Simultaneous Echocardiographic-Phonocardiographic Recordings At Rest and During Amyl Nitrite Administration in Patients with Mitral Valve Prolapse

By Roger A. Winkle, M.D., Daniel J. Goodman, M.D., and Richard L. Popp, M.D.

SUMMARY

Simultaneous electrocardiograms, phonocardiograms, and echocardiograms were recorded in 21 patients with mitral valve prolapse. Four patients with holosystolic mitral valve prolapse on echocardiogram had smaller resting end-diastolic volumes than the remaining 17 patients with late systolic echocardiographic prolapse (P < 0.01). Thirteen of the 17 patients with late systolic prolapse had phonocardiographically recorded auscultatory phenomena. The initial vibrations of the auscultatory phenomena occurred after the onset of echocardiographic prolapse, but prior to maximal echocardiographic mitral valve prolapse. Amyl nitrite was administered to all patients. Three of the 17 patients with late systolic prolapse developed holosystolic prolapse, while the remaining 14 retained the late systolic prolapse pattern during amyl nitrite inhalation. In these 14 patients, the onset of mitral prolapse occurred earlier in systole due to a decrease in the duration of systole prior to onset of mitral valve prolapse (P < 0.001). This corresponded with the occurrence of auscultatory phenomena earlier in systole. Twelve patients had left ventricular volumes recorded during amyl nitrite inhalation and all showed a decrease in left ventricular volumes (P < 0.001). These findings confirm the temporal relationship of mitral valve prolapse and onset of auscultatory phenomena in these patients. It suggests that the movement of auscultatory phenomena earlier in systole during amyl nitrite inhalation is related to earlier prolapse of the mitral valve, and that a decrease in left ventricular volume is a tenable explanation for the earlier onset of prolapse.

Additional Indexing Words:
Mid-late systolic click syndrome
Auscultation
Heart sounds

MITRAL VALVE PROLAPSE has been the subject of many articles in recent years.1–3 Mid-systolic clicks and late systolic murmurs were initially presumed to be extra-cardiac in origin.4 Following the postulates of Reid5 and the work of Barlow,6 attention was focused on the intracardiac origin of these sounds. Angiographic evidence for billowing or prolapse of the mitral valve into the left atrium during systole soon became available.7–8 Intracardiac phonocardiography localized these sounds to the region of the mitral valve.9,10 Investigations by Criley, in which combined angiography and phonocardiography was performed in four patients, indicated that these auscultatory phenomena were temporally related to the maximum prolapse of the mitral valve.11 Numerous investigators have reported the ability of amyl nitrite to move the clicks and murmurs earlier in systole.2,3,12 The explanation proposed for this movement is a decrease in left ventricular volume which allows earlier prolapse of the mitral valve.12 However, these changes have not been well documented.1

Recently, echocardiography has been shown to be a useful tool for evaluation of mitral valve prolapse.13,14 Left ventricular volumes may be determined by echocardiography at rest15 and during amyl nitrite administration.16 This study was undertaken to investigate the anatomic, auscultatory, and volume relationships in patients with mitral valve prolapse at rest and during amyl nitrite administration.

Methods

Twenty-one patients with echocardiographic evidence of mitral valve prolapse were studied at the Stanford University Medical Center after obtaining informed consent. There were 20 females and one male in this series. Four of these patients had a holosystolic pattern of mitral valve prolapse.

From the Cardiology Division, Stanford University School of Medicine, Stanford, California.

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Address for reprints: Richard L. Popp, M.D., Director, Non-Invasive Laboratory, Cardiology Division, Stanford University School of Medicine, Stanford, California 94305.

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and 17 had a late systolic pattern of mitral prolapse. Eighteen of the patients were being evaluated because of auscultatory abnormalities with or without associated symptoms. The three patients without auscultatory findings included one with arrhythmias, one with chest pain, and one patient detected during a routine screening echocardiogram. None of the patients had evidence of heart disease other than the mitral valve abnormality, and no patient had a clinical picture suggestive of ruptured chordae tendineae. All patients were in sinus rhythm at the time of the study.

Simultaneous echocardiogram, phonocardiogram, and lead II electrocardiogram were recorded with patients in the supine position and turned approximately 30 degrees into the left lateral decubitus position. The echocardiogram was performed using an Ekoline 20 Smith Kline ultrasonoscope using a 2.25 MHz, 0.5 cm diameter transducer with beam collimation to 5 cm depth. For the best recording of mitral valve prolapse, the transducer was usually positioned in the third or fourth left intercostal space at the left sternal border perpendicular to the chest wall. Left ventricular volumes were obtained by tilting the transducer slightly inferiorly and laterally to the position of maximum left ventricular dimension, just below the mitral valve level. The phonocardiogram was recorded at the apex using a Maico contact microphone which was filtered to display frequencies of 120 to 500 Hz. Oscilloscopic display of this information was available and a permanent strip chart recording was obtained by using an Electronics for Medicine DR8 recorder at a paper speed of 50 or 75 mm/sec.

With the echo transducer focused on the mitral valve, amyl nitrite was inhaled for three breaths and a continuous record was made. Primary attention was placed on mitral valve motion; however, in 12 patients, it was possible to rapidly sweep inferiorly and laterally and record an adequate left ventricular echocardiogram before the heart rate began to decrease. Technically adequate simultaneous phonocardiograms and mitral valve echocardiograms were obtained in 17 of the 21 patients during amyl nitrite administration. All of the resting measurements and calculations were repeated at or near the peak of the heart rate response to amyl nitrite. The effect of amyl nitrite on the intensity of the clicks and murmurs was determined.

Measurements

From these recordings various points were identified, and dimensions and time intervals were measured. In the 17 patients with the late systolic prolapse, an abrupt posterior motion of the mitral valve leaflet was identified during systole and the initiation of this motion was defined as the P (prolapse) point (fig. 1). The M point was defined as the point of maximum posterior prolapse of the mitral valve leaflet. The C and D points were identified as described by Edler, C being the point where the anterior and posterior mitral valve leaflets apparently come together at end-diastole and D being the point of abrupt anterior movement of the anterior mitral valve leaflet at the onset of diastolic valve opening. In those patients in whom a clear D point could not be determined because of the prolapse, D was defined as the intersection of a line passing through points C and P with the anterior motion of the mitral valve leaflet at end-systole (fig. 1). S1 was defined as the onset of the first high frequency vibrations of the first heart sound and S2 defined similarly for the second heart sound. An X point was defined as the onset of the earliest consistently recorded click on the phonocardiogram, the onset of a late systolic murmur if no clicks were present, the point of late systolic intensification of a holosystolic murmur, or the point of occurrence of the earliest click in a holosystolic murmur. From these reference points (fig. 1), the following time intervals were measured: the duration of systole (C–D), the prolapse interval (C–P), the duration of prolapse (P–D), the time to peak prolapse (P–M), the time from the onset of prolapse to the earliest auscultatory phenomena (P–X), and the intervals S1–S2 and S1–X. The fraction of systole occupied by prolapse (prolapse fraction) was determined by the ratio P–D and the fraction of systole occurring after X was determined by X–S2. A prolapse index (PI) was defined as the product of the duration of prolapse per cardiac cycle (P–D) and the heart rate and has the units of sec of prolapse/min.

Left ventricular end-diastolic and end-systolic dimensions were defined as the maximal and minimal separation of the left septal and left ventricular posterior endocardial echoes, respectively. Left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were determined by cubing these dimensions. Stroke volume (SV) and ejection fraction (EF) were determined according to the following equations:

\[
SV = LVEDV - LVESV \\
EF = \frac{SV}{LVEDV}
\]

All measurements were averaged over five beats to minimize respiratory variation.

Statistical analysis was performed using a preprogrammed Hewlett Packard 9100 A calculator. The two-tailed t-test for matched pairs was used for comparison of resting and amyl nitrite data, and the two-tailed t-test for groups with equal variance was used for comparison of resting subgroups.

**Results**

**Hemodynamics**

A summary of the hemodynamic data is given in table 1. The resting heart rate was 72.2 ± 9.8 beats/min for the 21 patients and this increased to 106.6 ± 16.0 with amyl nitrite (P < 0.001). For the 12 patients with left ventricular dimensions recorded during amyl nitrite administration, the left ventricular end-diastolic and end-systolic volumes and stroke volumes all decreased (P < 0.001). The ejection fraction increased slightly, but this change was not statistically significant. The heart rate response to amyl nitrite was similar for the entire group and for the group with volumes recorded; however, in the latter the resting volumes tended to be smaller, which indicates that technically adequate volume studies were more frequently obtained in patients with slightly smaller hearts. Evaluation of the 21 patients by pattern of prolapse revealed that the mean end-diastolic volume was smaller (83 ± 24 cc) for the four patients with holosystolic prolapse at rest than for the 17 patients with late systolic prolapse at rest (137 ± 33 cc) (P < 0.01).
Mitral Valve Motion

The pattern of echocardiographic prolapse remained holosystolic during amyl nitrite inhalation in the four patients in whom it was holosystolic at rest. The changes seen during amyl nitrite inhalation in 17 patients with late systolic prolapse are summarized in table 2. After administration of amyl nitrite the pattern of prolapse remained late systolic in 14 of these 17 (fig. 2) and became holosystolic in three (fig. 3). Compared with the 14 patients maintaining the late systolic pattern, the duration of prolapse (P-D) at rest was not statistically different for these latter three patients (table 2); however, the pre-prolapse interval (C-P) for these three patients (140 ± 10 msec) was shorter than for the 14 patients retaining a late systolic prolapse pattern (171 ± 26 msec) (P < 0.10).

The total echocardiographic duration of systole (C-D) was a function of heart rate both at rest and with amyl nitrite. (C-D) = −2.27 HR + 534; r = 0.90. For the whole group of 17 patients with resting late systolic prolapse, the average duration of prolapse/beat (P-D) was unchanged (fig. 4) during administration of amyl nitrite, but the pre-prolapse interval (C-P) decreased from 166 ± 26 msec to 86 ± 46 msec (P < 0.001) (fig. 5), demonstrating that the prolapse occurred earlier in systole. However, the three patients who developed the holosystolic pattern with amyl nitrite increased their prolapse (P-D) interval from 200 ± 10 msec to 287 ± 31 msec (P < 0.05). In the 14 patients maintaining the late systolic pattern during amyl nitrite inhalation, the P-D interval decreased from 214 ± 29 to 199 ± 24 msec (P < 0.025) (fig. 4). Despite this slight shortening of the P-D interval, the prolapse occurred earlier in systole and the percentage of systole occupied by prolapse (P-D/C-D) increased (P < 0.001) because the duration of systole (C-D) decreased even more than the decrease in the prolapse period (P-D). The mean time to peak prolapse (P-M) was 65.9 ± 17 msec at rest for the entire group. In those patients developing the holosystolic pattern with amyl nitrite, the time to peak prolapse (P-M) increased (P < 0.10), whereas in those maintaining the late systolic pattern, the time to peak prolapse (P-M) decreased from 65.7 ± 18 to 52.9 ± 23 (P < 0.05). Part of this lengthening of the

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All 21 patients</th>
<th>12 patients with LV study during amyl nitrite</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Amyl</td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>72.2 ± 9.8</td>
<td>108.7 ± 15.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>4.98 ± 0.51</td>
<td>4.77 ± 0.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVESD (cm)</td>
<td>2.98 ± 0.49</td>
<td>2.84 ± 0.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDV (cc)</td>
<td>127.0 ± 37.7</td>
<td>111.7 ± 33.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVESV (cc)</td>
<td>27.5 ± 12.2</td>
<td>24.0 ± 10.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SV (cc/beat)</td>
<td>99.4 ± 27.7</td>
<td>87.7 ± 25.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF</td>
<td>0.79 ± 0.05</td>
<td>0.79 ± 0.06</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: HR = heart rate; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; SV = stroke volume; EF = ejection fraction; NS = not statistically significant.
Circulation, Volume 51, March 1975

Table 2

Time Intervals Before and After Amyl Nitrite Inhalation in Patients with Late Systolic Prolapse at Rest

<table>
<thead>
<tr>
<th>Patients with LSP remaining</th>
<th>Patients with LSP becoming holosystolic with amyl</th>
<th>All patients with LSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSP with amyl (14)</td>
<td>LSP with amyl (3)</td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>Amyl</td>
<td>P</td>
</tr>
<tr>
<td>C-D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of systole (msec)</td>
<td>384 ± 34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-prolapse interval (msec)</td>
<td>171 ± 26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P-D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of prolapse (msec)</td>
<td>214 ± 29</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>P-M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to peak prolapse (msec)</td>
<td>65.7 ± 18</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>P-D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolapse fraction</td>
<td>0.56 ± 0.06</td>
<td>0.65 ± 0.03</td>
</tr>
<tr>
<td>PI</td>
<td>(See prolapse/min)</td>
<td>14.4 ± 1.9</td>
</tr>
</tbody>
</table>

Abbreviations: LSP = late systolic prolapse; NS = not statistically significant.

P-D and P-M intervals in patients who developed the holosystolic pattern with amyl nitrite may be artifactual, since as the P point moves very early into systole it merges with the normal early posterior motion of the mitral valve. This posterior early systolic motion may last up to 50 msec in normal patients, and thus the duration of prolapse (P-D) and time to peak prolapse (P-M) may be overestimated by this

Figure 2

A) Recording from a patient with the late systolic pattern of mitral valve prolapse at rest. As in figure 1, the earliest vibrations of the auscultatory phenomena (X) occur during the P-M interval. One-second time lines have been used for illustrative purposes. Again fainter echoes may be seen synchronous with and posterior to the labeled dominant mitral valve echo. Labels as in figure 1. B) Recording from the same patient during amyl nitrite inhalation. The onset of prolapse (P) occurs earlier in systole due to a decrease in the C-P interval. Time lines and paper speed same as in A.

Figure 3

Echo-phonoe-EKG from a patient with late systolic prolapse at rest which became holosystolic prolapse during amyl nitrite inhalation. Rest: Rest showing late systolic pattern of prolapse. There were no consistent auscultatory phenomena. Early amyl: Same patient very early during amyl nitrite inhalation. The prolapse became holosystolic. Late amyl: Near the peak heart rate response to amyl. The prolapse pattern remains holosystolic.
amount. The prolapse index increased significantly for all patients during amyl nitrite administration, reflecting the increase in heart rate. This indicated that the mitral valve is prolapsed for more of each minute during amyl nitrite administration than it is at rest.

**Phonocardiographic Findings and Correlation with the Echocardiogram**

Of the four patients with resting holosystolic prolapse, one had intermittent mid-systolic clicks, one had a holosystolic murmur, and two had no phonocardiographic abnormalities. During amyl nitrite administration three of these four had adequate phonocardiograms and they showed no changes.

Thirteen of the 17 patients with late systolic prolapse at rest had a well defined, consistently recorded X point. This X point was a single click in one patient, the first of a series of clicks in one patient, a click initiating a late systolic murmur in seven patients, the onset of a late systolic murmur without clicks in two patients, the point of late systolic increase in the intensity of a holosystolic murmur in one patient, and a click occurring in a holosystolic murmur in one patient. Of the remaining four patients without a consistent X point, two had normal phonocardiograms, one had an intermittent late systolic whoop, and one did not have an adequate phonocardiogram.

In the 13 patients with late systolic prolapse at rest and an X point, as defined above, the X point in the phonocardiogram followed the P point of the echocardiogram by an average 32 ± 12 msec, ranging from 10 to 50 msec. The X point occurred after the onset of prolapse (P point) but before the point of maximal prolapse (M point) (fig. 1). Although the X point occurred slightly before the maximal prolapse (M point), the peak intensity of the recorded clicks often coincided with the M point. Since S1 occurred synchronously with the C point of the echocardiogram in all instances, a direct comparison of the intervals S1-X and C-P may be made (fig. 6). S1-X exceeded C-P by the interval P-X and the correlation coefficient for these first two measurements was 0.94, which illustrates that the X point follows the echographic onset of prolapse and suggests that the two phenomena may be related.

Following amyl nitrite administration in the 17 patients with resting late systolic prolapse, a variety of changes were seen in the intensity of the clicks and murmurs. Clicks increased in intensity in four patients, and new clicks appeared in two. One patient developed several new clicks following a single click, which was present at rest. In one patient a click decreased in intensity. In three patients, murmurs decreased in intensity or disappeared, and in one patient the murmur increased following amyl nitrite. The intensity of four clicks and six murmurs was unchanged.

Of the 13 patients with an X point defined at rest, 11 had an X point defined during amyl nitrite administration. Of the remaining two, one did not have
an adequate phonocardiogram during amyl nitrite and the other was a patient who developed holosystolic prolapse and whose earliest click moved into the S₁ complex. Table 3 shows a comparison of the phonocardiographic intervals for these 11 patients before and after amyl nitrite inhalation, all of whom were among the 14 who maintained the late systolic prolapse pattern with amyl nitrite. S₂ consistently occurred before the D point of the echocardiogram so that S₁-S₂ was shorter than C-D. In all cases, the X point moved closer to S₁ compared to the resting S₁-X interval (P < 0.001) with no significant change in the X-S₂ interval. The echocardiographic P point preceded the X point by an average of 26 ± 14 m sec (range 10–60). Although the P-X interval was slightly shorter following amyl nitrite, this was not a statistically significant change.

**Discussion**

The noninvasive techniques utilized in this study permit evaluation of many postulates interrelating the auscultatory phenomena, volume changes, and mitral valve motion in patients with prolapse of the mitral valve. These events may be examined and correlated in a manner which has not been possible previously despite the application of such invasive techniques as angiography and intracardiac phonocardiography.

Many earlier reports suggested that the various auscultatory phenomena, such as mid-late systolic click, late systolic murmurs, or late systolic intensification of holosystolic murmurs, are related to the mitral valve prolapse seen on left ventricular angiography. Studies by Criley et al., using non-simultaneous phonocardiographic and angiographic techniques in four patients, showed that the clicks and murmurs seemed to occur near or after the time of maximal prolapse. In our experience the onset of echocardiographic prolapse may vary slightly from beat to beat, thus making simultaneous recordings mandatory. Using techniques similar to those in this study, earlier work by Kerber et al. indicated that the clicks followed the onset of the mitral valve prolapse by 50–60 msec in two patients. The present study demonstrates that some of the auscultatory phenomena in patients with mitral valve prolapse do appear to be related temporally to the abnormal echocardiographic systolic mitral valve movement. They usually begin after the onset of the abnormal posterior motion, but prior to the time of maximal prolapse. The peak intensity of the clicks usually coincides with the point of maximal prolapse. Presumably, maximal tensing of the valvular apparatus occurs at the point of maximal prolapse of the mitral valve into the left atrium. The onset of vibrations prior to this time, in most patients, seems to make the valvular apparatus an unlikely cause for these clicks. However, the mitral valve is a complex parachute-like structure and the single ultrasonic beam is unable to visualize all portions of the valve simultaneously. Figures 1 and 2 illustrate this with several faint echoes seen moving more posterior to, but synchronous with, the dominant echo. These faint echoes are more strikingly characteristic of mitral valve prolapse pattern from a diagnostic standpoint, but the strong echoes were labeled for clarity. It is possible that in some patients portions of the valve reach maximal prolapse slightly before or after the portion recorded on the echocardiogram at any given moment. Such asynchronous prolapse would also explain the genesis of the multiple
clicks seen in some patients. Although most clicks reported in patients with mitral valve prolapse have been mid-late systolic, early systolic clicks have been reported in association with early prolapse seen on angiography.19 These latter patients probably represent the group with the holosystolic type of prolapse at rest. The variable effect on intensity of these murmurs during amyl nitrite inhalation is similar to the report of several other investigators.9,12

All investigators have agreed that the clicks and murmurs move earlier in systole during the administration of amyl nitrite in these patients.2,3,15 The most widely accepted hypothesis for this movement has been earlier prolapse of the mitral valve due to a smaller left ventricular volume.12 However, neither of these factors has been well documented previously. Feigenbaum's group reported that two patients given amyl nitrite had prolapse earlier in systole as demonstrated echocardiographically.19 A single patient evaluated by Bittar and Sosa12 angiographically following amyl nitrite showed earlier onset of prolapse, but no phonocardiographic recording was made. In the present study, all patients with late systolic prolapse had the onset of mitral valve prolapse occurring earlier in systole during amyl nitrite administration and this earlier prolapse corresponded with the earlier occurrence of the onset of auscultatory phenomena. In all patients, this motion earlier in systole was associated with a significant decrease of the pre-prolapse interval. The majority of patients with late systolic prolapse retained their late systolic prolapse pattern with amyl nitrite and actually showed a small decrease in the total duration of prolapse (P-D) per cardiac cycle, although the total prolapse per minute was increased. A small number of patients with shorter resting pre-prolapse intervals (C-P) showed holosystolic prolapse during amyl nitrite. Although the various intervals and indices defined for mitral valve motion do not necessarily have clinical implications, we have found them useful for quantifying and describing the anatomical changes of the mitral valve detected echocardiographically during various interventions.

Left ventricular volume was shown to be significantly reduced during amyl nitrite inhalation in all patients in whom volume measurements were made. Similar changes were recently shown in normal patients,16 and the confirmation of similar decreased volumes in patients with mitral valve prolapse indicates that the smaller volume-earlier prolapse concept is tenable. The presumed mechanism for this hypothesis is that the chordae tendineae are of relatively fixed length, and as the left ventricular volume decreases and the axis of the left ventricular chamber shortens, the mitral valve leaflets are allowed to prolapse earlier in systole. The finding of smaller resting end-diastolic volumes in the patients with holosystolic prolapse compared with those with late systolic prolapse is also consistent with the smaller volume-earlier prolapse concept. Angiographic studies showing earlier prolapse during passive tilting also seems to be compatible with the volume change theory of earlier prolapse.20 However, recent work indicates that other factors influenced by amyl nitrite, such as contractility, heart rate, and afterload also may be important determinants of the timing of mitral valve prolapse.21 Future studies combining invasive and noninvasive techniques may be necessary to completely understand the factors involved in determining the mechanism, timing, generation of auscultatory phenomena, and extent of prolapse in these patients. Despite the probable diverse causes of redundancy of the mitral valve, this study demonstrates a general relationship between the size of the ventricle and the onset of echocardiographic prolapse that suggests a similar mechanism of valvular dysfunction once the redundancy has developed. Hemodynamic difficulties occurring during sinus or ectopic tachycardia, which has been observed in some patients with mitral valve prolapse in our laboratory (unpublished observations), may be partially explained by these findings.

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References

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