Echocardiographic Assessment of Left Ventricular Filling and Septal and Posterior Wall Dynamics in Idiopathic Hypertrophic Subaortic Stenosis

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SUMMARY In order to study left ventricular function in idiopathic hypertrophic subaortic stenosis (IHSS), left ventricular echograms were analyzed by computer and compared with results in normal subjects. Systolic function was consistently normal or above normal even in the presence of severe diastolic abnormalities. Wide variation in diastolic function in IHSS allowed separation of patients into three groups on the basis of the left ventricular peak filling rate. Because of the severe septal hypertrophy and hypokinesia, peak left ventricular filling rate is predominantly determined by the rate of free wall thinning. Patients in group 1 had rapid left ventricular filling rates, those in group 2 had normal filling rates, and those in group 3 had slow filling rates. With reduction in left ventricular peak filling rate caused by impaired free wall thinning, there was progressive increase in 1) duration of the rapid filling phase, 2) delay of mitral valve opening, 3) asynchrony between septum and posterior wall, 4) incidence of angina, and 5) incidence of atrial fibrillation.

ECHOCARDIOGRAPHY HAS MADE a major contribution to the noninvasive diagnosis of idiopathic hypertrophic subaortic stenosis (IHSS). The echocardiographic features of IHSS include anterior displacement of the mitral valve apparatus,1 systolic anterior movement of the mitral valve leaflet,2,3 asymmetric septal hypertrophy,4,5 septal hypokinesia,5,6 and mid-systolic closure of the aortic valve.7 Despite the wealth of data obtained by both echocardiography and angiocardiography, there is little information about the physiologic effects on left ventricular (LV) function resulting from these readily recognizable structural and histologic abnormalities. What is clearly evident is that IHSS is not a well-circumscribed disease entity; rather, it represents a broad spectrum of LV dysfunction.

In the present study we used echocardiography to assess LV function in patients with IHSS by analyzing septal, posterior wall, and LV cavity dynamics throughout the cardiac cycle with particular emphasis on wall movement during diastole. In addition, we studied the relation of wall dynamics to LV filling, mitral valve opening, and clinical symptoms. This allowed us to recognize three phases in the progression of this disease and tentatively suggest a pattern or natural history of this form of cardiomyopathy.

Patients

Forty-nine patients were studied and divided into two groups. One group consisted of 20 normal volunteers; 12 were female and eight male, with an age range of 19 to 63 years and a median age of 37 years. All were in sinus rhythm and had normal chest roentgenograms and echocardiograms.

The second group consisted of 29 patients with IHSS, seven of whom were females and 22 males, with an age range of 16 to 69 years and a median age of 45 years. All patients had echocardiograms showing systolic anterior movement of the mitral valve and asymmetric hypertrophy of the septum. All patients were in sinus rhythm when studied. Fourteen patients in this group underwent diagnostic cardiac catheterization and left ventricular angiography. No patient had any other condition that might have affected myocardial thickness or contractility. Twenty-four patients in this group were taking propranolol in doses varying from 20 to 480 mg daily, and the remaining patients were not receiving medication; no patient was taking digoxin or glyceryl trinitrate. No patient had undergone previous ventricular septal myotomy or myectomy.

Methods

Echocardiograms were obtained with the Ekoline 20 ultrasonoscope using a 1.25 cm diameter, 2.25 MHz transducer with a repetition frequency of 1,000 cycles/sec. The recordings were made with a Cambridge Scientific Instrument multichannel or a Honeywell 1856 strip-chart recorder at paper speeds of 50 to 100 mm/sec, with simultaneous electrocardiograms. Studies were made with patients recumbent in the left semilateral position. Echocardiograms of the right and left sides of the septum and the endocardium and epicardium of the posterior LV wall were obtained at the level of the mitral valve. Measurements were made only when these echoes were clear and continuous throughout the cardiac cycle. Echocardiograms were digitized as previously described on a Summagraphics digitizing table and processed by a Prime 300 computing system. Data points were generated both for endocardial surfaces of the septum and for the endocardial and epicardial surfaces of the posterior LV wall, so that strings of coordinates were obtained for the four surface boundaries. The echoes were calibrated with points defining a time interval of 500 msec, 1 cm depth, and two successive Q waves on the electrocardiogram enclosing the cardiac cycle to be analyzed.

With an on-line incremental plotter, plots were made of continuous instantaneous LV cavity dimension (D) and septal (VS) and posterior wall (PW) thickness, and from these, LV cavity, septal, and posterior wall dynamics were obtained.

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Supported in part by Research Grant HL-14196 from the NIH.

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Received May 19, 1977; revision accepted October 18, 1977.
Parameters of LV Cavity Dynamics Analyzed

Percentage Shortening of Cavity Minor Dimension. This was obtained by subtracting end-systolic dimension (ESD) from end-diastolic dimension (EDD) and expressing this difference as a percentage of end-diastolic dimension:

\[ \text{EDD} - \text{ESD} \times 100 \]

Ejection Fraction (EF). This was obtained by subtracting end-systolic volume (ESV) from end-diastolic volume (EDV) and expressing this as a percentage of EDV:

\[ \text{EF} = \frac{\text{EDV} - \text{ESV}}{\text{EDV}} \times 100 \]

The volumes were obtained using the Teichholz formula.

Peak Rate of Increase in LV Dimension during Diastole. This was obtained as dD/dt (diastole), where D is LV dimension in centimeters and t is time in seconds. This measurement henceforth will be referred to as the filling rate.

Normalized Peak Rate of LV Dimensional Shortening in Systole: \( \frac{1}{D} \cdot \frac{dD}{dt} \) (Systole). This was derived by dividing the peak rate of dimensional shortening, dD/dt (systole), by instantaneous LV dimension, 1/D. This also represents peak velocity of circumferential fiber shortening.

Duration of Rapid Filling Phase. This represents the time from minimum LV dimension to the time when the LV filling rate decreased to 20% of its maximum value. This point corresponds in normal subjects to the end of the rapid diastolic filling phase and is seen as the discontinuity in the plot of continuous LV dimension (fig. 1). Minimum LV dimension was accurately defined as the point at which LV filling rate, dD/dt (diastole), was zero.

Isovolumic Relaxation Period (IRP). In this study IRP was taken to represent the time from the minimum LV dimension to the onset of separation of mitral valve leaflets (opening). The IRP obtained as above underestimates the true isovolumic relaxation period because closure of the aortic valve usually precedes the minimum LV dimension.

Peak Closing Velocity of Anterior Mitral Valve Leaflet. This was obtained whenever the anterior mitral valve leaflet could be digitized throughout the cardiac cycle, as described by Upton et al.

Validation of Measurements. The validation of echographic measurements of LV minor dimension and its rate of change in diastole, dD/dt (diastole), has been established by comparison with data obtained angiographically in previous studies.

Parameters of Septal Dynamics Analyzed

Systolic Septal Thickening (Percent). This was obtained by subtracting end-diastolic thickness (VSD) from peak systolic thickness (VSS) and expressing the difference as a percentage of end-diastolic septal thickness:

\[ \frac{\text{VSS} - \text{VSD}}{\text{VSS}} \times 100 \]

Normalized Peak Rate of Systolic Septal Thickening: \( \frac{1}{\text{VSS}} \cdot \frac{dVSS}{dt} \) (Systole). This was obtained by dividing the peak rate of systolic septal thickening, dVSS/dt (systole), by the instantaneous septal thickness at the same point in time.

Normalized Peak Rate of Diastolic Thinning: \( \frac{1}{\text{VSS}} \cdot \frac{dVSD}{dt} \) (Diastole). This was obtained by dividing the peak rate of change of septal thickness during diastole, dVSS/dt (diastole), by the instantaneous septal thickness at the same point in time.

Time From Onset of QRS Complex to Peak Septal Thickness in Relation to Timing of Peak Posterior Wall Thickness. This time interval was obtained by subtracting the time from onset of QRS to peak posterior wall thickness from the time from onset of QRS to peak septal thickness.

Parameters of Posterior Wall Dynamics Analyzed

Percentage Systolic Thickening of Posterior Wall. This was obtained by subtracting end-diastolic thickness (PWM) from peak systolic thickness (PWM) and expressing the difference as a percentage of end-diastolic thickness:

\[ \frac{\text{PWM} - \text{PWd}}{\text{PWd}} \times 100 \]

Normalized Peak Rate of Systolic Posterior Wall Thickening: \( \frac{1}{\text{PWd}} \cdot \frac{dPW}{dt} \) (Systole). This was obtained by dividing the peak rate of systolic posterior wall thickening,
thickening at the same point in time.

**Normalized Peak Rate of Diastolic Posterior Wall Thickening:**

\[
\frac{1}{PW} \frac{dPW}{dt} \text{ (Diastole).}
\]

This was obtained by dividing the peak rate of change of posterior wall thickness during diastole, \( \frac{dPW}{dt} \) (diastole), by the instantaneous posterior wall thickness at the same point in time.

**Grouping of Patients**

The septal and posterior wall dynamics were related to each other, to cavity dimension, to left ventricular filling, and to mitral valve opening. The patients with IHSS were divided into three groups based on their ventricular filling rates, \( \frac{dD}{dt} \) (diastole). Group 1 had faster than normal filling rates; group 2 had normal filling rates; and group 3 had abnormally slow filling rates. Measurements of ventricular function in the three groups were compared as median values and ranges because sample sizes were small and variance was dissimilar. Tests of significance between the groups were by the rank-sum test (see tables 3 and 4).

**Results**

**Normal Subjects**

**Global Function.** Mean LV cavity dimensions at end systole and end diastole were 2.7 ± 0.3 cm and 4.6 ± 0.4 cm, respectively. Percent shortening of cavity dimension was 40.2 ± 1.2% and ejection fraction was 77.5 ± 4.2% (table 1).

The peak left ventricular filling rate was 14.5 ± 2.3 cm/sec (fig. 1) and occurred 50 ± 16 msec after end systole. End systole was identified by minimum LV dimension and when its first differential \( \frac{dD}{dt} \) was zero. The duration of the rapid filling phase was 160 ± 50 msec. Peak velocity of circumferential fiber shortening was 2.66 ± 0.36 sec⁻¹. The IRP was 1 ± 6 msec and the mean value for peak closing velocity of the anterior mitral valve leaflet was 250 ± 60 mm/sec.¹³

**Regional Function.** Septal and posterior wall thicknesses were 1.2 ± 0.3 cm and 1.5 ± 0.3 cm at end systole and 0.7 ± 0.2 cm and 0.9 ± 0.2 cm at end diastole, respectively. Percentage systolic thickening of the septum and posterior LV wall was 54 ± 13% and 68 ± 22%, respectively. Posterior movement of the septum occurred simultaneously with anterior movement of the posterior wall. Peak septal thickening preceded peak posterior wall thickening; the latter occurred 15 ± 13 msec later and was coincident with minimum LV dimension. Normalized peak rates of systolic thickening of the septum and posterior wall were 3.85 ± 0.78 sec⁻¹ and 4.08 ± 1.37 sec⁻¹, respectively (table 2), and normalized peak rates of diastolic thickening of the septum and posterior wall were 3.40 ± 0.90 sec⁻¹ and 8.69 ± 4.33 sec⁻¹ (table 2).

**Patients With IHSS**

**Global Function (Data from All 29 Patients Grouped Together).** Mean cavity dimensions at end systole and end diastole were 2.2 ± 0.6 cm and 4.2 ± 0.2 cm, respectively, both significantly smaller than normal (\( P < 0.01 \)) (table 1). Percentage shortening of LV cavity dimension (46 ± 5%), ejection fraction (80 ± 13%), and LV filling rate (15.5 ± 7.5 cm/sec) were normal. Velocity of circumferential fiber shortening was significantly increased (\( P < 0.02 \)) (table 1). The duration of the rapid filling phase was prolonged to 245 ± 85 msec (\( P < 0.01 \)) (fig. 2), and the IRP was prolonged to 71 ± 31 msec (\( P < 0.01 \)). The mean value for peak diastolic closing velocity of the anterior mitral valve leaflet was reduced to 36 mm/sec (\( P < 0.01 \)).

**Regional Function (Data from All 29 Patients Grouped Together).** Septal and posterior wall systolic thicknesses were increased: 2.5 ± 0.4 cm and 1.8 ± 0.4 cm, respectively (\( P < 0.01 \)) (table 2). End-diastolic thickness of the septum was 2.0 ± 0.5 cm (\( P < 0.01 \)) and of the posterior wall 0.9 ± 0.3 cm (table 2). Percentage systolic thickening of the septum was reduced — 17.8 ± 3.0% (\( P < 0.01 \)) — whereas posterior wall thickening was increased — 91.6 ± 20.2%. In addition to the reduction in systolic septal thickening, peak septal thickness developed significantly later than normal, a mean of 77 ± 11 msec after peak posterior wall thickness (\( P < 0.01 \)) (table 2).

Both normalized peak rates of septal systolic thickening and diastolic thickening were low: 1.76 ± 0.78 sec⁻¹ and 1.70 ± 0.87 sec⁻¹ (\( P < 0.01 \)). The normalized rate of diastolic thickening of the posterior wall was normal, 8.21 ± 5.01 sec⁻¹, but its normalized peak rate of systolic thickening was increased, 6.68 ± 3.28 sec⁻¹ (\( P < 0.01 \)) (table 2).

There was wide variation in LV peak filling rate, \( \frac{dD}{dt} \) (diastole), which allowed separation of these 29 patients into three distinct subgroups. Group 1 consisted of eight patients who had increased peak filling rates (rapid fillers) — in excess of 18 cm/sec (fig. 3); group 2, nine patients with normal filling rates (normal fillers) (fig. 4); and group 3, 12 patients with decreased filling rates — less than 12 cm/sec (slow fillers) (fig. 5). Filling periods also became significantly and progressively more prolonged from groups 1 to 3 (\( P < 0.01 \))

<table>
<thead>
<tr>
<th>Study group</th>
<th>No.</th>
<th>EDD (cm)</th>
<th>ESD (cm)</th>
<th>EF (%)</th>
<th>D. % change</th>
<th>Peak ( \frac{dD}{dt} ) (diastole) (cm/sec)</th>
<th>( \frac{1}{PW} \frac{dPW}{dt} ) (systole) (sec⁻¹)</th>
<th>Filling period (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>20</td>
<td>4.6</td>
<td>2.7</td>
<td>77.5</td>
<td>40.2</td>
<td>14.5</td>
<td>2.66</td>
<td>160</td>
</tr>
<tr>
<td>IHSS</td>
<td>29</td>
<td>4.2†</td>
<td>2.2†</td>
<td>80.4</td>
<td>46.2</td>
<td>15.5</td>
<td>4.69†</td>
<td>245†</td>
</tr>
</tbody>
</table>

†\( P < 0.01 \), difference from normal.

†\( P < 0.02 \), difference from normal.

Abbreviations: EDD = end-diastolic dimension; ESD = end-systolic dimension; EF = ejection fraction.
(table 3). It is worthy of emphasis here that in the three groups there were no significant differences in septal thickness, LV cavity dimension, percentage systolic shortening, ejection fraction, peak velocity of circumferential fiber shortening, isovolumic relaxation period, and diastolic closing velocity of the mitral valve (tables 3 and 4). Systolic septal thickening and normalized peak rates of change of septal thickness in systole and diastole were similarly reduced in all groups. Peak septal thickness developed a median time of 2 msec after peak posterior wall thickness in group 1 (the rapid fillers), whereas this interval was progressively longer in both group 2 (normal fillers) and group 3 (slow fillers) \( P < 0.01 \) (table 4). The posterior wall was significantly thicker in diastole in group 3 than in groups 1 and 2, and systolic thickening of the posterior wall had a median value of 160% in group 1, 97% in group 2, and 73% in group 3. These differences are significant from each other and, in groups 1 and 2, from the normal \( P < 0.01 \) (table 3). Normalized peak rates of systolic posterior wall thickening were elevated in groups 1 and 2 \( P < 0.01 \) and normal in group 3 (table 4, fig. 6 left), but there was greater variation in peak rates of diastolic wall thinning: group 2 was normal, group 1 was significantly faster than normal \( P < 0.01 \), and group 3 was slower than normal \( P < 0.01 \) (fig. 6 right).

**Hemodynamic Data**

Of the 14 patients undergoing cardiac catheterization, five belonged to group 1, five to group 2, and four to group 3. The median values and ranges for LV end-diastolic pressure and peak systolic outflow gradients in the three groups were

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Duration of filling. There is wide variation in LV filling period in patients with IHSS compared with normal \( N \). Mean value is significantly greater than normal and demonstrates increased resistance to LV filling \( P < 0.01 \).

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Computer output of a patient with IHSS from group 1, showing normal LV cavity dimension with very rapid filling rate \((dV/dt)\), increased septal thickness, and rapid rates of systolic posterior wall thickening and diastolic posterior wall thinning. At top left is instantaneous velocity of anterior and posterior mitral valve leaflets \((Mv. Valve Vel.; ) both are reduced. RSEP = right surface of septum; LSEP = left surface of septum; MV.A = anterior mitral valve leaflet; MV.P = posterior mitral valve leaflet; ENDO = endocardial surface; EPIC = epicardial surface. Other abbreviations and expressions as in figure 1.
The disease entity IHSS presents a variety of clinical, hemodynamic, angiographic, pathologic, and echocardiographic manifestations. Accordingly, there must exist a broad spectrum of LV dysfunction despite its suggested simple autosomal-dominant inheritance. 14

Symptoms of angina, syncope, and near syncope, palpitations (including electrocardiographic evidence of dysrhythmia), and dyspnea graded by the New York Heart Association classification were estimated within the three groups, and are presented in table 6. Angina and atrial fibrillation were most frequent in group 3 and dyspnea was most common in group 1. Twenty-three patients were taking propranolol (table 6), with similar dose ranges in the three groups. There was no correlation between the dose of propranolol and systolic or diastolic ventricular dynamics.

Left ventricular impairment, judged by the electrocardiographic criteria of LV hypertrophy alone occurred in 15 patients and with strain in six patients, and there was no difference in frequency among the three groups.

Table 3. Regional LV Function in Subgroups 1 to 3 of Patients With IHSS

<table>
<thead>
<tr>
<th>IHSS group</th>
<th>No.</th>
<th>EDD (cm)</th>
<th>ESD (cm)</th>
<th>(\frac{dD}{dt}) (cm/sec)</th>
<th>Filling period (msec)</th>
<th>Diast. Diast. PW Syst. PW % VS thickening</th>
<th>Diast. Syst. PW % VS thickening</th>
<th>Diast. Syst. PW % VS thickening</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Median</td>
<td>8</td>
<td>4.2</td>
<td>2.2</td>
<td>22.5</td>
<td>170†</td>
<td>2.3</td>
<td>2.6</td>
<td>14</td>
</tr>
<tr>
<td>2 Median</td>
<td>9</td>
<td>4.1</td>
<td>2.5</td>
<td>15.0</td>
<td>105-200</td>
<td>1.5-2.7</td>
<td>1.8-3.5</td>
<td>10-29</td>
</tr>
<tr>
<td>3 Median</td>
<td>12</td>
<td>4.1</td>
<td>2.3</td>
<td>9.0</td>
<td>285†</td>
<td>2.3</td>
<td>2.4</td>
<td>25</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td>3.1-5.1</td>
<td>2.1-3.3</td>
<td>12.1-18.1</td>
<td>140-300</td>
<td>1.6-3.1</td>
<td>1.8-3.4</td>
<td>9-64</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td>2.6-5.1</td>
<td>1.8-3.0</td>
<td>3.0-11.1</td>
<td>240-360</td>
<td>1.8-2.3</td>
<td>1.8-2.9</td>
<td>10-53</td>
</tr>
</tbody>
</table>

†Difference between groups 1 and 2, \(P < 0.01\); between groups 1 and 3, \(P < 0.01\); between groups 2 and 3, \(P < 0.05\).
‡Difference between groups 1 and 2, \(P < 0.01\); between groups 1 and 3, \(P < 0.01\); between groups 2 and 3, \(P < 0.01\).
Previous studies of LV function in IHSS have been confined to the assessment of global function and have utilized nonspecific parameters such as LV end-diastolic pressure, ejection fraction, diastolic closure rate of the anterior mitral valve leaflet, and velocity of circumferential fiber shortening. The last-named parameter should be interpreted with caution when there is regional variation in contractility such as exists in IHSS. In all previous reports, the above parameters of LV function have been analyzed with patients grouped together so that individual variation in ventricular function does not become apparent. This was also exemplified in our study when we initially assessed LV function in this way. Analysis of overall global function in these patients revealed that the minor dimension was significantly smaller than in normals throughout the cardiac cycle (table 1), peak filling rate and ejection fraction were normal, velocity of circumferential fiber shortening was increased, and isovolumic relaxation and the rapid diastolic filling periods were prolonged (tables 1 and 2)—findings that suggested moderate disturbance of diastolic function only. Hemodynamic data showed great variation in LV end-diastolic pressure and outflow tract gradients (table 5), which, when expressed as mean values for the group as a whole, rendered these data virtually meaningless.

Similarly, when regional function was assessed for the group as a whole, little new information was revealed: the septum was hypertrophied and hypokinetic, percent and peak rate of posterior wall systolic thickening were increased, and diastolic thinning of the posterior wall was normal.

When these echocardiographic (global and regional function) data were analyzed in this way, there was no correlation between symptoms and any measured parameter of LV function. The variability in global and regional ventricular function was only appreciated when patients were assessed individually in terms of diastolic function—that is, peak left ventricular filling rate, duration of the rapid filling phase, and posterior wall dynamics. This variation in diastolic LV function allowed emergence of three subgroups (groups 1 to 3). Patients in group 1 had faster than normal rates of ventricular filling, those in group 2 had normal rates of filling, and those in group 3 had slow filling. Since septal dynamics (that is, peak rates of systolic thickening and diastolic thinning) were similar in the three groups (table 3), an explanation must be sought for the differences in LV filling rates and periods. One factor that could account for the

Table 4. Regional LV Function in Subgroups 1 to 3 of Patients With IHSS

<table>
<thead>
<tr>
<th>IHSS group</th>
<th>1/VS-dVS/dt (sec⁻¹)</th>
<th>1/PW-dPW/dt (sec⁻¹)</th>
<th>MVO delay (msec)</th>
<th>Time between peak VS and PW dimension (msec)</th>
<th>VCF (sec⁻¹)</th>
<th>EF (%)</th>
<th>PCV (mm/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Median</td>
<td>1.50</td>
<td>1.56</td>
<td>14.80</td>
<td>25</td>
<td>5.9</td>
<td>90</td>
<td>32</td>
</tr>
<tr>
<td>Range</td>
<td>0.83-2.23</td>
<td>0.96-2.83</td>
<td>8.86-20.96</td>
<td>50.0</td>
<td>12.0</td>
<td>56-96</td>
<td>15-98</td>
</tr>
<tr>
<td>2 Median</td>
<td>1.46</td>
<td>1.50</td>
<td>7.59</td>
<td>64.0</td>
<td>3.1</td>
<td>86</td>
<td>34</td>
</tr>
<tr>
<td>Range</td>
<td>0.70-2.60</td>
<td>0.71-3.11</td>
<td>3.89-13.62</td>
<td>10-108.0</td>
<td>2.7</td>
<td>57-93</td>
<td>10-60</td>
</tr>
<tr>
<td>3 Median</td>
<td>2.62</td>
<td>2.09</td>
<td>4.22</td>
<td>77.0</td>
<td>3.0</td>
<td>77</td>
<td>28</td>
</tr>
<tr>
<td>Range</td>
<td>0.63-4.21</td>
<td>0.96-3.66</td>
<td>1.88-7.93</td>
<td>50-170</td>
<td>1.3</td>
<td>47-93</td>
<td>17-35</td>
</tr>
</tbody>
</table>

†Difference between groups 1 and 2, P < 0.01; between groups 1 and 3, P < 0.01; between groups 2 and 3, P < 0.01. *Difference between groups 1 and 2, P < 0.01; between groups 1 and 3, P < 0.01; not significant.

†Difference between groups 1 and 2, P < 0.01; between groups 1 and 3, P < 0.01; between groups 2 and 3, not significant.

Abbreviations: MVO = mitral valve opening; EJ = ejection fraction; PCV = peak closing velocity of anterior mitral valve leaflet; VS = ventricular septum; PW = posterior wall.
wide range of filling rates was variation in posterior wall dynamics, reflecting the changes in LV distensibility due to reduced compliance.  

Group 1 patients (rapid fillers) had markedly increased posterior wall dynamics. Normalized peak rates of diastolic wall thinning, systolic thickening, and percent systolic thickening were significantly greater than normal and groups 2 and 3. The peak rate of change of posterior wall thickness was faster during relaxation than during contraction, as occurs in normal subjects. These factors explained not only the rapid diastolic filling rates but also the apparently above normal ventricular function suggested by the markedly elevated peak velocity of circumferential fiber shortening and ejection fraction (table 3). The greatly enhanced posterior wall dynamics probably represent a compensatory response for loss of the normal septal contribution to LV cavity obliteration during ejection and also suggest that in this group the posterior wall has not yet become seriously involved with the myopathic process. Only in group 1 are the normal close-time relations between peak septal and posterior wall thickness and minimum LV dimension maintained by synchronous septal and posterior wall contraction.

Patients in group 3 had the slowest filling rates and also the most prolonged filling periods. This is clearly shown in the plot of the continuous LV dimension (fig. 5), in which there is no longer a true rapid filling phase. There is loss of the normal period of diastasis because filling continues throughout diastole. This slow filling rate is a result of the marked reduction in normalized peak diastolic thinning rate of the posterior wall and possibly in part to its increased thickness. Percentage systolic thickening of the posterior

Table 6. Analysis of Symptoms and Signs

<table>
<thead>
<tr>
<th>IHSS group</th>
<th>Mean age (yr)</th>
<th>Sex</th>
<th>Angina</th>
<th>Dyshrhythmia</th>
<th>LV hypertrophy</th>
<th>Strain</th>
<th>ECG</th>
<th>Propranolol Dose range (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8 39.4</td>
<td>M</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>4 1 8 40-300</td>
</tr>
<tr>
<td>2</td>
<td>9 44.0</td>
<td>M</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>5 2 6 20-480</td>
</tr>
<tr>
<td>3</td>
<td>12 47.4</td>
<td>M</td>
<td>9</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>6 3 9 60-400</td>
</tr>
</tbody>
</table>
wall was also reduced as compared with patients in groups 1 and 2. Unlike the normals and patients in group 1, the peak rate of diastolic wall thinning was slower than was systolic thickening; this indicated a greater impairment of relaxation than of contraction. In these patients, not only was there reduction in peak diastolic wall thinning, presumably brought about by progressive pathologic change in the posterior wall, but they had also developed severe disturbances in the temporal sequence of septal and posterior wall contraction — peak septal thickness occurred almost 200 msec after peak posterior wall thickness (table 4). This loss of coordination between septum and posterior wall may explain the prolongation of isovolumic relaxation and delay in mitral valve opening (table 4). In spite of these serious diastolic abnormalities of LV function, ejection fraction and velocity of circumferential fiber shortening were normal, and this emphasizes that the usual indices of pump function are insensitive even to severe diastolic disturbances.

Patients in group 2 had normal filling rates but moderately prolonged filling periods, findings that suggested intermediate resistance to LV filling. Normalized peak rate of systolic posterior wall thinning was the same as in group 1, but normalized diastolic thinning rate was reduced by 40%; this indicated deterioration in diastolic function but no change in systolic function. Although there was asynchrony between septal and posterior wall contraction, it was not as severe as in group 3.

The cause of the symptoms in IHSS is largely unexplained. There was no clear correlation between the incidence of symptoms and hemodynamic data (LV end-diastolic pressure and LV outflow gradients). We were unable to explain the high incidence of dyspnea in the rapid fillers (group 1), the majority of whom had normal LV end-diastolic pressures and no mitral reflux (table 5).

Angina was uncommon in patients with rapid filling, and the high incidence in those with slow filling could not be explained solely in terms of reduced perfusion of the subendocardial myocardium by increased wall/septal thickness, because this was the same in the three groups. It was possibly due to this in combination with two other factors: 1) The significantly decreased normalized peak rate of posterior wall thinning in this group may result in systolic wall tension being only slowly released, thereby shortening the time available for diastolic coronary blood flow. 2) The development of incoordinate septal contraction and relaxation, which was most severe in group 3, may also have resulted in reduction of intramyocardial blood flow.

Paroxysmal atrial fibrillation occurred only in patients in groups 2 and 3. Atrial size in the three groups increased with reduction of peak filling rates, although the increase did not reach statistical significance. Since the filling rate is determined by the rate of diastolic thinning of the free wall, the increasing atrial size from groups 1 to 3 reflects decreasing LV distensibility. Increased left atrial size, with its attendant propensity to develop atrial fibrillation, therefore, represents increased resistance to LV filling resulting from impaired wall dynamics, which was most severe in patients in group 3. Atrial fibrillation occurs late in the natural history of IHSS, and the reason it is so poorly tolerated is that it usually occurs in patients who already have slow filling rates and long filling periods (that is, group 3), which are manifestations of severe disturbance of diastolic LV function and reduced LV distensibility. Development of atrial fibrillation in IHSS may be regarded therefore as an index of advanced LV disease.

LV filling is complex, and peak filling rates and filling periods are only two factors in this process. The regional variation in LV function in IHSS makes interpretation of results difficult, particularly as only a limited region of the LV wall, cavity, and septum can be studied echocardiographically. However, endocardial and epicardial position and motion can be defined clearly throughout the heart cycle and this permits accurate analysis ofventricular dynamics. In IHSS, the septum makes little contribution to either ejection or filling, and peak filling rates and filling periods reliably reflect the properties and dynamics of the free wall, on which filling and ejection depend. These diastolic parameters provide a useful way of assessing the degree of LV dysfunction.

We suggest that the rapid fillers (group 1) are patients in whom the histopathologic process remains predominantly confined to the septum and involves the free LV wall only minimally, thus allowing compensatory increase in systolic thickening and rapid rates of change of posterior wall thickness in systole and diastole. As the myopathic process progressively involves the free wall, this compensatory mechanism is limited by reduction in posterior wall dynamics, with earlier and disproportionately greater effect on diastolic function. This results in a decrease in peak filling rate, prolongation of the filling and isovolumic relaxation periods and, finally, development of asynchrony between septal and posterior wall contraction. The cause of this asynchrony between the septum and the posterior wall is unexplained but may possibly reflect the greatly prolonged rate of repolarization observed electrophysiologically to occur differentially in the septum and the posterior wall. The natural history of this disease, therefore, is determined by the degree of pathologic change involving the free ventricular wall; as this change increases, it imposes progressive mechanical restraint on wall dynamics and cavity function.

We submit that assessment of LV function by computer analysis of the standard LV echocardiograms is a useful and reproducible noninvasive means of determining the status of patients with IHSS at periodic follow-up. It may also offer an explanation for the angina in patients with IHSS. And it may have clinical application in distinguishing between patients with normal and rapid LV filling (groups 1 and 2), who might benefit from surgical relief of their outflow tract obstruction, and those with slow filling (group 3) and the most severe LV disease, in whom surgery may not be helpful.

References

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Disproportionate Ventricular Septal Thickening in the Developing Normal Human Heart

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SUMMARY A disproportionally thickened ventricular septum containing numerous disorganized cardiac muscle cells is the most characteristic anatomic feature of hypertrophic cardiomyopathy. Since information concerning ventricular wall thicknesses and cellular arrangement in the developing heart may be pertinent to understanding the genesis of hypertrophic cardiomyopathy, morphologic observations were made in 151 normal human embryos, fetuses and term infants. Disproportionate ventricular septal thickening (septal-free wall ratio ≥1.3) was present in 94% of embryos and young fetuses; in over one-third disproportion thickening was particularly pronounced (septal-free ratio ≥ 2.0). Disproportionate septal thickening was also present in 65% of older fetuses, but in only 12% of infants over two weeks of age. Septal-free wall ratio decreased in a curvilinear fashion with increasing age and approximated unity in the newborn. This phenomenon occurred because, while both ventricular septal and left ventricular free wall thicknesses increased directly with age, free wall thickness increased at a greater rate than septal thickness, particularly after birth. Marked cellular disorganization in the septum was not a feature of the hearts studied.

HYPTERTROPHIC CARDIOMYOPATHY (asymmetric septal hypertrophy or ASH) is a disease of cardiac muscle that is usually genetically transmitted as an autosomal dominant trait.1,2 The most characteristic anatomic feature of patients with hypertrophic cardiomyopathy is a disproportionately thickened ventricular septum (with respect to the left ventricular free wall)3-10 containing numerous disorganized cardiac muscle cells.11-13 Although hypertrophic cardiomyopathy is usually identified clinically in adulthood,9,14-18 disproportionate ventricular septal thickening and disorganized septal architecture may be present from birth.19 Little information is available regarding ventricular wall thicknesses and arrangement of cardiac muscle cells in the ventricular septum of the normal embryonic, fetal or newborn human heart. Because such data would potentially enhance our understanding of the genesis of hypertrophic cardiomyopathy, the present morphologic study of developmental changes in the normal human heart was undertaken.

Materials and Methods

Selection of Specimens

Morphologic observations were made on 151 normal human heart specimens encompassing the developmental period from five weeks gestation (Carnegie stage 17, at which time the ventricular septum has divided the ventricular cavities) to 20 months of age. Heart specimens were obtained from the following sources:

1) Thirty-five serially sectioned embryos with crown-rump (C-R) lengths* of 12.6 mm to 29.5 mm (5½ to 8 weeks

* Crown-rump length was used in this study as the standard measure of embryonic and fetal growth (i.e., gestational age). Postovulatory gestational ages were obtained by extrapolation from crown-rump lengths, using available conversion tables.20 21 The term "embryo" refers, by convention, to specimens with crown-rump length of <30 mm (less than 8 weeks gestation).
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_Circulation_. 1978;57:512-520
doi: 10.1161/01.CIR.57.3.512

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
http://circ.ahajournals.org/content/57/3/512

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