61%)</td>
<td>6 (67%)</td>
<td>5 (56%)</td>
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<tr>
<td>History of hypertension</td>
<td>4 (19%)</td>
<td>0</td>
<td>4 (33%)</td>
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<tr>
<td>Regular sports activity</td>
<td>6 (29%)</td>
<td>3 (33%)</td>
<td>3 (25%)</td>
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<tr>
<td>Wall thickness (mm)</td>
<td></td>
<td></td>
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<tr>
<td>Ventricular septum</td>
<td>21±1</td>
<td>20±2</td>
<td>22±2</td>
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<tr>
<td>Posterior wall</td>
<td>14±1</td>
<td>12±1</td>
<td>15±1</td>
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<td>Baseline hemodynamics</td>
<td></td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>64±2</td>
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<tr>
<td>Blood pressure (mmHg)</td>
<td>125±4</td>
<td>123±7</td>
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<tr>
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<td>68±4</td>
<td>60±5</td>
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<tr>
<td>Diastolic</td>
<td></td>
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<td>Left ventricular dimension (mm)</td>
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<tr>
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<td>24±1</td>
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<td>Fractional shortening (%)</td>
<td>47±2</td>
<td>48±3</td>
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<tr>
<td>Peak PWV (mm/sec)</td>
<td>75±4</td>
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<td>74±5</td>
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<tr>
<td>LVEDP (mmHg)</td>
<td>15±1</td>
<td>15±2</td>
<td>15±1</td>
</tr>
</tbody>
</table>

Values are number of cases (%) or mean±SEM.
† Family survey was conducted on 18 patients.

Abbreviations: HCM=hypertrophic cardiomyopathy; PWV=systolic velocity of the left ventricular posterior wall; LVEDP=left ventricular end-diastolic pressure.
wall in patients with HCM. Neither wall thickness differed significantly between the younger and older HCM groups, although 3 of 4 patients with apical hypertrophy were included in the older group.

In the baseline hemodynamic measurements (Table I), there were no differences between the HCM group and controls in heart rate and systolic blood pressure, whereas diastolic blood pressure was significantly lower in the HCM group. Left ventricular dimensions at end-diastole and at end-systole were significantly smaller in the HCM group. Fractional shortening and peak systolic velocity of the left ventricular posterior wall were significantly greater in the HCM group, showing enhanced systolic performance of the left ventricle at baseline. There were no significant differences in baseline

Table II. Percent Change of Hemodynamic Measurements during Low (0.037 μg/Kg/min) and High (0.074 μg/Kg/min) Dose Infusion of Epinephrine

<table>
<thead>
<tr>
<th></th>
<th>Total (n=21)</th>
<th>Younger (n=9) (&lt;35 years)</th>
<th>Older (n=12) (≥35 years)</th>
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<tbody>
<tr>
<td></td>
<td>HCM</td>
<td>Control</td>
<td>HCM</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>9±3</td>
<td>8±2</td>
<td>11±4</td>
</tr>
<tr>
<td>High dose</td>
<td>17±3</td>
<td>13±2</td>
<td>20±5*</td>
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<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
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<tr>
<td>Systolic</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Low dose</td>
<td>0±2</td>
<td>0±1</td>
<td>3±3</td>
</tr>
<tr>
<td>High dose</td>
<td>7±2</td>
<td>2±2</td>
<td>11±2</td>
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<tr>
<td>Diastolic</td>
<td></td>
<td></td>
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<tr>
<td>Low dose</td>
<td>-18±4</td>
<td>-8±1</td>
<td>-29±4**</td>
</tr>
<tr>
<td>High dose</td>
<td>-26±4*</td>
<td>-12±3</td>
<td>-36±7**</td>
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<tr>
<td><strong>Left ventricular dimension</strong></td>
<td></td>
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<tr>
<td>End-diastole</td>
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<tr>
<td>Low dose</td>
<td>1±1</td>
<td>1±0</td>
<td>2±1</td>
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<tr>
<td>High dose</td>
<td>3±1</td>
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<tr>
<td>End-systole</td>
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<tr>
<td>Low dose</td>
<td>-8±1*</td>
<td>-4±1</td>
<td>-10±2**</td>
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<tr>
<td>High dose</td>
<td>-12±2</td>
<td>-12±1</td>
<td>-15±3</td>
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<tr>
<td><strong>Fractional shortening</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Low dose</td>
<td>12±2*</td>
<td>7±1</td>
<td>15±4</td>
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<tr>
<td>High dose</td>
<td>19±2</td>
<td>23±2</td>
<td>23±5</td>
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<tr>
<td><strong>Peak PWV</strong></td>
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<td></td>
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<tr>
<td>Low dose</td>
<td>32±5*</td>
<td>15±4</td>
<td>44±9*</td>
</tr>
<tr>
<td>High dose</td>
<td>61±6</td>
<td>51±7</td>
<td>66±11</td>
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</table>

Values are mean±SEM.
* p<0.05, ** p<0.01 compared with control.
Abbreviations: HCM=hypertrophic cardiomyopathy; PWV=systolic velocity of the left ventricular posterior wall.
hemodynamics between the younger and older HCM groups, except for lower diastolic blood pressure in the former.

Table II summarizes percent changes in hemodynamic parameters from the baseline values during low (0.037 μg/Kg/min) and high dose (0.074 μg/Kg/min) infusion of epinephrine. Low dose epinephrine increased heart rate similarly in the HCM group (9±3%) and in controls (8±2%). Systolic blood pressure remained unchanged in both groups, but diastolic blood pressure decreased by 18±4% in the HCM group and by 8±1% in controls; the reduction tended to be greater in the HCM group. End-diastolic dimension of the left ventricle did not change appreciably during low dose epinephrine infusion. End-systolic dimension decreased by 8±1% in the HCM group and by 4±1% in controls. Fractional shortening and peak systolic velocity of the left ventricular posterior wall increased by 12±2% and 32±5%, respectively, in the HCM group and by 7±1% and 15±4%, respectively, in controls. These changes were significantly higher in the HCM group (Fig. 2).

High dose infusion (0.074 μg/Kg/min) of epinephrine (Fig. 2) further increased heart rate, fractional shortening and peak systolic velocity of the posterior wall and decreased end-systolic dimension of the left ventricle. These responses were greater in controls and the different effects of epinephrine on end-systolic dimension, fractional shortening and peak systolic

![Fig. 2](image-url)

**Fig. 2.** Hemodynamic responses to low (0.037 μg/Kg/min) and high dose (0.074 μg/Kg/min) infusion of epinephrine in patients with hypertrophic cardiomyopathy (closed circles) and in controls (open circles). Values are expressed as mean percent change ±1 standard error.
velocity of the posterior wall observed between HCM and control groups during low dose infusion became insignificant during high dose infusion. In a linear regression analysis, response of fractional shortening to epinephrine showed a significant inverse correlation with that of the baseline condition in patients with HCM (Table III). Hence the smaller increase in fractional shortening during high dose epinephrine in patients with HCM seemed to be a consequence of the higher baseline value. On the other hand, the difference in response of diastolic blood pressure between the 2 groups became statistically significant during high dose infusion.

The effects of epinephrine were further analyzed by dividing the subjects arbitrarily into younger (less than 35 years) and older (35 years or more) groups (Table II). In the younger group, responses of diastolic blood pressure, end-systolic dimension and peak systolic velocity of the posterior wall to low dose epinephrine were $-29\pm 4\%$, $-10\pm 2\%$ and $+44\pm 9\%$, respectively, in the HCM group and $-7\pm 2\%$, $-3\pm 1\%$ and $+17\pm 6\%$, respectively, in controls. These responses were significantly higher in the HCM group ($p<0.01$, $p<0.01$ and $p<0.05$). Low dose epinephrine tended to increase fractional shortening ($+15\pm 4\%$) to a greater extent in the younger HCM group, although the difference from controls was not statistically significant ($0.10>p>0.05$). With high dose infusion of epinephrine, responses of end-systolic dimension and posterior wall velocity in controls reached levels similar to those of the younger HCM group and the different responses to epinephrine during low dose infusion were not observed. On the other hand, the non-significant increase in heart rate during low dose infusion in the younger HCM group became significant ($20\pm 5\%$, $p<0.05$) during high dose infusion.

In the older group, the HCM group and controls responded to epinephrine similarly and no statistically significant differences were observed (Table II).
DISCUSSION

This study demonstrated that responses of systolic performance of the left ventricle to low dose infusion of epinephrine were significantly greater in patients with hypertrophic cardiomyopathy (HCM). The greater increase in systolic performance of controls and disappearance of the significant difference during high dose infusion were contrary to our expectations. However, this could be explained by the curvilinear relationship between left ventricular contractility and pump function, where increases in stroke volume and ejection fraction become much smaller after reaching a certain level (ejection fraction of approximately 60–70%) despite a constant increase in contractility. Patients with HCM who show augmented pump function in the baseline condition could easily attain this near maximal level during epinephrine infusion. In the present study, response of fractional shortening to epinephrine was again inversely related to the baseline reading in patients with HCM.

Thus, the curvilinear relationship between left ventricular contractility and pump function would be a possible explanation for the smaller changes in patients with HCM and disappearance of significant differences in left ventricular end-systolic dimension, fractional shortening and peak systolic velocity of the posterior wall during high dose infusion of epinephrine. Therefore it seems reasonable to postulate that left ventricular systolic performance in patients with HCM started to respond to epinephrine earlier in the low dose infusion, which had no appreciable effects on controls.

Response of diastolic blood pressure to epinephrine was greater in patients with HCM and attained a statistically significant difference during high dose infusion. Although cardiac output and hence systemic vascular resistance were not determined in the present study, this might imply increased vasodilatory response of the peripheral arteries in patients with HCM. Increase in heart rate again tended to be greater in patients with HCM and the difference became significant during high dose infusion in the younger group. This suggested that the chronotropic response of the sinus node to epinephrine may be increased in this condition. In addition, the different responses of diastolic blood pressure and heart rate during high dose infusion would support our speculation that the curvilinear relationship to contractility might be responsible for a decrease in the difference of systolic performance of the left ventricle to an insignificant level during high dose infusion.

We excluded obstructive patients from the present study, because outflow obstruction may alter the left ventricular response to epinephrine. Although there remains a possibility that patients with a small systolic an-
terior movement of the mitral valve developed outflow obstruction during epinephrine infusion, this would depress left ventricular performance. Hence the possible effect of provoked left ventricular outflow obstruction is opposite to the present observation and is unlikely to alter the result of the present study. We determined left ventricular performance using end-systolic dimension, fractional shortening and peak systolic velocity of the left ventricular posterior wall. These indices are known to be dependent on preload and afterload of the ventricle. In the present study, end-diastolic dimension of the left ventricle and probably preload remained unchanged during epinephrine infusion both in patients with HCM and controls. Decrease in diastolic blood pressure during epinephrine infusion was greater in patients with HCM, but only attained a statistically significant level during high dose infusion, when enhancement of left ventricular performance became similar in HCM and controls. Increase in systolic blood pressure, which mainly determines end-systolic dimension and hence fractional shortening in the absence of change in end-diastolic dimension, was even greater in patients with HCM. Accordingly, the observed difference in left ventricular performance between the 2 groups during low dose infusion did not seem to be only due to altered preload and afterload, but was considered to indicate increased responsiveness of the ventricular muscle to epinephrine in patients with HCM.

The above observations suggested that mechanical and chronotropic responses of the heart and vasodilating response of the peripheral artery to epinephrine are augmented in patients with HCM. Hence, we postulated that sensitivity of β-adrenergic receptors in the cardiovascular system is increased in this condition. Iida et al.21) infused isoproterenol, 0.02 μg/Kg/min, in 8 patients with HCM and observed a greater increase in the normalized peak systolic shortening rate of the left ventricular dimension. They suggested that patients with HCM have abnormal β-adrenergic receptors in the cardiac muscle, which is consistent with the present observation.

A number of reports22)-24) have indicated that experimental cardiac hypertrophy is accompanied by depletion of cardiac catecholamine. In human cardiac muscle obtained from the right and left atrium at the time of cardiac surgery, Borchard25) reported that epinephrine and norepinephrine content decreased with an increase in myocardial cell diameter and cardiac hypertrophy. It is well known that the depletion of catecholamine in experimental animals leads to an up-regulation of adrenergic receptor number and a supersensitivity of the tissue to catecholamine.26) Limas27) reported that the number of β-adrenergic receptors actually increased in experimental hypertrophy in rats. Therefore, up-regulation of the β-adrenergic receptor
in the hypertrophied heart could be one possible explanation for the enhanced response to epinephrine in patients with HCM. However, this cannot explain the increased response of the peripheral artery which does not seem to be involved in the disease process of HCM.

An alternative speculation would be that increased sensitivity of the β-adrenergic receptor is a primary abnormality in HCM. Perloff[28] summarized the evidence for the pathogenesis of HCM based on the catecholamine hypothesis. He implied that faulty interaction between the adrenergic stimulus and myocardial receptor sites in utero may play a fundamental role in initiating myocardial cellular disarray and in setting the stage for subsequent progression to clinically overt HCM. Raum et al.[29] recently noted that the septal β-receptor-adenyl cyclase system in the canine heart has the highest adenyl cyclase activity, cyclic AMP content and sensitivity to β-agonist stimulation, as compared with the right and left ventricular free wall. They postulated that the enhanced septal sensitivity to catecholamines in dogs would be similar to that in patients who are prone to develop HCM. Therefore, if the increased sensitivity of adrenergic receptors, as suggested in the present study, could be considered to be a primary abnormality, this would be an attractive postulate in the pathogenesis of HCM. This would again explain controversial results concerning the myocardial content[12]-[15] and peripheral blood level[16]-[18] of catecholamines in HCM, despite the number of reports suggesting a link between catecholamine and this condition. Increased response of the peripheral arteries may be additional evidence that increased sensitivity of the adrenergic receptor may not be secondary to up-regulation in the hypertrophied heart. However, this attractive speculation awaits further investigation.

Another interesting observation in the present study was the relationship of cardiovascular responses to epinephrine to age. When the study subjects were divided arbitrarily into younger (<35 years) and older (≥35 years) groups, increased responses of left ventricular performance, heart rate and diastolic blood pressure in HCM became more evident in the younger group. On the other hand, older patients with HCM did not show significant differences from controls in their responses to epinephrine. More advanced myocardial damage in older patients could be one possible explanation for this observation, but this would be less likely because of comparable systolic performance, left ventricular wall thickness and end-diastolic pressure in the 2 groups. On the other hand, we[30] have previously suggested that older patients with HCM may include a subgroup who have a milder form of the disease, probably of late onset, associated with acquired factors such as hypertension. Although the present subjects differed in sex distribution and familial
occurrence, they showed characteristics similar to our experience in the larger series: 58% of the older patients had a history of hypertension or regular sports activity and left ventricular end-diastolic pressure and systolic performance were comparable to those of younger patients despite their older age. In addition, the older group in the present series included 3 patients with apical hypertrophy, which is frequently associated with hypertension but uncommon in familial occurrence. Thus older patients with HCM in the present study again seemed to include a subgroup with a milder form of HCM associated with acquired factors. In contrast, younger patients with HCM usually demonstrated a typical form of the disease with a familial occurrence consistent with autosomal dominant inheritance. Therefore another possible explanation would be that genetic factors might be related to the more evident increase in the cardiovascular responses to epinephrine in younger patients with HCM.

In summary, the present study suggests that responses of the cardiovascular system to epinephrine are increased in patients with HCM and implies that the sensitivity of the β-adrenergic receptor is enhanced in this condition. As augmented responses to epinephrine were more evident in younger patients, the abnormal sensitivity of β-adrenergic receptors was postulated to be genetically determined and to be related to the development of massive hypertrophy in patients with HCM.

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