Differences in Distribution of Myocardial Abnormalities in Patients with Obstructive and Nonobstructive Asymmetric Septal Hypertrophy (ASH)

Light and Electron Microscopic Findings


SUMMARY

Previous studies have shown that abnormal cellular morphology is present in the ventricular septum of patients with asymmetric septal hypertrophy (ASH). The present study was undertaken to determine whether these morphologic abnormalities are limited to the ventricular septum of patients with ASH or are more diffusely distributed throughout the heart, and whether different patterns of distribution of the cellular abnormalities exist in patients with and without left ventricular outflow obstruction. Myocardium was obtained at operation or necropsy from 22 patients, including 14 with obstructive and 8 with nonobstructive ASH. Many hypertrophied, bizarrely shaped, and abnormally arranged cardiac muscle cells, presumably a morphologic manifestation of the genetically transmitted myocardial defect in ASH, were present in the ventricular septum of all patients. In patients with obstructive ASH, these abnormalities were either absent or rarely found in muscle from the left and right ventricular free walls. This observation suggests that functional limitation in these patients is due largely to left ventricular outflow obstruction. In contrast, numerous disorganized cells were extensively distributed in the left and right ventricular free walls of patients with nonobstructive ASH, suggesting that these abnormalities probably contribute importantly to functional impairment in such patients.

Additional Indexing Words:

Ultrastructure  Idiopathic hypertrophic subaortic stenosis  Ventricular hypertrophy  Myocardium

Asymmetric septal hypertrophy (ASH) comprises a disease spectrum in which only some patients have obstruction to left ventricular outflow under basal conditions; in most patients, however, obstruction is absent.1,2 Despite this hemodynamic difference, virtually all patients with this disease have disproportionate hypertrophy of the ventricular septum with respect to the posterobasal left ventricular wall.3-4

Light and electron microscopic studies have demonstrated that the ventricular septum in patients with ASH and left ventricular outflow obstruction contains many hypertrophied, bizarrely shaped, and abnormally arranged cardiac muscle cells.5-7 Because these histologic abnormalities are present only rarely in other forms of heart disease,5-8 we believe that this bizarre cardiac architecture may be a manifestation of the genetically transmitted myocardial defect in ASH. Furthermore, it has been suggested that the left ventricular free wall thickening present in some patients indicates that the myocardial disorder is diffusely distributed in the heart.10 This concept has led some investigators to view the role of operative intervention, even in patients who have obstruction, with extreme skepticism.11 On the other hand, it has been shown that operation is of benefit to virtually all patients with ASH and obstruction,12 suggesting that the myocardial defect in these patients is not diffuse.

In order to resolve this controversy, and to define further the extent and severity of myocardial abnormalities in the hearts of patients with obstructive and

From the Cardiology Branch, Section of Pathology and Clinic of Surgery, National Heart and Lung Institute, Bethesda, Maryland.
Address for reprints: Dr. Barry J. Maron, Cardiology Branch, National Heart and Lung Institute, Bldg. 10, Room 7B-15, Bethesda, Maryland 20014.
Received November 1, 1973; revision accepted for publication April 3, 1974.

436

Circulation, Volume 50, September 1974
nonobstructive ASH, two studies were undertaken. The first study, which forms the basis of this communication, describes the distribution of morphologic abnormalities in the heart by light and electron microscopy. The second study\(^1\) describes the distribution of wall thickening as determined by echocardiography and by examination of necropsy specimens.

**Methods**

**Patient Selection**

The morphologic studies reported in this communication were made on myocardium obtained from 22 patients with ASH. The diagnosis of ASH (i.e., the ratio of the thickness of the ventricular septum to that of the posterobasal left ventricular wall is greater than 1.3) was established in all 22 patients by echocardiography, necropsy examination, or both. Patients were selected for operation (left ventricular myotomy-myectomy) if they had cardiac symptoms sufficient to produce significant functional limitation (New York Heart Association functional classes 3 or 4) and did not respond adequately to propranolol.

Clinical and hemodynamic data from the patients (12 men and ten women; aged 8 to 67 years) are summarized in table 1. Measurements of the peak systolic pressure gradient between left ventricle and a systemic artery were obtained in all patients under basal conditions and during provocative interventions (Valsalva maneuver or administration of isoproterenol). Patients were divided into three groups on the basis of the magnitude of the gradient: 1) **Obstructed group**: any gradient present under basal conditions. This group includes 12 patients with gradients of 65 to 162 mm Hg under basal conditions; 2) **Provable obstruction group**: no basal gradient but provokable gradients greater than 30 mm Hg. This group includes two patients who had no gradients under basal conditions but developed gradients greater than 30 mm Hg after provocative maneuvers; 3) **Nonobstructed group**: no pressure gradient under basal conditions and a provokable peak gradient of less than 30 mm Hg. This group includes eight patients.

None of the patients without obstruction had had clinical evidence of obstruction prior to the time of cardiac catheterization (i.e., murmurs louder than grade II were not described and carotid tracings did not demonstrate the typical bisferious contour characteristic of most patients with obstruction). Mitral regurgitation was demonstrated by angiogram in seven patients (severe in patient #18, Table 1

**Clinical and Hemodynamic Data in 22 Patients with ASH**

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Age</th>
<th>Sex</th>
<th>FC</th>
<th>PA (S/D)</th>
<th>RV (S/D)</th>
<th>LV (S/D)</th>
<th>Aorta (S/D)</th>
<th>Basal</th>
<th>Provoked</th>
<th>PSG</th>
<th>CI (L/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>M</td>
<td>3</td>
<td>32/15</td>
<td>32/5</td>
<td>190/12</td>
<td>125/75</td>
<td>65</td>
<td>150</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>M</td>
<td>3</td>
<td>22/10</td>
<td>22/6</td>
<td>180/11</td>
<td>110/75</td>
<td>70</td>
<td>90</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>M</td>
<td>3</td>
<td>36/14</td>
<td>38/8</td>
<td>190/24</td>
<td>115/70*</td>
<td>75</td>
<td>95</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>F</td>
<td>3</td>
<td>32/16</td>
<td>32/9</td>
<td>180/10</td>
<td>100/68</td>
<td>90</td>
<td></td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>F</td>
<td>3</td>
<td>24/11</td>
<td>24/7</td>
<td>200/12</td>
<td>110/65</td>
<td>90</td>
<td>100</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>F</td>
<td>3</td>
<td>22/11</td>
<td>25/4</td>
<td>210/16</td>
<td>115/70</td>
<td>95</td>
<td></td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>F</td>
<td>3</td>
<td>24/12</td>
<td>24/6</td>
<td>180/20</td>
<td>80/45</td>
<td>100</td>
<td>90</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>67</td>
<td>F</td>
<td>3</td>
<td>40/15</td>
<td>40/5</td>
<td>205/11</td>
<td>105/65</td>
<td>100</td>
<td>130</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>22</td>
<td>M</td>
<td>3</td>
<td>42/18</td>
<td>42/10</td>
<td>220/32</td>
<td>118/60</td>
<td>102</td>
<td>140</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>57</td>
<td>M</td>
<td>4</td>
<td>24/8</td>
<td>30/6</td>
<td>220/20</td>
<td>105/80</td>
<td>115</td>
<td></td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>11†</td>
<td>34</td>
<td>F</td>
<td>3</td>
<td>23/12</td>
<td>20/3</td>
<td>160/18</td>
<td>85/50*</td>
<td>75</td>
<td>125</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>12†</td>
<td>19</td>
<td>F</td>
<td>3</td>
<td>62/12</td>
<td>28/20</td>
<td>260/20</td>
<td>98/75</td>
<td>162</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>18</td>
<td>M</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>130/12</td>
<td>130/92</td>
<td>0</td>
<td>70</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>50</td>
<td>M</td>
<td>3</td>
<td>22/12</td>
<td>24/6</td>
<td>135/12</td>
<td>135/75</td>
<td>0</td>
<td>70</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>15†</td>
<td>62‡</td>
<td>F</td>
<td>3</td>
<td>55/10</td>
<td>70/11</td>
<td>140/24</td>
<td>140/55</td>
<td>0</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>95/20</td>
<td>—</td>
<td>97/52*</td>
<td>0</td>
<td>0–34</td>
<td>2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16†</td>
<td>33</td>
<td>M</td>
<td>3</td>
<td>52/25</td>
<td>52/15</td>
<td>120/26</td>
<td>120/80*</td>
<td>0</td>
<td>29</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>17†</td>
<td>30</td>
<td>M</td>
<td>3</td>
<td>29/14</td>
<td>29/7</td>
<td>115/28</td>
<td>117/70*</td>
<td>0</td>
<td>17</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>18†</td>
<td>40</td>
<td>F</td>
<td>4</td>
<td>34/17</td>
<td>34/5</td>
<td>112/11</td>
<td>122/65*</td>
<td>0</td>
<td>0</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>19†</td>
<td>29</td>
<td>F</td>
<td>3</td>
<td>70/30</td>
<td>70/17</td>
<td>130/38</td>
<td>130/80</td>
<td>0</td>
<td>0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>20†</td>
<td>59</td>
<td>M</td>
<td>3</td>
<td>30/14</td>
<td>30/7</td>
<td>115/22</td>
<td>115/65</td>
<td>0</td>
<td>0</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>21†</td>
<td>24</td>
<td>M</td>
<td>2</td>
<td>22/12</td>
<td>22/7</td>
<td>110/10</td>
<td>110/70</td>
<td>0</td>
<td>0</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>22†</td>
<td>8</td>
<td>M</td>
<td>3</td>
<td>90/55</td>
<td>90/27</td>
<td>90/34</td>
<td>103/90</td>
<td>0</td>
<td></td>
<td></td>
<td>1.6</td>
</tr>
</tbody>
</table>

*Brachial artery pressure.
†Died.
‡Ventricular septal defect (Pulmonary-to-systemic flow ratio = 2.4), which had been produced during the course of left ventricular myotomy-myectomy three years previously.
¶Pulmonary sarcoidosis demonstrated on open lung biopsy; myocardial biopsy showed no evidence of sarcoidosis.

Abbreviations: FC = functional class (New York Heart Association); PA = pulmonary artery; RV = right ventricle; S/D = systolic/diastolic; LV = left ventricle; PSG = peak systolic gradient; CI = cardiac index.

*Circulation, Volume 50, September 1974*
moderate in patients #2 and #20, and mild in patients #10, #14, #15, and #16. The period of time between cardiac catheterization and operative biopsy ranged from one week to 11 months (median, two months), and between cardiac catheterization and death (for the patients studied at necropsy) from one day to three years (median, four months).

Eight patients in this study had died; two of these had obstructive ASH (#11, #12) and the remaining six patients had nonobstructive ASH (#15–19, #22). Four patients (#11, #15, #17 and #22) died suddenly (presumably of their cardiac disease); three (#12, #18 and #19) died at operation, and one (#16) died of severe congestive heart failure and thromboemboli to the brain. In addition to ASH, one patient (#16) was found at necropsy to have severe coronary arterial luminal narrowing by atherosclerotic plaques.

Selection and Preparation of Tissue

In 14 patients myocardial biopsies were taken only at operation. In seven other patients myocardium was obtained only at necropsy and in one other patient (#19) myocardium was taken at both operation and necropsy.

Operative biopsies

In 12 patients myocardium was taken during the course of left ventricular myotomy–myectomy. Eleven of these patients had obstructive ASH. The other patient (#19) was severely symptomatic with nonobstructive ASH and continued to deteriorate rapidly in spite of intensive medical therapy; myotomy–myectomy was attempted to increase left ventricular compliance. Myocardium was obtained in the other three patients at the time of thoracotomy for other conditions: patient #21 had a diagnostic lung biopsy for suspected sarcoidosis; patient #20 had an aorto-coronary artery saphenous vein bypass operation for coexistent coronary arterial disease, and patient #14 underwent closure of a ventricular septal defect which had been produced during the course of left ventricular myotomy–myectomy three years previously.

The sites from which myocardial tissues were obtained included: the cephalad portion of the left side of the ventricular septum (12 patients); the cephalad portion of the right side of the ventricular septum (two patients); the left ventricular apex (13 patients); the left ventricular posterior wall, about halfway between the left ventricular apex and the atrioventricular groove (12 patients), and the right ventricular anterior wall, in the area of the outflow tract (seven patients).

In patients undergoing left ventricular myotomy–myectomy, tissue (about 10 x 10 x 15 mm) was resected from the ventricular septum after 20 to 40 min of cardiopulmonary bypass and after a period of 10 to 12 min of cardiac arrest. During the latter period the aorta was clamped, the heart was cooled to approximately 30°C, and the coronary arteries were not perfused.

Biopsies from the left and right ventricular free walls were obtained after 2 to 5 min of cardiopulmonary bypass but before institution of cardiac arrest. Cylindrical biopsies (about 2 x 10 mm), representing either approximately three-fourths of the thickness or the full thickness of the ventricular wall, were obtained by epicardial puncture of the left ventricular posterior wall and right ventricular anterior wall with a 14 gauge Vim-Silverman biopsy needle (modified Franklin type) having a 16 gauge split inner cannula. Biopsies of the left ventricular apex (about 3 x 4 x 5 mm) were taken with a scalpel.

The myocardial specimens were immediately fixed with cold 3% glutaraldehyde in 0.1 M phosphate buffer, pH 7.2. After washing with several changes of cold 5% sucrose in 0.1 M phosphate buffer, pH 7.2, the tissues were post-fixed with 1% osmium tetroxide in Millonig’s phosphate buffer, pH 7.2, dehydrated with a graded series of ethanol and propylene oxide and embedded in Maraglas. Semithin (0.5 μ thick) sections were cut from all tissue blocks from each biopsy, stained with alkaline toluidine blue, and examined by light microscopy. Five to 40 semithin sections, each measuring 1-4 mm² in area, were available from each biopsy for analysis. Final choice of tissue areas for electron microscopic study was limited to those areas that contained artifact-free, longitudinally oriented muscle cells. Ultrathin sections were stained with uranyl acetate and lead citrate and examined with an RCA EMU-3G electron microscope.

Necropsy Specimens

Myocardium was obtained at necropsy from eight patients, including six with nonobstructive ASH and two with obstructive ASH. In each patient, multiple blocks of myocardium were taken from the full thickness of the ventricular septum, the left ventricular anterior and posterior walls, and the right ventricular anterior wall. Tissue was sectioned at 6 μ thickness and stained with hematoxylin and eosin.

Microscopic Analysis

The pattern of arrangement of cardiac muscle cells was analyzed by light and electron microscopy (electron microscopic analysis was not performed on the necropsy specimens) and rated independently by two investigators (B. J. M. and V. J. F.) according to the grading system presented in table 2. The purposes of this assessment were to determine whether or not cardiac muscle cells in a given area of tissue were normal in shape and normally aligned with respect to each other; i.e., arranged in parallel and connected at their ends by intercellular junctions (intercalated discs). For this reason, evaluation of cellular arrangement was limited to cardiac muscle cells in longitudinal or slightly oblique sections. Transverse diameters of muscle cells were measured from sections of biopsy tissue with a calibrated micrometer eyepiece. Measurements were made on 35 to 50 longitudinally oriented muscle cells and the average of these measurements was used to define the cell diameters characteristic of each biopsy.

Results

Arrangement, Size, and Shape of Cardiac Muscle Cells in the Ventricular Septum

The morphology of cardiac muscle cells from the ventricular septum was indistinguishable in patients with or without left ventricular outflow tract obstruction and corresponded to that previously described in patients with obstructive ASH (typical IHSS). Many of the cells in the ventricular septum demonstrated great variation in size and were irregularly shaped (figs. 1–4); many were markedly enlarged, with transverse diameters ranging from 10 to 70 μ (average 28 μ; normal 10–15 μ). Multiple intercalated discs, presumably representing lateral cytoplasmic processes
Table 2

Morphologic Assessment of Cellular Arrangement in 22 Patients with ASH*

<table>
<thead>
<tr>
<th>Patient #</th>
<th>VS</th>
<th>LV PW</th>
<th>LV APEX</th>
<th>RV ANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1+</td>
<td>0</td>
<td>0</td>
<td>0†</td>
</tr>
<tr>
<td>3</td>
<td>1+</td>
<td>0</td>
<td>0</td>
<td>0§</td>
</tr>
<tr>
<td>4</td>
<td>2+</td>
<td>—</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>1+</td>
<td>0†</td>
<td>0‡</td>
<td>0†</td>
</tr>
<tr>
<td>6</td>
<td>2+</td>
<td>—</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>2+</td>
<td>0</td>
<td>0‡</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>2+</td>
<td>0</td>
<td>0‡</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>2+</td>
<td>—</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>1+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11†</td>
<td>2+</td>
<td>0‡</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>12†</td>
<td>2+</td>
<td>0§</td>
<td>—</td>
<td>0</td>
</tr>
</tbody>
</table>

ASH with Obstruction

ASH with Provocable Obstruction

ASH Without Obstruction

*Grading system: 0 = normal cellular arrangement; 1+ = mild to moderate disorganization of cells; 2+ = severe disorganization of cells; — = not examined.
†Myofibrillar and/or myofilament disarray present which involved only a few cells of a tissue block area. Muscle cells were hypertrophied but normally arranged.
‡Necropsy data.
§Small, rare foci of hypertrophied, bizarrely shaped, and disoriented cardiac muscle cells; all other cells were hypertrophied but normally arranged.
¶Necropsy and biopsy data.

Abbreviations: VS = ventricular septum; PW = posterior wall; LV = left ventricle; RV = right ventricle; ANT = anterior.

Rare features of the hearts of patients with ASH, when compared with the commonly observed bizarrely shaped and disorganized cardiac muscle cells.

Arrangement, Size, and Shape of Cardiac Muscle Cells in the Left and Right Ventricle Free Walls

The morphology of cardiac muscle cells in the ventricular free walls differed distinctly in patients with obstruction compared to those without obstruction (table 2).

ASH with obstruction

In the 12 patients having ASH and left ventricular outflow obstruction, the vast majority of muscle cells...
from the left and right ventricular free walls did not show the bizarre shapes or severe malalignment characteristic of cells in the ventricular septum. Cells from the ventricular free walls usually appeared rectangular in longitudinal section and were relatively uniform in size and shape (figs. 6–8). These cells, however, were hypertrophied with transverse cell diameters ranging from 10 to 66 μ (average 28 μ). The degree of cellular enlargement did not differ in the left ventricular apex, left ventricular posterior wall, or ventricular septum. Muscle cells from the right ventricular free wall ranged from 10 to 45 μ (average 23 μ) in diameter. Cardiac muscle cells from the left ventricular free wall of five patients with moderate to severe aortic valvular stenosis (gradients of 40 to 90 mm Hg) were studied for comparison and showed transverse cell diameters of 13 to 70 μ (average 28 μ).

Of the 12 patients with ASH and left ventricular outflow obstruction, only two (†3 and †12) demonstrated rare, small foci of hypertrophied, abnormally arranged cardiac muscle cells in the left or right ventricular free walls.

ASH Without Obstruction

In seven of the eight patients having ASH without outflow obstruction, the majority of cardiac muscle cells from the left and right ventricular free walls were hypertrophied, bizarrely shaped, and abnormally arranged (figs. 9, 10). Some cardiac muscle cells from these seven hearts were hypertrophied but regularly shaped and normally arranged. The remaining patient (†20) was severely symptomatic but had coexisting coronary arterial disease; this patient had large, abnormally arranged cardiac muscle cells in a biopsy specimen from the ventricular septum but normally arranged cells in a biopsy from the left ventricular posterior wall.

The transverse diameters of cells from the left ventricular posterior wall in patients with nonobstructive ASH were increased, ranging from 10 to 63 μ (average 33 μ). The right ventricular muscle cells also were greatly enlarged (average transverse diameter 37 μ) in patient †19 with nonobstructive ASH and severe pulmonary arterial hypertension.
ASH with Provocable Obstruction

In one of the two patients (#13) in this intermediate category, abnormally arranged muscle cells were found in the ventricular septum but not in a left ventricular free wall biopsy. In the other patient (#14), however, large, bizarrely shaped, and disorganized cardiac muscle cells were present in biopsy specimens from both the ventricular septum and left ventricular posterior wall.

Arrangement of Myofibrils and Myofilaments in the Ventricular Septum and Ventricular Free Walls

In six of the 12 patients with obstructive ASH and six of the eight patients with nonobstructive ASH,
many of the bizarrely shaped muscle cells from the ventricular septum contained myofibrils that showed marked disarray. Adjacent myofibrils were oriented obliquely or perpendicularly to each other (figs. 2–4, 9, 11, 12). In the left and right ventricular free walls, disorganized myofibrils were often found in hypertrophied, abnormally arranged cardiac muscle cells of three patients with nonobstructive ASH and occasionally in hypertrophied, normally arranged muscle cells of four patients with obstructive ASH and one patient with provacable obstruction (table 2). In addition, myofilaments commonly originated from the Z band of one myofibril and inserted into the Z bands of other myofibrils (fig. 12).

Alterations in Other Cellular Components

Several other ultrastructural abnormalities were identified in myocardium from the ventricular septum and ventricular free walls in the 15 patients with operative biopsies. The extent and severity of these additional abnormalities did not differ in patients with obstructive ASH, ASH with provacable obstruction, or nonobstructive ASH. Abnormalities in Z band structure were present in muscle from 12 patients and were generally most prominent in the ventricular septum. These abnormalities consisted of widening and spreading of Z bands (fig. 12) and increased amounts of Z band-like material at points of attachment of myofibrils to intercellular junctions (intercalated discs). These alterations in Z band structure were of the type considered suggestive of the formation of new sarcotubes.16

Mitochondrial damage was present in 14 patients and consisted of swelling of mitochondria and disruption of cristae. These abnormalities were more marked in the ventricular septum than in the left ventricular free walls in 11 of the 14 patients, and may have been due to the cardiac arrest under hypothermic and hypoxic conditions.17

Markedly convoluted intercellular junctions (intercalated discs) were a consistent finding in biopsies from all 15 patients. Side-to-side intercellular junctions were present instead of, or in addition to, the more usual end-to-end junctions of muscle cells in seven patients. These side-to-side junctions were usually seen in muscle cells from the ventricular septum in areas of myofibrillar disarray. Areas of separation of the plasma membranes of the undifferentiated segments of intercellular junctions were present in 12 patients (fig. 13). These abnormalities, which resemble those described in other forms of cardiac hypertrophy,18 were more marked in the left and right ventricular walls than in the ventricular septum in 11 of the 12 patients.

In 11 of the 15 patients, all glycogen granules in cardiac muscle cells were in the usual monoparticulate β-form (diameter 225 to 375 Å); in the other four patients, some glycogen particles were in the form of large rosettes (α-glycogen) with diameters of 1300 to 2400 Å.19

Dilatation of the transverse tubular system was present in 11 of the 15 patients and was most prominent in the left ventricular wall in seven patients (fig. 14). The sarcoplasmic reticulum was normal in hypertrophied cardiac muscle cells from all patients. A few markedly enlarged nuclei with bizarre convolutions of the nuclear membrane were found in biopsies from all patients and were most common in the ventricular septum. Ribosomes were present in increased numbers in most cells from both the ventricular septum and ventricular free walls, and were usually free in perinuclear areas, between myofibrils and near intercellular junctions as well as attached to the membranes of the sarcoplasmic reticulum. Lipofuscin

Figure 10

Light micrograph of semithin section from left ventricular posterior wall of patient #19 with nonobstructive ASH. The muscle cells have bizarre shapes and are markedly disorganized. Alkaline toluidine blue stain. X 200. Scale bar = 50 μ.
CELL ABNORMALITIES IN ASH

Figure 11

Electron micrograph of part of a cardiac muscle cell showing an area of myofibrillar disarray. Compare with figure 3 which shows a light micrograph of a similar area. Ventricular septum from patient #8 with obstructive ASH. X 5,900. Scale bar = 4 μ.

granules were increased in number in all hearts. Variable amounts of interstitial fibrosis, characterized by increased numbers of mature and developing collagen fibrils, were present in myocardium from the ventricular septum and ventricular free walls of all patients.

Degenerated cardiac muscle cells were present in the ventricular septum or left ventricular free wall in six patients. These cells were usually present in areas of fibrosis and often appeared isolated, having no contact with other muscle cells. These degenerated cells demonstrated the following features: preferential loss of thick myofilaments; accumulations of abnormal Z band-like material attached to thin myofilaments; decreased numbers of myofibrils and T tubules; many small mitochondria; proliferation and dilatation of sarcoplasmic reticulum; and thickening of the basement membranes. Cardiac muscle cells of this type are not unique to ASH but are also seen in left ventricular myocardium from patients with aortic valvular stenosis and/or regurgitation.

Discussion

This investigation confirms the data of previous studies showing that cardiac muscle cells which are hypertrophied, bizarrely shaped, and abnormally arranged are invariably present in the ventricular septum of patients with ASH and left ventricular outflow tract obstruction. The observations in this communication further demonstrate that these cells also are found in the ventricular septum of patients without obstruction. The occurrence of these cells in patients with ASH and no present or previous evidence of outflow obstruction suggests that high ventricular pressure is not the primary mechanism responsible for their unusual morphologic features or their increased size. Moreover, cells with these characteristics are rarely found in patients with cardiac hypertrophy from causes other than ASH. For example, we have observed foci of bizarrely shaped and abnormally arranged cardiac muscle cells in some patients with congenital heart diseases associated with right ventricular outflow tract obstruction (and unpublished observations), but have not observed these cells in patients with congestive cardiomyopathies or in patients with left ventricular hypertrophy due to aortic valvular disease. Thus, it appears reasonable to assume that these hypertrophied, bizarrely shaped,
and disorganized cardiac muscle cells, while not an absolutely specific finding in patients with ASH, are morphologic manifestations of a genetically transmitted myocardial defect.

Although all patients with either obstructive or non-obstructive ASH have this cellular abnormality in the...
ventricular septum, the distribution of these bizarre cells in other areas of myocardium is markedly different in these two groups of patients. The abnormal cardiac muscle cells were distributed widely in the left and right ventricular free walls of symptomatic patients with nonobstructive ASH. In contrast, these bizarre cells were absent or rarely found in the left and right ventricular free walls of symptomatic patients with ASH who had outflow obstruction. In fact, the majority of cardiac muscle cells found in tissue sections from the left ventricular free wall of patients with obstructive ASH were indistinguishable from those hypertrophied and normally arranged cardiac muscle cells present in the left ventricular free wall of patients with fixed left ventricular outflow obstruction. This observation suggests that the hypertrophy present in the left ventricular free wall of patients with obstructive ASH is due to high ventricular pressures. It should be emphasized that these morphologic observations were made primarily in severely symptomatic patients; therefore, it is possible that the bizarrely shaped and maloriented cardiac muscle cells are not as widely distributed in the hearts of asymptomatic patients with nonobstructive ASH. Indeed, the one patient with nonobstructive ASH and mild symptoms (patient #21) had only mild disorganization of muscle cells in the left ventricular posterior wall.

Two patients (#13 and #14) in this study had no outflow obstruction under basal conditions, but had large gradients after provocative interventions. Hypertrophy, bizarrely shaped, and abnormally arranged muscle cells were present in a biopsy from the left ventricular posterior wall of one of these two patients, while no abnormal cells were present in the left ventricular free wall biopsies from the other patient. Definitive conclusions cannot be drawn from the data of this small subgroup of patients. It is interesting to speculate, however, that the left ventricular free wall in patients with provokable gradients may be involved by cellular abnormalities that are intermediate in extent between those found in patients with outflow obstruction under basal conditions and in patients without outflow obstruction.

Some normally or abnormally oriented cardiac muscle cells from patients with ASH showed intracellular abnormalities such as disarray of myofibrils and myofilaments. Such morphologic abnormalities are relatively nonspecific findings, since they occur in patients with other forms of ventricular hypertrophy in which bizarrely shaped and disorganized cells are not present. Thus, the precise significance of myofibrillar and myofilament disarray in cardiac muscle cells of patients with ASH is presently unclear. In addition, we observed small muscle bundles (composed of hypertrophied, but otherwise normal cells) coursing in a disorderly fashion through larger, normally arranged bundles. These bundles, although distinctive in appearance, were an inconsistent and uncommon feature of the hearts studied; the relation of these muscle bundles to the genetically transmitted myocardial defect in ASH is uncertain.

The bizarrely shaped and abnormally arranged cardiac muscle cells present in patients with ASH were greatly hypertrophied, having transverse diameters ranging from 10–70 μ (average of 28 μ). Cells present in the left ventricular free wall of patients with obstructive ASH or severe aortic valvular stenosis, however, also had transverse diameters within the same range. Although these data suggest that the degree of hypertrophy of the muscle cells is the same in ASH and in fixed left ventricular outflow obstruction, we do not believe that this is actually the case. We consider that the measurement of transverse diameter is a poor index of cell size when cells are stellate shaped rather than cylindrical. Indeed, we had the distinct impression that the area (in contrast to the transverse diameter) of the bizarrely shaped cells characteristic of ASH was considerably greater than that of the hypertrophied cells present in patients with fixed left ventricular outflow obstruction.

The biopsy technique employed in this study yielded a relatively small amount of tissue and thus the possibility of a sampling error must be considered. Indeed, other investigators have shown that the abnormal muscle cells in patients with ASH are irregularly distributed within the heart and may be found predominantly in the middle layer of the ventricular septum and ventricular free walls. The morphologic characteristics of the cardiac muscle cells from tissue removed at operation in this study were, however, remarkably consistent within each of the two groups of patients (obstructive and nonobstructive ASH). More importantly, the morphologic findings in the necropsy specimens, in which multiple full thickness blocks from different areas of the ventricular walls were examined, were similar to those in the operative biopsies. Thus, it appears unlikely that the biopsy data were significantly influenced by sampling error.

In conclusion, our observations indicate that hypertrophy, bizarrely shaped, and disorganized cardiac muscle cells, presumably a morphologic manifestation of the myocardial defect in ASH, are invariably present in the ventricular septum of patients with nonobstructive and with obstructive ASH. These abnormal cells involve the ventricular free walls extensively in symptomatic patients with nonobstructive ASH and probably are responsible for functional impairment. In symptomatic patients with obstructive ASH,
however, the abnormal cells are localized principally to the ventricular septum, an observation suggesting that the functional limitation in this group is due largely to left ventricular outflow tract obstruction.

References
18. KAWAMURA K, JAMES TN: Comparative ultrastructure of cellular junctions in working myocardium and the conduc- tion system under normal and pathologic conditions. J Molec Cell Cardiol 3: 31, 1971
Differences in Distribution of Myocardial Abnormalities in Patients with Obstructive and Nonobstructive Asymmetric Septal Hypertrophy (ASH): Light and Electron Microscopic Findings
BARRY J. MARON, VICTOR J. FERRANS, WALTER L. HENRY, CHESTER E. CLARK, DAVID R. REDWOOD, WILLIAM C. ROBERTS, ANDREW G. MORROW and STEPHEN E. EPSTEIN

Circulation. 1974;50:436-446
doi: 10.1161/01.CIR.50.3.436
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1974 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/50/3/436

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/