Echocardiographic Detection of Mitral Valve Prolapse
Exclusion of False Positive Diagnosis and Determination of Inheritance

By Alan N. Weiss, M.D., James W. Mimbs, M.D., Philip A. Ludbrook, M.D., and Burton E. Sobel, M.D.

SUMMARY
An important potential source of error in the echocardiographic diagnosis of mitral valve prolapse has been identified — namely a systolic hammock-like pattern of the anterior and/or posterior mitral leaflet echoes, similar to that associated with true mitral valve prolapse, produced artfactually when the ultrasonic transducer is angulated inferiorly.

Utilizing a modified, more specific technique we characterized the mode of inheritance and familial prevalence of this disorder. Among 74 subjects, composed of 57 first-degree relatives and 17 probands with mitral valve prolapse, mitral valve prolapse was detected in 27 of 57 (47%) of the first-degree relatives. Fifty-three percent of female and 36% of male progeny of probands were affected. Furthermore, familial transmission occurred from proband to both sexes. Results of this study indicate that mitral valve prolapse is transmitted in an autosomal dominant mode with reduced male expressivity and a familial prevalence of 47% and that appropriate echocardiographic techniques must be employed to avoid a high incidence of false positive diagnosis.

WIDESPREAD UTILIZATION of single-plane echocardiography has demonstrated a high incidence of mitral valve prolapse in the general population. Clinical studies have suggested that familial transmission of this disorder occurs frequently.1-3

Echocardiography has proven to be a useful, sensitive method for detecting mitral valve prolapse.4-7 Popp et al. have recently emphasized important aspects of echocardiographic technique including consistent placement, direction, and localization of the ultrasound beam through the interventricular septum, posterior mitral valve leaflet near the annulus, and posterior left ventricular wall to achieve vertical transmission of the ultrasound beam through the plane of the mitral valve.6 The possible production of and need for recognition of ultrasound “reverberations” with multiple systolic echoes from single structures has also been emphasized.6 However, the possibility that current echocardiographic criteria of mitral leaflet prolapse may result in false positive diagnosis has been raised.8

Obviously, accurate characterization of the familial prevalence of mitral valve prolapse depends on sufficiently specific as well as sensitive diagnostic criteria. Accordingly, the present study was designed to identify and exclude potential technical causes of false positive echocardiographic diagnosis of mitral valve prolapse and to employ a more specific modified technique to define the mode of inheritance of this condition.

Methods

During preliminary studies we observed that transcription of the mitral valve by a nonvertical ultrasound beam resulted in production of several conventionally accepted echocardiographic criteria of mitral valve prolapse in normal subjects. This phenomenon occurred whenever transducer placement led to excessive inferior angulation. Because of these preliminary observations we studied ten patients without suspected mitral valve prolapse who had undergone biplane left ventriculography performed during diagnostic cardiac catheterization for other conditions. In addition, we evaluated 30 apparently normal individuals under 30 years of age. All subjects were examined echocardiographically to determine whether the recording of mitral valve prolapse could be produced by nonvertical, inferior inclination of the ultrasound beam. On the basis of these studies, a modified technique was developed to improve the specificity of echocardiographic detection of mitral valve prolapse and to avoid false positive diagnosis in subjects without cine-
angiographic or other manifestations of prolapse. These criteria were then utilized in a study of 57 first-degree relatives of 17 individuals with unequivocal mitral valve prolapse to define the familial prevalence of the disorder.

Selection of Propositi

The propositi were 17 subjects (nine females and eight males, aged 14 to 56 years) with characteristic clinical manifestations of mitral valve prolapse, namely, a typical mid-systolic click and late systolic murmur. The propositi were selected from a population of patients referred for echocardiographic evaluation of mitral valve prolapse. In each of three patients over age 45 studied invasively, cineangiographic confirmation of mitral valve prolapse was obtained. Patients with evidence of atherosclerotic, rheumatic, or other valvular disorders, valvular prostheses, congenital heart disease, pericardial disease or myocardial disease, or permanent pacemakers were excluded as propositi in this study.

First-degree Relatives Studied

Fifty-seven first-degree relatives of the propositi, in whom mitral valve prolapse had been diagnosed on the basis of characteristic clinical manifestations and typical mid-systolic buckling pattern in the echocardiogram, were studied to determine the familial prevalence of the syndrome. In each case, clinical, electrocardiographic, and radiographic evaluation was performed by an independent observer who did not participate in the echocardiographic assessment of the subject.

Echocardiograms were obtained with a Picker Echoview 10 utilizing a 0.5 inch diameter 2.25 or 3.5 MHz transducer focused at 7.5 cm with a repetition rate of 1000 per second and recorded on a Honeywell Strip Chart Recorder. Initial echocardiograms were obtained using previously described echocardiographic techniques. 

Recordings were made at the left sternal edge, using the “standard interspace” (most frequently the fourth), defined using the mitral valve as the landmark, with particular attention to transducer orientation. Employing this technique optimal valve excursion was recorded, with slight medial, and no superior or inferior angulation of the transducer. Strictly vertical placement of the transducer was consistently maintained throughout all studies, thus avoiding the possibility of false positive diagnosis of prolapse observed in our laboratory when the transducer is angulated inferiorly. In addition, the possibility of false negative diagnosis of prolapse was avoided, by insuring the absence of superior angulation of the transducer.

In all cases, both anterior and posterior mitral leaflets were simultaneously visualized during the procedure, clearly distinguishing both leaflet echoes from artifactual ultrasonic reverberations, and from other cardiac structures. However, optimal recording of leaflet prolapse, while maintaining strict vertical transducer placement in the “standard interspace,” did not always include both leaflets. Diagnostic echocardiographic criteria of mitral valve prolapse included mid-systolic buckling and pansystolic hammock-like posterior motion of the valve leaflets. The hammock-like pattern criterion was considered to be met only when motion of the mitral valve leaflets posterior to the C point throughout systole was observed with associated increased mitral valve excursion and multiple leaflet echoes. While an early systolic “step” was not accepted as a criterion of prolapse, a late systolic step was considered confirmatory diagnostic evidence. This pattern, which could not be produced artifactually, was observed in the majority of propositi in whom prolapse was considered to be present. In the three patients studied by biplane ventriculography, distinct posterior billowing of the posterior and/or anterior mitral leaflet was demonstrated.

Results

Subjects without Mitral Valve Prolapse

Table 1 shows results from normal subjects in whom the echocardiographic pattern of mitral valve prolapse could be produced artifactually. When inferior angulation of the transducer was employed, echocardiographic criteria suggesting mitral valve prolapse were obtained in 83% of 30 normal subjects. In addition, false positive echocardiograms indicative of mitral valve prolapse were obtained in 50% of ten patients undergoing diagnostic cardiac catheterization for other conditions, all of whom had no evidence of mitral valve prolapse on biplane left ventriculography.

Relatives of Propositi with Mitral Valve Prolapse

Nonvertical Technique

Using nonvertical transducer orientation, particularly when the second or third interspaces were

<table>
<thead>
<tr>
<th>Table 1</th>
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Summary of Echocardiographic Findings

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients</th>
<th>Patients with positive echocardiograms</th>
<th>Patients with negative physical examinations among those with positive echocardiograms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects without mitral valve prolapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. Normal subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Non-vertical echocardiographic technique</td>
<td>30</td>
<td>25 (83%)</td>
<td>25 (100%)</td>
</tr>
<tr>
<td>B. Modified echocardiographic technique</td>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II. Patients with negative cineangiograms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Non-vertical echocardiographic technique</td>
<td>10</td>
<td>5 (50%)</td>
<td>5 (100%)</td>
</tr>
<tr>
<td>B. Modified echocardiographic technique</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>First-degree relatives of propositi with mitral valve prolapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Non-vertical echocardiographic technique</td>
<td>57</td>
<td>37 (65%)</td>
<td>9 (24%)</td>
</tr>
<tr>
<td>B. Modified echocardiographic technique</td>
<td>57</td>
<td>27 (47%)</td>
<td>2 (7%)</td>
</tr>
</tbody>
</table>
employed, 65% of 57 first-degree relatives of propositi exhibited diagnostic echocardiographic criteria of mitral valve prolapse. When the progeny population, comprising 17 subjects aged 11 to 20 years, was evaluated in this fashion, an extraordinary incidence of 82% was detected. However, no physical findings suggestive of mitral valve prolapse were noted in five of these 17 subjects. The high frequency of positivity and notable absence of physical findings suggests the presence of a false positive population among this group. Among subjects studied, it was noted that nearly all had thin chest configurations permitting echocardiographic examination from intercostal spaces above the fourth intercostal space. These observations led to the hypothesis that inferior angulation of the transducer could produce an echographic pattern suggesting mitral valve prolapse in the absence of the disorder.

Vertical Technique

When echograms were obtained under conditions in which inferior angulation of the transducer was avoided, no positive echograms were obtained from the normal subjects (table 1). However, false positive findings could be produced by inferior angulation of the transducer. For example, figure 1 (left) shows the normal echocardiogram of the mitral valve obtained with transducer orientation perpendicular to the chest wall, in the fourth interspace. Figure 1 (right) demonstrates apparent mitral prolapse from the same normal subject when the third interspace was employed, and the transducer angulated inferiorly. Figure 2 represents similar but less marked findings obtained from a patient in whom mitral valve prolapse was excluded by biplane cineangiography.

Among first-degree relatives of patients with mitral valve prolapse, the conventional technique was associated with 65% apparent positivity despite a 24% incidence of absent physical findings. In contrast, when inferior angulation was avoided, the observed positivity among 57 first-degree relatives was 47% with only 7% of 27 subjects with absent physical findings (table 1).

Familial Transmission of Mitral Valve Prolapse

The results with the use of the vertical technique to avoid false positive diagnoses are shown in table 2. As can be seen, transmission detected by criteria with the modified technique from propositi to their progeny

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**Figure 1**

An echocardiogram obtained from a normal subject. The left panel was obtained with the transducer at the fourth intercostal space perpendicular to the chest wall. The right panel was obtained from the same subject with the transducer placed in the third intercostal space resulting in inferior angulation. As can be seen, this resulted in the production of conventional criteria of mitral prolapse. The arrow in right panel shows apparent posterior displacement of the posterior mitral valve leaflet.

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according to sex of the propositus and the offspring is consistent with an autosomal dominant mode of inheritance. The 12 propositi had 36 progeny of whom 30 were available for study. The remaining five propositi had no progeny. Results shown in table 3 indicate that: 1) transmission may occur from parents of either sex to both female and male offspring, excluding X-linked dominant transmission; and 2) increased expression appears to occur among female subjects with ten of 19 (53%) positive females compared to four of 11 (36%) positive males. Increased prevalence among female subjects appears to be reflected also by the findings that seven of nine mothers of propositi were affected.

The nature of the genetic transmission of mitral valve prolapse is evident from results obtained from evaluation of parents and siblings of the propositi (table 3). Of the nine propositi who had living parents, one parent was found to have echocardiographic evidence of mitral valve prolapse among each parental pair with only one exception, occurring in a family in which only one parent member could be studied adequately.

Discussion

Echocardiography for the diagnosis of mitral valve prolapse was described initially by Shah and Gamiak.1 Recently, several investigators have refined the echocardiographic criteria of mitral valve prolapse and identified a spectrum of patterns now considered to be diagnostic.6,7 As a result, the syndrome is being diagnosed echocardiographically with increasing frequency. However, the specificity of criteria must be questioned. For example, a recent communication reports a 12% incidence of prolapse among all patients referred to a community hospital echocardiography laboratory.8

In the present study, an important potential source of error in the echocardiographic technique for diagnosis of mitral prolapse, namely, artifactual systolic posterior bowing of the anterior and/or posterior mitral leaflets produced by inferior angulation of the ultrasonic transducer, particularly when the transducer is placed in the second or third left interspaces, has been identified. Appearance of criteria of mitral valve prolapse in normal subjects and their occurrence despite exclusion of mitral prolapse in
patients studied cineangiographically underscore the fact that false positive echocardiographic criteria must be avoided, particularly in young individuals with thin chest configurations.

Although results of previous studies have suggested that mitral valve prolapse is a familial disorder, the conclusion has been based on results of physical examination and occasionally phonocardiography.\textsuperscript{1, 3, 10} Because of the insensitivity of these techniques, it has been difficult to ascertain the true familial prevalence and mode of inheritance of the disorder.

Barlow et al. described the syndrome of mitral valve prolapse and suspected a familial occurrence.\textsuperscript{1} Shell et al. investigated four families in detail, using physical examination and phonocardiography as the basis for diagnosis. They concluded that an autosomal dominant mode of transmission was probable.\textsuperscript{3} The same conclusion was reached by Hunt and Sloman after detailed study of a single family.\textsuperscript{10}

In the present investigation, echocardiographic techniques avoiding false positive diagnosis due to inferior angulation of the transducer were employed to study 17 families. The prevalence of mitral valve prolapse among progeny was 47%. Of nine propositi with living parents, one parent of each propositus was found to have mitral valve prolapse with only one exception. Thus, mitral valve prolapse occurred in a pattern consistent with autosomal dominant inheritance.

Fifty-three percent of female compared to 36% of male progeny of propositi exhibited positive findings after study with the modified echocardiographic technique. A greater percentage of overt transmission from mothers of propositi (seven of nine) was also noted. Thus, expressivity among female subjects appears to be more complete (table 3).

Because of the significantly increased incidence of bacterial endocarditis,\textsuperscript{11, 12} mitral valve dysfunction,\textsuperscript{13, 14} serious dysrhythmia,\textsuperscript{15, 16} and sudden death\textsuperscript{17-20} in association with mitral valve prolapse, early recognition of prolapse is of considerable clinical importance. Since mitral valve prolapse appears to be inherited in an autosomal dominant mode with reduced penetrance in males, it seems appropriate to screen all first-degree relatives of patients with this disorder echocardiographically. On the other hand, to avoid false positive diagnoses, adequate precautions should be taken to prevent inferior angulation of the transducer leading to false positive results.

\textbf{Table 3}

\begin{tabular}{|l|c|c|c|c|c|}
\hline
Propositi & Subjects & Subjects with positive echocardiograms & Male & Positive echocardiograms & Female & Positive echocardiograms \\
\hline
Progeny & 30 & 14 (46\%) & 11 & 4 (30\%) & 19 & 10 (53\%) \\
Parents & 15 & 8 (53\%) & 6 & 1 (17\%) & 9 & 7 (78\%) \\
Siblings & 12 & 5 (41\%) & 5 & 1 (20\%) & 7 & 4 (57\%) \\
All first-degree relatives & 57 & 27 (47\%) & 22 & 6 (27\%) & 35 & 21 (60\%) \\
Propositi & 17 & 17 & 7 & 7 (100\%) & 10 & 10 (100\%) \\
Total & 74 & 44 (59\%) & 29 & 13 (45\%) & 45 & 31 (69\%) \\
\hline
\end{tabular}

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