Mitral Valve Prolapse in One Hundred Presumably Healthy Young Females

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SUMMARY Clinical, electrocardiographic, phonocardiographic, and echocardiographic examinations were performed in 100 presumably healthy young females. Treadmill testing and ambulatory electrocardiographic monitoring were performed in a selected group of these subjects. Phonocardiograms, recorded with the subjects supine at rest, after inhalation of amyl nitrite, and in the upright position, revealed a 17% incidence of nonejection clicks and/or late or mid- to late systolic murmurs (PHONO-MSCLSM). Echocardiographic studies were performed in the second, third, fourth, and fifth intercostal space with emphasis on the importance of transducer angulation on the chest. Studies obtained with the transducer perpendicular to the chest in the sagittal plane, or pointing cephalad at a time when both mitral leaflets and left atrium are recorded, are optimal to study the mitral valve systolic motion. With the transducer in this position, 21 subjects were found to have pansystolic or late systolic prolapse, as previously defined on the echocardiogram. The presence of these echocardiographic findings was statistically related to the presence of PHONO-MSCLSM. Other echocardiographic patterns were identified and their relation to PHONO-MSCLSM and transducer position is discussed. Ten subjects with both echocardiographic evidence of mitral valve prolapse and PHONO-MSCLSM were identified (group EP), while 18 other subjects had either echocardiographic or phonocardiographic findings suggestive of mitral valve abnormality (group EorP). Seventy-two subjects had no abnormality (group noEP). The incidence of various clinical, electrocardiographic, and echocardiographic findings in these three groups was determined. Some findings said to be common in patients with proven mitral valve prolapse were seen more frequently in group EP subjects. Echocardiographic and phonocardiographic findings suggesting mitral valve abnormalities were found more commonly than expected in a population of presumably healthy young females.

NUMEROUS REPORTS have documented the association of abnormalities of the mitral valve with nonejection clicks and late systolic murmurs.1-9 Recent studies correlating echocardiographic findings suggesting mitral valve prolapse and left ventricular angiography have demonstrated the high sensitivity of the ultrasound technique.10-13 Also, it has been shown that an abnormal echocardiographic systolic motion of the mitral valve could be demonstrated in patients who did not present with the typical auscultatory findings of mid- to late systolic click or murmur.12-14 We have been impressed recently by the frequency with which echocardiographic patterns reported previously to occur in patients with angiographically proven mitral valve prolapse were recorded in apparently healthy subjects. This study was undertaken in order to define more accurately the normal echocardiographic pattern of the mitral valve during systole, to observe the prevalence of the echocardiographic patterns suggesting mitral valve prolapse in a population of presumably healthy young females, and to correlate these patterns with specific clinical, phonocardiographic, and electrocardiographic features.

Methods

Patient Selection

Studies were performed in 101 paid volunteers recruited through advertisements placed in campus newspapers and on posters. Females aged 17-35 years making a statement of presumed good health were accepted for study. After ob-
taining informed consent, the subjects filled out a question-
naire regarding the presence or absence of symptoms such as
chest discomfort, palpitations, unusual shortness of breath
or fainting. This questionnaire also inquired about a past
history of chest trauma, heart murmur, rheumatic or scarlet
fever, frequent sore throat, high blood pressure, major
medical problems of any kind, and a family history of heart
disease. When a positive answer was registered, a physician
asked specifically about the characteristics of complaints or
past history. Symptoms were classified as being either
possibly suggestive of heart disease, or as probably insignifi-
cant, and only those symptoms considered compatible with
heart disease were considered for further analysis. A
physical examination limited to the cardiovascular system
was made. Stigmata of the Marfan syndrome and abnorm-
alities of the thorax were specifically looked for. The
distance between mid-sternum and spine was measured (chest
AP diameter). Auscultation of the heart was performed in
both supine and sitting position. A 12-lead electrocardiogram
was recorded. Phonocardiograms were recorded using Maico contact microphones placed at the pulmonary and
apical areas and filtered to display medium (100–500
Hz) and low (40–100 Hz) frequencies. Recordings were
taken in the supine, semi-left lateral decubitus and standing
positions, and supine after inhalation of amyl nitrite, at
a speed of 100 mm/sec on an Electronics for Medicine DR8
or an Irex Continutrace 101 recorder. Records were also
obtained at the aortic area and lower left sternal border
(LLSB). Lead II of an electrocardiogram was recorded
simultaneously with all phonocardiograms and the carotid
pulse was recorded with the phonocardiograms taken in the
supine position. Apexcardiograms were recorded with the
subject in the semi-left lateral decubitus position. Echocar-
diograms were performed using a Smith Kline Ekoline 20A
ultrasonoscope and 2.25 MHz transducer of 0.5 inch diameter
with beam collimation to 5 cm depth. The echocardiograms
were recorded at a speed of 50 or 100 mm/sec using an Elec-
tronics for Medicine DR8, Irex Continutrace 101 or Honeywell No. 1856 recorder. All subjects were studied in
the left lateral decubitus position (approximately 30°) with
the head and right shoulder elevated by a foam rubber
wedge. The transducer was positioned close to the left sternal
border in the second, third, fourth, and fifth intercostal
spaces (ICS) sequentially. In each ICS an attempt was made
to record both mitral leaflets with the beam also en-
countering the left atrium. The angulation of the transducer
on the chest was noted. Slow M-mode sector scans were
made by rocking the transducer to encompass the area from
the posterolateral left atrium across the mitral annulus to
the posterior left ventricle. The transducer was then directed
cephalad and medial to record the dimensions of the aortic
root and left atrium. All subjects initially suspected of hav-
ing mitral valve prolapse on any basis were asked to perform
two additional studies: a submaximal treadmill exercise test,
using the Bruce protocol,14 stopped when a heart rate of 180
beats/min was reached, or when the subject complained of
marked symptoms; and Holter electrocardiographic
monitoring for ten hours.

Echocardiographic Measurements

Left ventricular dimensions were taken from the standard
position previously reported from this laboratory.16 Atrial
and aortic dimensions were measured using standard
criteria.13 Left ventricular end-diastolic volume was deter-
mined by cubing the end-diastolic dimension. The C point
was defined as the point where the anterior and posterior
mitral leaflets apparently come together at end-diastole. A
single systolic echo could usually be identified after the C
point. This was considered to represent the echo common to
both mitral leaflets during systole. The systolic mitral echo
was followed until either a sharp anterior motion of the
anterior leaflet or a sharp posterior motion of the posterior
leaflet defined the D point in early diastole. When such a
sharp opening motion of either leaflet was clearly seen in
early diastole but did not intersect the systolic echo, a line
prolonging the opening motion of either leaflet was drawn
and its intersection with the common systolic echo was
declared as being the D point. When the D point could not
be defined with reasonable accuracy, the beat was not con-
sidered for quantitative analysis. In each ICS at least three
consecutive beats were chosen for analysis in which the C
and D points could be clearly defined with the beam also
recording the left atrium. A line joining the C and D point
was drawn (CD line). The vertical distance between the D
point and a horizontal line extended from the C point was
measured (CD motion) and was presumed to represent the
anterior or posterior displacement of the mitral valve
leaflets during systole relative to the transducer. When the
mitral leaflet systolic motion was not a straight line and
deviated from the drawn CD line, the maximal deviation
was measured.

Echocardiographic Patterns

A series of systolic mitral valve patterns were established
describing the variations seen in our prior experience. This
allowed correlation of patterns with transducer position and
direction, and with other nonechocardiographic findings
without prejudging the significance of the patterns.
Representative drawings of these patterns are shown in
figure 1. Only those patterns present for at least three cycles
in a single recording position were included. It was common
to see multiple patterns while recording from one transducer
position, and all patterns were then tabulated. An exception
to this practice included omission of pattern 5 in the
presence of pattern 7, since the latter seemed only an ex-
aggeration of the former. The role of the sound beam's path
relative to cardiac motion was assessed by analyzing the
recorded mitral valve pattern as a function of transducer
orientation independent of the absolute ICS used. “Caudal
position” designates small-to-large degrees of caudal
transducer angulation in the sagittal plane when recording
the mitral valve leaflet from any ICS. “Perpendicular
position” designates no transducer angulation in the sagittal
plane, or cephalad angulation when recording the mitral
valve leaflet from any ICS.

The patient records were coded, and each phonocardi-
diagram, echocardiogram and electrocardiogram was read
independently, without knowledge of the results of other
tests, by one investigator (R.L.P.).

Statistical analysis of the data was performed, using the
Statistical Package for the Social Sciences Program, on an
IBM 360 computer.
Results

Group Characteristics

One hundred and one subjects were initially accepted in the study. One volunteer had clinical and echocardiographic evidence of an early form of cardiomyopathy and was excluded from the study. Mean age was 23½ years. Twenty-nine had experienced discomfort in the chest at least once, and in six of these, the pain was considered possibly related to the heart. None had typical angina pectoris. Four subjects had sustained chest trauma; 30 had noted palpitations, and seven of these were felt to have a history compatible with extrasystoles or short runs of paroxysmal tachycardia. Nine subjects complained of dyspnea on exertion, and in two of these the symptoms were judged to be compatible with cardiac dyspnea. Fifty-three patients had fainted at least once in their lives, and in each case the event could be related to a non-cardiac cause. Ten subjects were told that they had a possible "heart problem" at some time by a physician or a nurse; most commonly a murmur had been heard during a routine examination. None of these ten subjects considered themselves to have heart disease presently. One subject gave a history of rheumatic fever but was told later that her heart had not been damaged. Fifty-one subjects had suffered from either recurrent sore throats or scarlet fever. Six had medical problems requiring regular visits to a physician, but none of their diseases were thought to affect the findings of the present study. No subject gave a history of pleural or pericardial disease. Four had been told in the past that their blood pressure was elevated; none had ever been treated with antihypertensive drugs. Thirty-one were taking contraceptive medications, while 29 had taken another medication in the week prior to the study, most commonly an analgesic or a tranquilizer. Twenty-seven subjects gave a history of heart disease in their first-degree relatives. Ninety-four of our volunteers were Caucasian.

On clinical examination, none had the classical features of the Marfan syndrome. Eleven had a chest or spine abnormality of a mild degree. None had a systolic pressure over 140 mm Hg or a diastolic pressure over 90 mm Hg. None had clear evidence of left ventricular enlargement on palpation. Murmurs were heard in 49 subjects in the supine position. None of these were judged to be late or mid-to-late systolic, and none were louder than grade II/VI. Mid-to-late systolic clicks were heard in two subjects in the supine position. These clicks persisted on standing and were present in two additional subjects in this position.

Phonocardiographic Findings

These are summarized in table 1 and illustrated in figures 2 and 3.

**Table 1. Phonocardiographic Findings in 100 Presumably Healthy Females**

<table>
<thead>
<tr>
<th></th>
<th>Supine (100 subjects)</th>
<th>Amyl nitrite (96 subjects)</th>
<th>Standing (100 subjects)</th>
<th>Supine, amyl or standing (100 subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ao PA LLSB Ap All</td>
<td>PA Ap All</td>
<td>PA Ap All</td>
<td>PA Ap All</td>
</tr>
<tr>
<td>No murmurs</td>
<td>86 77 56 58 35</td>
<td>36 31 24</td>
<td>83 83 77</td>
<td>15</td>
</tr>
<tr>
<td>Early SM</td>
<td>7 7 20 19 33</td>
<td>21 33 38</td>
<td>12 7 15</td>
<td>54</td>
</tr>
<tr>
<td>Mid SM</td>
<td>2 5 6 6 15</td>
<td>7 1 7 1 22</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Early-mid-SM</td>
<td>5 10 17 12 28</td>
<td>21 20 28</td>
<td>3 6 6</td>
<td>44</td>
</tr>
<tr>
<td>Late or mid-late SM</td>
<td>0 0 1 3 3</td>
<td>5 5 6</td>
<td>0 0 0</td>
<td>7</td>
</tr>
<tr>
<td>Pan SM</td>
<td>0 1 0 2 3</td>
<td>6 6 9</td>
<td>1 2 2</td>
<td>12</td>
</tr>
<tr>
<td>No clicks</td>
<td>98 98 98 99 86</td>
<td>96 91 87</td>
<td>99 86 86</td>
<td>78</td>
</tr>
<tr>
<td>Early SC</td>
<td>2 2 1 4 7</td>
<td>0 5 5</td>
<td>1 6 7</td>
<td>14</td>
</tr>
<tr>
<td>Mid, late or multiple SC</td>
<td>0 0 1 7 7</td>
<td>0 4 4</td>
<td>0 8 8</td>
<td>14</td>
</tr>
<tr>
<td>PHONO-MSCLSM</td>
<td>0 0 2 8 8</td>
<td>5 7 8</td>
<td>0 8 8</td>
<td>17</td>
</tr>
</tbody>
</table>

Abbreviations: Ao = aortic area; PA = pulmonary area; LLSB = lower left sternal border area; Ap = apical area; All = either aortic, pulmonary, lower left sternal border or apical areas; SM = systolic murmur; SC = systolic click; PHONO-MSCLSM = mid-late systolic click and/or murmur.
Supine Position. An apical murmur was recorded in 42 subjects in the supine position. A pansystolic murmur was recorded in two subjects at the apex and in one subject at the pulmonary area. Late or mid-to-late systolic murmurs were recorded in only three subjects at the apex, in the supine position, and in one of these the murmur was also recorded at the LLSB. Mid- to late systolic clicks were recorded in seven subjects at the apex.

Amyl Nitrite. After inhalation of amyl nitrite murmurs were recorded at the apex in 65 subjects. Six subjects had a pansystolic and five had mid-to-late systolic murmurs. Apical clicks were recorded in nine subjects after amyl nitrite and four of these clicks were mid- or late systolic.

Upright. In the upright position, murmurs were recorded at the apex in 17 subjects. Two of the apical murmurs were pansystolic, none were mid-to-late or late systolic. Eight subjects had mid-to-late or multiple clicks recorded at the apex. Third heart sounds were recorded at rest or after inhalation of amyl nitrite in the supine position in 45 subjects and fourth heart sounds were recorded in four. A total of 17 subjects had at least one of the following phonocardiographic features judged to be most compatible with a mitral valve abnormality: mid- or late systolic click; multiple clicks; mid-to-late or late systolic murmur, recorded in the supine position, upright position, or after inhalation of amyl nitrite. These 17 will be referred to as subjects with PHONO-MSCLSM and represent the phonocardiographic (P) findings of group EP and group EorP. Only eight of these 17 subjects with PHONO-MSCLSM would have been detected by a phonocardiographic examination performed in the resting supine position. The subjects with a pansystolic murmur alone were tabulated separately. A grade II/VI short early diastolic murmur was heard in one subject, no other diastolic murmurs were heard or recorded.

A carotid pulse tracing of adequate quality was recorded in 98 subjects and had a normal shape in all. An adequate apexcardiogram was recorded in 72 subjects, ten showed a sustained systolic impulse and three a mid-systolic retraction. Fifty-nine apexcardiograms were considered entirely normal.

Electrocardiogram

A resting electrocardiogram was available in all subjects. Sinus rhythm was present in all. A single ventricular premature beat (VPB) was seen in one record, marked sinus bradycardia (45 beats/min) in another. P wave abnormalities were present in four subjects. One subject had a short (0.10 sec) P-R interval and another had a prolonged P-R interval (0.24 sec). An incomplete right bundle branch block pattern was present in two subjects. Junctional ST-segment changes were seen in 35 subjects while nonjunctioal ST-segment changes were recorded in ten subjects: none had an ST-segment depression of more than 0.5 mm. T waves were flattened or negative in lead II or aVF in seven subjects and in the left precordial leads in one subject.

Echocardiographic Measurements

These are listed in table 2. Right ventricular dimensions over 22 mm were seen in four subjects. One had a left ventricular dimension at end-diastole larger than 53 mm, and another had a left atrium dimension over 40 mm. None had aortic dimension larger than 38 mm, septal thickness over 13 mm or a posterior left ventricular wall thicker than 12 mm. One subject had a left ventricular posterior wall/interventricular septum thickness ratio over 1.3. Thus, most echocardiographic values fell within the previously established normal range.

Echocardiographic Pattern According to Transducer Angulation on the Chest. Studies adequate to define the
systolic mitral echo were available in 79 subjects in causal position and in 99 subjects in perpendicular position. A curvilinear systolic motion of the mitral echo posterior to the drawn CD line was commonly seen in causal position, but more rarely in perpendicular position. Conversely, a systolic motion anterior to the CD line by more than 2 mm (pattern 3) was not seen in causal position, but frequently recorded in perpendicular position. Generally speaking, at a time when both mitral leaflets were seen, with the beam recording the left atrium, the transducer was pointing markedly caudal in the second ICS, causal or perpendicular to the chest in the third ICS, perpendicular to the chest or pointing cephalad in the fourth ICS, and markedly cephalad in the fifth ICS. Examination was easier in the third or fourth ICS.

**Echo-Phonocardiographic Correlations**

With the transducer in causal position, no echocardiographic pattern was significantly correlated with PHONO-MSCLSM.* In perpendicular position, patterns 1, 2, 3, 4, 5 and 6 (fig. 1) were not statistically related to the presence of PHONO-MSCLSM. Twenty-one subjects had either pattern 7 or 8 in perpendicular position. This group will be referred to as ECHO-7, 8, for comparison with the other findings (table 3, figs. 4, 5) and will represent the echocardiographic (E) features of groups EP and EoP. Ten of the ECHO-7, 8 group (48%) also had PHONO-MSCLSM and are termed group EP. These ten subjects represent 59% of the total findings of PHONO-MSCLSM (P < 0.001).

Many patterns were frequently associated in the same subject (fig. 6). Pattern 8 (alone or associated with other patterns) was seen in eight subjects, six of whom also had PHONO-MSCLSM (75%), while another had a pansystolic murmur. Conversely, the six subjects with pattern 8 represent 35% of the 17 subjects with PHONO-MSCLSM (P < 0.001). Eight of the 18 subjects with pattern 7 (alone or associated with other patterns) in perpendicular position also had PHONO-MSCLSM (44%), while another four of these 18 subjects had apical pansystolic murmurs (22%). Pattern 7 was seen in 47% of the 17 subjects with PHONO-MSCLSM (P < 0.001). Pattern 9 (fig. 1) was recorded in five subjects, three of whom also had PHONO-MSCLSM (P < 0.05). Patterns 10 and 11 (fig. 1) were seen in only three subjects each, two of whom also had PHONO-MSCLSM.

**Table 2. Echocardiographic Measurements in 100 Presumably Healthy Females**

<table>
<thead>
<tr>
<th></th>
<th>Mean ± sd (mm)</th>
<th>Range (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricle (ED)</td>
<td>16.4 ± 3.9</td>
<td>9-29</td>
</tr>
<tr>
<td>Left ventricle (ED)</td>
<td>44.8 ± 4.5</td>
<td>33-58</td>
</tr>
<tr>
<td>Left ventricle (ES)</td>
<td>28.5 ± 4.5</td>
<td>20-48</td>
</tr>
<tr>
<td>Left atrium (ES)</td>
<td>30.5 ± 3.6</td>
<td>22-43</td>
</tr>
<tr>
<td>Aorta (ED)</td>
<td>26.0 ± 3.0</td>
<td>20-34</td>
</tr>
<tr>
<td>IVS (ED)</td>
<td>8.5 ± 1.3</td>
<td>6-12</td>
</tr>
<tr>
<td>LV PW (ED)</td>
<td>8.2 ± 1.3</td>
<td>6-12</td>
</tr>
<tr>
<td>IVS/LV PW</td>
<td>1.1 ± 0.1</td>
<td>0.8-1.4</td>
</tr>
</tbody>
</table>

Abbreviations: ED = end diastole; ES = end systole; IVS = interventricular septum; LVPW = left ventricular posterior wall.

**Table 3. Correlation Between Phonocardiographic Findings and Echocardiographic Data Obtained with the Transducer in Perpendicular Position**

<table>
<thead>
<tr>
<th>Echo pattern*</th>
<th>Present (N)</th>
<th>PHONO-MSCLSM (%)</th>
<th>Absent (N)</th>
<th>PHONO-MSCLSM (%)</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>83</td>
<td>15.7</td>
<td>17</td>
<td>29.5</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>11.9</td>
<td>58</td>
<td>20.7</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>6.5</td>
<td>69</td>
<td>21.7</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>30.0</td>
<td>80</td>
<td>13.7</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>20.0</td>
<td>90</td>
<td>16.6</td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>35.3</td>
<td>83</td>
<td>134</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>44.4†</td>
<td>82</td>
<td>11.0</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>72.6$\dagger$</td>
<td>92</td>
<td>12.0</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>60.0†</td>
<td>95</td>
<td>14.7</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>66.7</td>
<td>97</td>
<td>15.5</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>66.7</td>
<td>97</td>
<td>15.5</td>
</tr>
<tr>
<td>ECHO 7,8</td>
<td>21</td>
<td>47.6$\dagger$</td>
<td>79</td>
<td>8.9</td>
</tr>
</tbody>
</table>

Abbreviations: Perpendicular position = transducer orientation cephalad or perpendicular to the chest in the sagittal plane; ECHO-7,8 = echocardiographic pattern 7 and/or pattern 8; MSCLSM = mid-late systolic click and/or murmur; N = number of subjects with (present) or without (absent) a given echocardiographic pattern; % = percentage of PHONO-MSCLSM recorded in those subjects with or without each echocardiographic pattern.

MSCLSM. No statistically significant relation could be demonstrated between either of these latter two patterns and PHONO-MSCLSM, owing to the small number of subjects. An early systolic click was recorded in 13 subjects at either the pulmonary area, LLSB, or apex. Six of these 13 subjects also had PHONO-MSCLSM (P < 0.01); however, in the absence of PHONO-MSCLSM, an early systolic click was not significantly related to ECHO-7, 8. A statistically significant relation was found between the presence of an apical systolic murmur, at rest or after amyl nitrite inhalation, and ECHO-7, 8. All four subjects with mid- or late systolic clicks on auscultation had ECHO-7, 8. All five subjects with mid-to-late, late, or pansystolic murmurs recorded at the apical area in the resting supine position had ECHO-7, 8.

**Clinical, Electrocardiographic, and Echocardiographic Correlations**

These are presented in table 4. Subjects belonging to group EP presented more frequently with some characteristics said to be common in the mitral valve prolapse syndrome such as palpitations, chest abnormality and an asthenic build when compared to group noEP subjects. None of these differences reached statistical significance. The difference between group noEP and the other groups regarding the incidence of past history of heart disease, history of familial heart disease, chest discomfort, third or fourth heart sounds, abnormal systolic pattern on the apexcardiogram or ST-T wave abnormalities on the resting electrocardiogram was not statistically significant. Both subjects with abnormal P-R interval belonged to group EP as did the only subject with a VPB on the resting electrocardiogram. Group EP subjects compared with group noEP subjects had statistically wider aortas and thinner left ventricular posterior walls. When compared to group noEP, subjects belonging to group EoP had some characteristics resem-
blowing those seen in group EP such as smaller chest AP diameter ($P < 0.01$), smaller end-diastolic dimension ($P < 0.05$), thinner interventricular septum and thinner left ventricular posterior wall ($P < 0.01$).

**Treadmill and Holter Tests**

Results are presented in table 5. Treadmill exercise tests were done in all ten group EP subjects and in the 13 group EorP subjects consenting to perform the test. Seven of the remaining 72 noEP subjects also performed a treadmill test. These seven subjects had pattern 5, 7, or 8 on their echocardiogram with the transducer in caudal position and were suspected of having mitral valve prolapse early in the study. A total of 31 ambulatory electrocardiographic monitoring tests were also performed. The number of treadmill tests and Holter electrocardiographic recordings performed is too small for statistical comparison among the three groups, but a few findings should be noted: two asymptomatic group EP subjects had frequent VPBs detected during the monitored ten-hour period (more than ten VPBs per any 15 minute interval) one of whom had long runs of bigeminy. Rare VPBs (less than ten per any 15 minute interval) were seen in two group EP and two group noEP subjects. Atrial arrhythmias were not found. Sinus arrhythmia of an unusual degree was seen in two group EP subjects. Treadmill test duration and maximal heart rate achieved were very similar in each group. One group EP subject complained of sharp chest pain during the treadmill test, another group EP subject had frequent VPBs during the recovery period and such beats were also recorded during ambulatory Holter monitoring.

**Discussion**

The results of this study do not allow us to define the echocardiographic or phonocardiographic criteria of anatomic mitral valve prolapse. Unfortunately there is no pre-mortem "gold standard" for this diagnosis. This study exercised a "double standard" in the logic of data analysis. First the incidence of each echocardiographic mitral valve pattern was tabulated in subjects with and without phonocardiographic features previously associated with the mitral valve prolapse syndrome in order to place each echocardiographic pattern in rank order of significance suggesting an abnormality. Second, subjects with both phonocardiographic and echocardiographic patterns suggesting mitral valve prolapse were then presumed to have this diagnosis in order to establish the prevalence of these markers and to correlate them with the clinical findings.

The present study demonstrated a 17% incidence of mid-to-late systolic clicks or murmurs in a population of presumably healthy young females. We are not aware of a report of such a high incidence of this finding and were quite
gallop” disclosed by phonocardiogram but the abnormal sound was noticed through auscultation in only eight of these cases.\textsuperscript{20} Many authors now believe that most nonejection clicks and mid-to-late or late systolic murmurs originate from the mitral valve apparatus in the absence of demonstrable pleuro-pericardial disease. Whether nonejection clicks or late systolic murmurs can occur transiently in subjects with no demonstrable abnormalities in the mitral valve apparatus in the presence of abrupt changes in left ventricular volume or contractility such as occur with inhalation of amyl nitrite or assumption of the upright position has not been determined. This may partially account for the frequency of these findings here. Such auscultatory findings have been reported in patients suffering from a variety of heart conditions.\textsuperscript{7, 8} Pathologic examination of the heart and of the heart valves usually has been performed in those patients dying suddenly or presenting with mitral regurgitation of sufficient severity to require surgery. Huge valve cusps, thin and elongated chordae tendineae, with diffuse myxomatous tissue throughout both anterior and posterior cusps are usually described.\textsuperscript{21–24} The aortic valve and the aorta are commonly involved,\textsuperscript{21} and it has been suggested that the syndrome of late-systolic click or murmur and the “floppy valve” syndrome\textsuperscript{25} represent points on a spectrum of mitral valve deformity due to connective tissue disease, possibly related to the Marfan syndrome.\textsuperscript{21} Ballooning or “floppy” deformity of the mitral valve has been reported in 1–5% of routine autopsies,\textsuperscript{26, 27} but the incidence of less marked changes in the leaflets and chordae is not known. In specific age groups the pathologic examination shows up to 8% incidence of these findings.\textsuperscript{22}

Two echocardiographic patterns have been described in patients with proven mitral valve prolapse: a late systolic posterior motion of the closed mitral valve (pattern 8), and a smooth posterior motion of the mitral leaflet echoes toward the left atrium from the start of systole (pattern 7), other patterns have also been described more recently.\textsuperscript{19} The posterior motion of the closed mitral leaflets echoes presumably was due to prolapse of the mitral leaflets towards the left atrium. The motion of the mitral valve has been studied carefully in the intact dog: at no time after ventricular systole begins do the edges of the valve cusps move toward the atrium.\textsuperscript{27} In the isolated or exposed heart, the valve cusps tend to bulge upward toward the atrium but this is attributed to the shrinkage in ventricular volume which follows thoracotomy. Since the atrioventricular valves and chordae tendineae are fibrous structures, they do not participate in this shrinkage of the heart.\textsuperscript{27} In the human heart, mitral valve prolapse could be facilitated by a small end-diastolic volume,\textsuperscript{28, 29} and it is of interest that subjects belonging to group EP and group EorP taken together had smaller left ventricular end-diastolic dimensions and volumes when compared to group noEP.

Our study has shown the importance of transducer position in recording and interpreting the echocardiographic study: a smooth posterior motion concave anteriorly (patterns 5 or 7) is commonly seen with the transducer located high on the chest and pointing caudal. In such a position, the absolute \textit{CD} motion was usually small or even negative and a smooth anterior motion, convex anteriorly (pattern 3) was not seen. Conversely, with the transducer located lower on the chest (fourth or fifth ICS), pattern 5 or
7 was rarely recorded while pattern 3 was very common. Pattern 7 or 8 may be recorded in the second or third ICS while patterns 1 or 3 are seen in the fourth or fifth ICS in the same patient (fig. 6). This phenomenon appears to be related to the path of the sound beam and of the mitral valve apparatus during systole. The base of the heart, including the annulus fibrosus, moves downward and anteriorly toward the apex during systole.27,30,31,32 and the closed mitral leaflets follow the motion of the annulus. When the ultrasonic beam is coming from high on the chest (caudal angulation), the mitral ring and leaflets may move perpendicular to the sound beam or even away from the transducer, as the apex to base dimension decreases, so the echocardiogram will register no motion or motion away from the transducer. The normal mitral systolic echo may then produce a "hammock" shaped posterior motion previously associated with mitral valve prolapse. Conversely, when the ultrasonic beam is coming from low on the chest (cephalad angulation), the motion of the mitral ring and leaflets toward the transducer during systole will be registered by the sound beam as a positive or accentuated anterior motion on the echocardiogram. Our results suggest recording both mitral leaflets and left atrium with the transducer either perpendicular or pointing slightly upward is the optimal way to analyze for mitral valve prolapse by echocardiography. The third ICS appears to be the location of choice in most patients provided that an adequate study can be obtained with the transducer in perpendicular position. Mitral valve prolapse will rarely be diagnosed when the transducer is pointing markedly cephalad.

### Table 4. Correlation of Echophonocardiographic Findings with Personal History and with Selected Clinical, Echocardiographic and Electrocardiographic Findings

<table>
<thead>
<tr>
<th>Personal history (%)</th>
<th>Group EP (10 subjects)</th>
<th>Group EorP (18 subjects)</th>
<th>Group noEP (72 subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest discomfort</td>
<td>0</td>
<td>5.6</td>
<td>6.9</td>
</tr>
<tr>
<td>Palpitation</td>
<td>20</td>
<td>5.6</td>
<td>5.6</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>0</td>
<td>0</td>
<td>2.8</td>
</tr>
<tr>
<td>Fainting</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&quot;Heart problem&quot;</td>
<td>0</td>
<td>22.2</td>
<td>8.3</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>0</td>
<td>5.6</td>
<td>0</td>
</tr>
<tr>
<td>Frequent sore throat</td>
<td>40.0</td>
<td>44.4</td>
<td>54.2</td>
</tr>
<tr>
<td>Scarlet fever</td>
<td>10.0</td>
<td>0</td>
<td>6.9</td>
</tr>
<tr>
<td>Recent medical</td>
<td>10.0</td>
<td>0</td>
<td>4.2</td>
</tr>
<tr>
<td>Family trauma</td>
<td>0</td>
<td>11.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Family heart disease</td>
<td>30.0</td>
<td>22.2</td>
<td>27.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Findings (%)</th>
<th>Group EP (10 subjects)</th>
<th>Group EorP (18 subjects)</th>
<th>Group noEP (72 subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest abnormality</td>
<td>20</td>
<td>16.7</td>
<td>8.3</td>
</tr>
<tr>
<td>Third heart sound</td>
<td>50</td>
<td>61.1</td>
<td>40.3</td>
</tr>
<tr>
<td>Fourth heart sound</td>
<td>10</td>
<td>0</td>
<td>4.2</td>
</tr>
<tr>
<td>Sustained systolic ACG</td>
<td>28.6</td>
<td>7.1</td>
<td>13.7</td>
</tr>
<tr>
<td>Retracted systolic ACG</td>
<td>14.3</td>
<td>0</td>
<td>3.9</td>
</tr>
<tr>
<td>P wave changes</td>
<td>0</td>
<td>5.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Abnormal P-R interval</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IRBBB pattern</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Junctional/ST-segment changes</td>
<td>20</td>
<td>27.8</td>
<td>38.9</td>
</tr>
<tr>
<td>Nonjunctional ST-segment changes</td>
<td>10</td>
<td>22.2</td>
<td>6.9</td>
</tr>
<tr>
<td>T wave changes (lead II or aVF)</td>
<td>10</td>
<td>5.6</td>
<td>6.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical measurements (Mean ± SD)</th>
<th>Group EP (10 subjects)</th>
<th>Group EorP (18 subjects)</th>
<th>Group noEP (72 subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>168.8 ± 6.4</td>
<td>163.8 ± 5.0</td>
<td>165.7 ± 6.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>54.9 ± 5.8</td>
<td>56.1 ± 7.9</td>
<td>58.7 ± 8.6</td>
</tr>
<tr>
<td>Chest AP diameter (cm)</td>
<td>17.6 ± 1.0</td>
<td>17.4 ± 0.9†</td>
<td>18.2 ± 1.5</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>116.1 ± 8.9</td>
<td>117.9 ± 11.6</td>
<td>117.3 ± 9.2</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>75.2 ± 8.2</td>
<td>76.7 ± 8.6</td>
<td>77.4 ± 7.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Echocardiographic measurements (Mean ± SD)</th>
<th>Group EP (10 subjects)</th>
<th>Group EorP (18 subjects)</th>
<th>Group noEP (72 subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricle (ED, mm)</td>
<td>16.4 ± 4.2</td>
<td>16.4 ± 3.0</td>
<td>16.4 ± 4.1</td>
</tr>
<tr>
<td>Left ventricle (ED, mm)</td>
<td>44.4 ± 3.4</td>
<td>42.6 ± 3.9*</td>
<td>45.4 ± 4.6</td>
</tr>
<tr>
<td>Left ventricle (ES, mm)</td>
<td>26.8 ± 3.2</td>
<td>28.4 ± 4.0</td>
<td>28.7 ± 4.8</td>
</tr>
<tr>
<td>Left ventricle (EDV, cm³)</td>
<td>88.9 ± 20.6</td>
<td>78.9 ± 20.1†</td>
<td>96.5 ± 30.4</td>
</tr>
<tr>
<td>Left atrium (ES, mm)</td>
<td>29.5 ± 4.3</td>
<td>29.6 ± 3.4</td>
<td>30.9 ± 3.6</td>
</tr>
<tr>
<td>Aorta (ED, mm)</td>
<td>27.6 ± 2.4*</td>
<td>26.6 ± 3.4</td>
<td>25.6 ± 2.9</td>
</tr>
<tr>
<td>IVS (ED, mm)</td>
<td>7.9 ± 1.1 (P = 0.05)</td>
<td>8.0 ± 1.1*</td>
<td>8.8 ± 1.3</td>
</tr>
<tr>
<td>LV PW (ED, mm)</td>
<td>7.2 ± 0.6†</td>
<td>7.8 ± 1.1*</td>
<td>8.5 ± 1.3</td>
</tr>
<tr>
<td>IVS/LV PW</td>
<td>1.04 ± 0.16</td>
<td>1.10 ± 0.12</td>
<td>1.07 ± 0.11</td>
</tr>
<tr>
<td>R-R interval (msec)</td>
<td>876.0 ± 186.1</td>
<td>893.2 ± 163.9</td>
<td>819.7 ± 140.1</td>
</tr>
<tr>
<td>Systole length (CD interval, msec)</td>
<td>374.0 ± 47.2</td>
<td>341.1 ± 54.7</td>
<td>346.7 ± 45.3</td>
</tr>
</tbody>
</table>

Statistical analysis tests the significance of differences between findings in Groups EP and EorP, versus Group noEP.

- *P < 0.05.
- †P < 0.01.
- ‡P < 0.001.

Abbreviations: ACG = apex cardiogram; IRBBB = incomplete right bundle branch block pattern; Chest AP diameter = distance between mid-sternum and spine; BP = blood pressure; EDV = end-diastolic volume; IVS = interventricular septum; others as in table 2.
TABLE 5. Correlation of Echophonocardiographic Findings with Treadmill Exercise Test and Ambulatory Electrocardiographic Monitoring

<table>
<thead>
<tr>
<th></th>
<th>Group EP (10 subjects)</th>
<th>Group EorP (18 subjects)</th>
<th>Group noEP (72 subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treadmill Exercise Test</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number performed</td>
<td>10</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>VPB (%)</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chest pain (%)</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean test duration (sec)</td>
<td>639</td>
<td>624</td>
<td>643</td>
</tr>
<tr>
<td>Mean HR reached (beats/min)</td>
<td>181</td>
<td>184</td>
<td>182</td>
</tr>
<tr>
<td><strong>Ambulatory Electrocardiographic Monitoring</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number performed</td>
<td>10</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Rare VPB (%)</td>
<td>20</td>
<td>0</td>
<td>28.6</td>
</tr>
<tr>
<td>Frequent VPB (%)</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atrial arrhythmias (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Marked sinus arrhythmia (%)</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: VPB = ventricular premature beat; Rare VPB = less than 10 VPB per any 15 minutes; Frequent VPB = more than 10 VPB per any 15 minutes; HR = heart rate.

In the absence of angiographic and pathologic evidence of mitral valve prolapse no absolute conclusion can be drawn from the presence of these findings, but the specificity and sensitivity of various echocardiographic patterns previously described in patients with proven mitral valve prolapse may be inferred from their association with the phonocardiographic findings. Patterns 7, 8, and 9 were significantly correlated with the presence of PHONO-MSCLSM in perpendicular position. Pattern 8 gave the best correlation and only one of the eight subjects with this pattern was devoid of phonocardiographic findings. Pattern 7 was also significantly correlated with PHONO-MSCLSM, but this pattern was recorded in ten subjects without the PHONO-MSCLSM findings. Four of these ten pattern 7 subjects had a pansystolic murmur however. Patterns 9, 10, and 11 were rarely seen in the absence of either patterns 7 or 8, and we believe that series including larger numbers of subjects will be required before the implication of patterns 9, 10, and 11 can be established in relation to mitral valve prolapse. An early sharp posterior motion, lasting from 20–80 msec after the C point (pattern 2) was commonly seen and appears to be a normal finding. Pattern 3 is also a normal finding and will be seen frequently with the transducer pointing cephalad. Single or multiple echoes, posterior to the main straight systolic echo (pattern 4), are probably a nonspecific finding. These echoes may be as thick as the true systolic echo and may at times mimic the late or pansystolic type of prolapse. Care must be taken in identifying the C point when this phenomenon is recognized. This study also indicates patterns 5 or 6 alone are not good evidence for mitral valve prolapse.

Our findings suggest that isolated apical pansystolic murmurs recorded supine, either at rest or after inhalation of amyl nitrite in the absence of evidence of previous rheumatic fever may be related to mitral valve prolapse. Early systolic clicks have been described in patients with angiocardiographic evidence of mitral valve prolapse; our results indicate this finding should not be regarded as suggestive of mitral valve prolapse in the absence of other supportive evidence.

The ten subjects which we designate group EP have the most evidence for abnormality of the mitral valve. The significance of an isolated echocardiographic or phonocardiographic finding suggesting mitral valve prolapse seen in 18% of the subjects is less clear for this diagnosis. Group EP subjects have statistically significantly larger aortas and thinner left ventricular posterior walls compared with group noEP subjects. Whether these findings are related to the disease of the aortic wall frequently seen in patients with the "floppy valve" syndrome and also to the abnormality of the left ventricular contraction described in this entity is a possibility which will require further investigation.

Ventricular arrhythmias are said to be common in patients with mitral valve prolapse. However, most published series have included large numbers of patients who came to medical attention because of multiple symptoms. Our data show that frequent VPBs are seen in 20% of subjects with presumptive evidence of mitral valve prolapse. The finding of such a high percentage of subjects with either phono or echocardiographic evidence of mitral valve abnormalities was unexpected and raises the question of patient selection in our group of presumably healthy volunteers. This group clearly is not a random population sample. Subjects with complaints related to the chest may have responded to our advertisement. However none of the subjects with a history of chest discomfort, shortness of breath, or with a past history of heart problems fell into our group EP. Nevertheless group EP included a higher percentage of subjects complaining of palpitations, and group EorP included four subjects with a past history of "heart problems."

Echocardiographic and phonocardiographic findings suggesting mitral valve prolapse are more commonly found in a population of presumably healthy young females than previously recognized. This raises the following points:

1) These findings could be at one end of the spectrum of normality for this age and sex group. The absolute percentage of "abnormalities" recorded is consistent with this hypothesis. Similarly complaints of palpitation (without documented arrhythmia), chest discomfort, shortness of breath on exertion, or fainting were rather common in all 100 subjects without regard to findings suggesting a valvular abnormality.

2) The techniques and criteria of abnormality used could lack sensitivity and specificity. However, correlation of angiographic and pathologic findings both with strict echocardiographic (ECHO-7, 8) and phonocardiographic (MSCLSM) criteria has been shown in other investigations. These findings make it unlikely that criteria of abnormality were imprecise.

3) The preceding points lead us to speculate that echocardiography and phonocardiography may identify a large segment of the normal population susceptible to valvular abnormality, and that the patients presenting with significant levels of signs and symptoms we associate as the mitral valve prolapse syndrome are a small subset of this large population segment.

Further studies combining invasive techniques and longitudinal studies of apparently healthy identified subjects may clarify these possibilities.
MITRAL VALVE PROLAPSE IN HEALTHY FEMALES/Markiewicz et al.

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Mitral valve prolapse in one hundred presumably healthy young females.
W Markiewicz, J Stoner, E London, S A Hunt and R L Popp

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