Mitral Valve Prolapse*
Cross Sectional and Provocative M-Mode Echocardiography

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False-negative supine M-mode echocardiograms occur in some patients with proved mitral valve prolapse. To investigate further, we performed M-mode echocardiography (MME) during standing and after the inhalation of amyl nitrite in 17 patients (group 1) selected for auscultatory evidence of mitral valve prolapse (MVP) but negative supine MME. To validate the standing MME technique, eight patients with classic auscultatory MVP with positive supine MME for MVP (group 2) and 15 control subjects (group 3) were studied. Supine cross-sectional echocardiography (CSE) was compared to MME in all three groups. Standing MME elicited echocardiographic evidence of MVP in 14/17 (82 percent) of group 1—auscultatory evidence of MVP but negative supine MME; CSE demonstrated MVP in 8/13 (62 percent) of the same patients. There was no clear advantage of the CSE long axis view over the CSE apical four chamber view in the diagnosis of MVP in these selected subjects; however, the two views were complementary. Amyl nitrite was ineffective in eliciting echocardiographic evidence of MVP.

Mitral valve prolapse, or "systolic click-murmur syndrome," has been the subject of great interest, research and debate since the mitral valve was first implicated as the source of the click and/or late systolic murmur by Reid in 1961.¹ The usefulness of M-mode echocardiography in the diagnosis of this entity was first described by Shah and Gramiak.² Subsequent population studies have reported the prevalence of MVP to be between 5-20 percent.³¹⁴ Up to 20 percent of patients with clinical click-murmur syndrome will have a "false-negative" supine M-mode echocardiogram.³⁶⁷ Provocative maneuvers such as standing and the administration of amyl nitrite can accentuate the auscultatory finding of mitral valve prolapse.⁸ However, no systematic study using M-mode echocardiography has been done in this subset of patients with clinical mitral valve prolapse to determine whether standing or amyl nitrite inhalation can provoke M-mode echocardiographic evidence of mitral prolapse. Cross-sectional echocardiography (CSE) has recently been reported to be useful in the diagnosis of mitral valve prolapse.⁹¹¹¹ Nonetheless, the precise standards and the usefulness of CSE for diagnosis of MVP are not uniformly accepted¹²,¹³ and thus, the M-mode echocardiogram has continued as the echocardiographic standard for diagnosis of mitral valve prolapse.¹³ Accordingly, we undertook an M-mode and cross-sectional echocardiographic study of patients selected for auscultatory evidence of mitral valve prolapse, but with negative supine M-mode echocardiograms (group 1) to determine if M-mode echocardiograms performed in the standing position or after amyl nitrite inhalation could establish an echocardiographic diagnosis of mitral valve prolapse. To validate the standing M-mode pattern, two additional groups of subjects were studied: group 2 consisted of patients with auscultatory and supine M-mode evidence of mitral valve prolapse, and group 3 consisted of control subjects with normal auscultatory and supine M-mode examinations. In addition, in the majority of studied patients, cross-sectional echocardiography was done in the supine position to determine its relative efficacy in the diagnosis of mitral valve prolapse in these patients.

METHODS

Forty subjects were studied. Group 1 comprised 17 patients (16 women and one man, mean age 24 years, range 23-45) selected for auscultatory evidence of mitral valve prolapse and a negative supine MME. Group 2 consisted

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of eight patients (seven women and one man, mean age 30 years, range 21 to 48) with “classic” mitral valve prolapse, namely: auscultatory evidence of mitral valve prolapse and a positive supine M-mode echocardiogram. Group 3 included 15 normal control subjects (ten women and five men, mean age 30 years, range 21 to 35) without evidence of mitral valve prolapse on auscultation and on M-mode echocardiogram. After a thorough history, all patients and control subjects were examined independently by two cardiologists immediately prior to study. Presence of a mid-systolic click(s) and/or late systolic murmur which moved appropriately with postural maneuvers was the standard for auscultatory mitral valve prolapse.

Echocardiographic Technique

M-mode echocardiograms were performed using a commercially available Smith-Kline Ekoline 20A echocardiograph interfaced with a Honeywell model 1856 fiberoptic strip chart recorder as previously described. First, a supine M-mode echocardiogram was performed. Then, another was performed with the patient in the standing position. Finally, a repeat supine M-mode echocardiogram was done during and immediately after sufficient inhalation of amyl nitrite, to increase the heart rate ≥ 15 percent above baseline. Particular attention was given to the perpendicular orientation of the transducer to the chest wall during visualization of the mitral valve in order to avoid the artifact recording of a pattern of mitral valve prolapse. In addition, a routine sweep from the aorta toward the left ventricular apex was recorded. Mitral valve prolapse was diagnosed as previously described using the criteria of mid- to late-systolic bowing of the mitral valve closure line ≥ 2mm behind a straight line intersecting the mitral C and D points.

Cross-sectional echocardiograms were performed in the supine and left lateral decubitus position in 31 subjects. With the Smith-Kline Ekoscope I system using 30° and 80° mechanical sector transducers or with the Toshiba Sonolayer V (SSL-503M) with an electronically phased array 80° transducer, recordings were made on a Sanyo or Sony 8 inch videotape recorder, and studied frame-by-frame and in real-time. Unfortunately, stop frame images suffer from severe image degradation when compared with the visual integration of moving images that normally accompanies real-time imaging. A standard left parasternal long-axis view was obtained to evaluate the mitral valve for prolapse as described by Gilbert et al. The entire mitral valve was examined by sweeping the sector arc from a medial to a lateral position. A standard four-chamber apical view was also obtained; mitral prolapse was diagnosed by the criteria of Morganroth et al.

All echocardiograms were reviewed independently by four echocardiographers blinded to the subject identity, to the opinion of each echocardiographer, and, in the case of cross-sectional echocardiograms, to the M-mode. For this study, three of the four echocardiographers had to agree before the diagnosis of echocardiographic mitral valve prolapse was made. In the cross-sectional echocardiograms, a diagnosis of mitral valve prolapse in either the parasternal long-axis or four-chamber apical view was considered sufficient to make the diagnosis.

Statistical Methods

A contingency 2 × 2 table analysis of the standing M-mode echo vs supine cross-sectional echocardiographic diagnosis of mitral valve prolapse in all subjects who had both examinations, and of the cross-sectional parasternal long-axis view vs the cross-sectional four-chamber apical view diagnosis of mitral valve prolapse only in those subjects with an auscultatory diagnosis, was performed and Chi-square values were generated. Level of significance was chosen as P ≤ 0.05.

**Results**

**Inter-observer Variability**

**M-mode:** At least three of four echocardiographers agreed on the presence or absence of mitral valve prolapse on the supine, standing, and amyl nitrite M-mode echocardiograms in all 40 subjects.

**Cross-sectional:** Agreement regarding diagnosis was reached in 29/31 (94 percent) patients who underwent cross-sectional echocardiographic examination. There was lack of agreement in two patients (6,7) in group 1 (Table 1) and none in groups 2 and 3 (Tables 2 and 3).

**Group Characteristics**

**Group 1:** While standing, seven patients had both a systolic click and murmur, nine patients had a

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*Number of echocardiographers diagnosing MVP
†ND — Not Done
squatting, and earlier in systole upon standing (Table 1). Fourteen patients (82 percent) had a positive standing M-mode echocardiogram (Fig 1). Amylnitrite did not induce echocardiographic mitral valve prolapse in any group 1 patients. Thirteen patients with standing M-mode systolic mitral valve prolapse were also studied by cross-sectional echocardiography; 8/13 (62 percent) had cross-sectional evidence of mitral valve prolapse either in the parasternal long-axis view or in the four-chamber apical view or both (Table 1). Only one patient with a negative standing M-mode echo had cross-sectional echocardiography and it was negative.

Group 2: While standing, seven patients had a systolic click or clicks only, and one patient had systolic click and murmur; in each the systolic click(s) came later in systole upon squatting and earlier in systole upon standing (Table 2). In some patients, a transient late systolic murmur was heard only while squatting. The supine M-mode echo in three patients showed a pattern of late systolic prolapse and five patients had a pattern of pansystolic prolapse; all eight patients with mitral valve prolapse on the standing M-mode echocardiogram, in each pansystolic. Six of eight patients had cross sectional echocardiograms and five of these six (83 percent) were "positive" for mitral prolapse (Fig 2).

Group 3: Fifteen subjects had standing M-mode echocardiograms (Table 3, Fig 3). Despite lack of auscultatory or supine M-mode evidence of MVP, three subjects (20 percent) demonstrated echocardiographic evidence of mitral valve prolapse in the standing position. Twelve of 15 control subjects underwent cross-sectional echo examination; none had prolapse on cross-sectional echo, and all three subjects with a positive standing M-mode echo had no mitral valve prolapse on cross-sectional echocardiograms.

**Diagnosis of Mitral Valve Prolapse: Standing MME vs Supine CSE**

Contingency (2 × 2) table analysis revealed a significant (p ≤ .001) relationship between the presence or absence of mitral valve prolapse on cross-sectional echocardiography versus standing M-mode echocardiography. No subject with a negative standing M-mode echo had mitral valve prolapse diagnosed on supine cross-sectional echocardiogram; however, eight subjects had a positive (for prolapse) standing M-mode echo with a negative supine cross-sectional echocardiogram. Both supine cross sectional and standing M-mode echocardiographic diagnosis of mitral valve prolapse had a significant relationship to the presence or absence
of auscultatory mitral valve prolapse. Using our results: predictive value of supine cross-sectional echocardiography = 52 percent, and of standing M-mode = 65 percent; sensitivity of supine cross-sectional echocardiography = 68 percent, and standing M-mode = 88 percent; specificity of supine cross-sectional echocardiography = 100 percent, and standing M-mode = 80 percent. Thus, predictive value and sensitivity of the standing M-mode would be better than supine cross-sectional echocardiogram at the cost of specificity if these data are applicable to the larger population. Accuracy for supine cross-sectional echocardiography = 81 percent and for standing M-mode echocardiograms = 80 percent.

Cross-Sectional Echocardiographic Diagnosis of Mitral Valve Prolapse; Four Chamber Apical View vs Parasternal Long Axis View: Though there was a tendency for the four-chamber apical (4CA) view to be read as positive more often (11/19 = 58 percent) than the parasternal long-axis view (7/19 = 37 percent), contingency (2 x 2) table

![Figure 1A](left). Negative supine M-mode echocardiogram of a group 1 patient with auscultatory evidence of mitral valve prolapse. Though the systolic motion of the leaflets are recorded as horizontal, the "classic" sagging is not identified and thus the MME was not interpreted as mitral valve prolapse. B (right). Echocardiogram of same patient in the standing position reveals evidence (3 small arrows) of pansystolic mitral valve prolapse. AML = anterior mitral leaflet; cm = centimeters; IVS = interventricular septum; PML = posterior mitral leaflet; RV = right ventricle; sec = second.

![Figure 2A](Long-axis cross-sectional echocardiogram in a group 2 patient. The white line indicates the plane of the mitral annulus. The arrows indicate the hinge points of the mitral leaflet identified during real-time analysis. AO = aorta; LA = leaflet atrium; LV = left ventricle. B. Four chamber apical cross-sectional echocardiogram in same patient also demonstrates mitral valve prolapse which began early in systole and was pansystolic. Both leaflets of the mitral valve can be seen posterior to the mitral annulus in systole as identified by the white line which is drawn from the mitral leaflet hinge points (arrows) as identified during real-time analysis. LA = left atrium; LV = left ventricle.)
analysis revealed no significant difference. Only one of the two views was positive in 8/19 = 42 percent, and both views were negative in 6/19 = 32 percent.

DISCUSSION

Despite the demonstrated utility of the ultrasound technique, at least 7-10 percent of patients with auscultatory evidence of mitral valve prolapse have negative supine M-mode echocardiogram findings. Previous investigators have utilized physiologic maneuvers to accentuate or elicit the auscultatory or phonocardiographic findings of mitral valve prolapse. Fontana et al studied 22 patients with phonocardiographic evidence of a systolic click and murmur in the supine and 45° head-up tilt positions during angiography. Twelve patients had earlier onset of systolic prolapse when tilted to the 45° head-up position. Markiewicz et al studied 100 healthy young women by phonocardiography in the supine and standing positions and after administration of amyl nitrite. Seventeen subjects had evidence of a click and/or murmur after these provocative maneuvers, whereas only 8 of 17 were detected by resting supine phonocardiograms alone.

"False-negative" standard supine M-mode echocardiograms clearly occur. No systematic study of the usefulness of echocardiograms performed during provocative physiologic maneuvers in patients with auscultatory evidence of mitral valve prolapse and negative supine M-mode echocardiograms has been done. Furthermore, the utility of cross-sectional echocardiograms has not been examined in this particular group of patients. Accordingly, in 17 patients selected because they had the auscultatory "click-murmur syndrome" and a "negative" M-mode, M-mode echocardiograms during standing produced evidence of prolapse in 82 percent and cross-sectional echocardiograms demonstrated mitral valve prolapse in 62 percent (the difference was not statistically significant). To validate the standing technique, eight patients (group 2) with the "classic" auscultatory mitral valve prolapse and a positive supine M-mode echocardiogram were studied with standing M-mode. All eight (100 percent) gave positive results on standing. In group 2, cross-sectional echocardiography revealed mitral valve prolapse in 83 percent. There was no statistically significant difference between the parasternal long axis and the four-chamber apical views in their ability to detect mitral valve prolapse in these two groups of patients; however, the sample size is small. The two cross-sectional views were complementary.

It was disturbing that 3/15 control subjects had evidence of mitral valve prolapse on the standing M-mode echocardiogram in the absence of auscultatory evidence of a mitral prolapse and in the absence of a supine M-mode pattern of prolapse. None of those control subjects, also studied with cross-sectional echocardiography, had mitral valve prolapse by that technique, including all three subjects who had positive findings on standing M-mode echocardiograms. These three subjects may be false positive; though their normal cross-sectional echo results are reassuring, these subjects could fit into the spectrum of silent mitral valve prolapse described by Naggar.

Though position of the heart undoubtedly changed within the chest upon assumption of a standing posture, care was taken to avoid inferior angulation of the transducer which otherwise could induce a "false positive" finding on M-mode. As shown in Figure 1B, the transducer actually transected the left atrial wall behind the mitral valve leaflets when the mitral prolapse pattern was recorded (the transducer was perpendicular to the chest wall) confirming the fact that the heart had changed position. However, if any artifact were to occur, this "superior" angulation of the transducer relative to the mitral valve usually results in a "false-negative" pattern in mitral valve prolapse. Thus, change in position of the heart relative to the transducer probably does not account for the pattern of mitral valve prolapse seen in the standing M-mode, though this is not proved.
The search for a “gold standard” by which to judge the presence or absence of mitral prolapse continues. Angiography has clearly been demonstrated to be inadequate for a “gold standard.” Supine cross-sectional echocardiography, particularly the four-chamber apical view, has recently been suggested as the standard by which we should make the diagnosis, though not all observers would agree. We concur with Ginzon and Crliey that a firm clinical diagnosis of mitral valve prolapse can be established on an auscultatory basis and we would not be dissuaded by a non-diagnostic echocardiogram or cineangiogram.

The predictive value (likelihood that a positive test is true), sensitivity (index of capability to detect abnormality) and specificity (ability of test to recognize a normal subject) are dependent upon the prevalence of the disease in the population tested (Bayes theorem). Because this study group was highly selected, the predictive values for supine cross-sectional and for standing M-mode echocardiograms should be cautiously applied to the larger population.

We conclude that both standing M-mode and supine cross-sectional echocardiograms significantly increase the yield of echocardiographic evidence of mitral valve prolapse in patients with auscultatory evidence of prolapse but negative supine M-mode findings. Validation of this standing M-mode echocardiographic technique was aided by comparison with supine cross-sectional echocardiography, by studying patients with positive findings on supine M-mode echocardiography, and by studying normal subjects. The lack of usefulness of amyl nitrite was unexpected and is not readily explained. Cross-sectional echocardiograms proved as accurate as, and more specific than, standing M-mode. In contrast to the reports of Morganroth et al neither of the two cross-sectional views (parasternal long-axis and four-chamber apical) were statistically superior to the other. Thus, in the patient with auscultatory findings of mitral valve prolapse but a negative supine M-mode echocardiogram, either a supine cross-sectional or standing M-mode echocardiogram may secure the diagnosis and both techniques might prove to be complementary. We do not suggest, however, that a working clinical diagnosis of mitral valve prolapse be made by standing M-mode echocardiography alone in the absence of the appropriate clinical findings given the state of our current knowledge.

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