The Determinants of Onset of Mitral Valve Prolapse in the Systolic Click-Late Systolic Murmur Syndrome

DETELF G. MATHEY, M.D., PIERRE R. DECOODT, M.D., HOWARD N. ALLEN, M.D., and H. J. C. SWAN, M.D., Ph.D.

SUMMARY The onset of mitral valve prolapse and its close correlate, the time of systolic click, vary considerably with different physiologic and pharmacologic interventions. In order to explain the mechanism responsible for these alterations, the effects of tilt and amyl nitrite inhalation on left ventricular dynamics and the time of the systolic click were studied by analyzing phonocardiograms and simultaneously recorded echocardiograms in 14 patients with mitral valve prolapse and mid-systolic click. The patients were studied in the supine position, with 40–60° head-up tilt and after amyl nitrite inhalation. Computer analysis of the recordings was used to measure the left ventricular end-diastolic diameter, the click diameter (left ventricular diameter at the time of mid-systolic click), the maximal velocity of circumferential fiber shortening (max V_{cr}), and the time interval between the first heart sound and systolic click (S-X). With factors provides better understanding of the mechanism of mitral valve prolapse.

MITRAL VALVE PROLAPSE is frequently recognized by the auscultatory finding of a mid-systolic click, which is thought to be due to sudden tensing of redundant chordae or mitral leaflets. The click usually occurs at the time of valve prolapse and is closely correlated with its onset. Following many different physiologic and pharmacologic maneuvers, the time of systolic click and prolapse varies considerably.

In addition, standing, tilt, Valsalva maneuver, amyl nitrite, or isoproterenol, click and prolapse move earlier in systole; whereas squatting, handgrip, propranolol, or phenylephrine delay their occurrence. This characteristic response is commonly explained by a decrease in the left ventricular end-diastolic volume induced by those maneuvers that result in earlier prolapse and an increase in left ventricular end-diastolic volume produced by those that result in later prolapse. This hypothesis, however, does not explain why the mid-systolic click occurs earlier in postextrasystolic beats or after termination of rapid atrial pacing, when the end-diastolic volume increases and later prolapse would be expected.

The present study was performed to define the factors that control the onset of mitral valve prolapse. It was found that the left ventricular chamber size at which the prolapse occurred was virtually constant for an individual patient. This finding was not unexpected considering the fibrous, nonelastic tissue of the mitral valve apparatus. It was also demonstrated that in addition to end-diastolic dimensions, the rate of dimensional change was an equally important determinant of the onset of prolapse. Knowledge of these

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Eighty-two

Methods

Fourteen patients (mean age 40 years, range 25 to 79 years) with mid-systolic click and echocardiographic evidence of mitral valve prolapse were studied. Their clinical findings are listed in table I. Ten of fourteen patients were asymptomatic. In five patients, the mid-systolic click was followed by a late systolic murmur; in two patients, the systolic murmur preceded the click. All patients were normotensive. Four patients (#6, 9, 10, and 14) had a high left ventricular end-diastolic diameter at rest. In patient 13, this was probably due to coronary artery disease since significant obstructive lesions of the left anterior descending and circumflex coronary arteries and hypokinesia of the anterior left ventricular wall were demonstrated angiographically. There was no obvious cause for left ventricular enlargement in patients 6, 9 and 10. Left atrial size was normal in these patients making it unlikely that the valvar lesion had caused the left ventricular enlargement. The latter was probably due to myocardial abnormalities frequently associated with mitral valve prolapse.

A strip-chart echocardiogram was recorded at 50 mm/sec paper speed using an Ekoline 20 ultrasound unit, which was interfaced with an Electronics for Medicine DR 8 recorder. In order to obtain a continuous recording of the ventricular septum and the left ventricular posterior wall, the transducer was placed in the third or fourth intercostal space. The ultrasound beam was directed to identify the top of the anterior mitral leaflet or the chordae just below the mitral valve. A lead II electrocardiogram and a phonocardiogram from the mitral area, filtered to display frequencies between 200 and 500 Hz, were recorded simultaneously.

The patients were initially studied in the supine position. They were then tilted to a 40–60° head-up position and recordings were performed after the heart rate had stabi-
Table 1. Clinical Findings

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Abbreviations: MSC = mid-systolic click; LSM = late systolic murmur; ESM = early systolic murmur; S3 = third heart sound; S4 = fourth heart sound; WNL = within normal limits; PVC = premature ventricular complex.

lized. The patients were returned to the supine position and a second set of control data was recorded. The patients then inhaled three deep breaths of amyl nitrite and within 15 seconds echo and phonocardiographic recordings were obtained. During this time, reflex tachycardia was present in all patients. The transducer was maintained in the same intercostal space throughout the study. Only those tracings where continuous, well-defined septal and posterior wall endocardium was seen were included in the study.

In order to measure the instantaneous left ventricular diameter and to calculate the instantaneous velocity of circumferential fiber shortening (VCF) the tracings were analyzed by computer. Figure 1 illustrates the sequence of operations. A hand-controlled articulated cursor was used to digitize the echocardiographic recordings. Any movement of the cursor resulted in a change of voltage across the two potentiometers placed at the joints of the cursor. These voltage changes were sampled at a rate of 1 KHz using an analog-digital converter and were stored in the core memory of a Sigma 3 computer. First, multiple calibration points distributed throughout the recording were sampled. For optimal transformation of the coordinates of the digitizing table to those of the echocardiographic recording, a previously developed algorithm was used, which minimized the error between given and computed calibration points. This method resulted in an accuracy of 0.2 ± 0.1 mm (mean ± SD). Then the time of onset of the QRS complex, the first heart sound and the systolic click were sampled. At a paper speed of 50 mm/sec, the first heart sound-click interval could be calculated with a maximal error of 1 msec. Finally, septal and posterior wall endocardial echoes, as well as the electrocardiogram and phonocardiogram were outlined beat by beat. The endocardial echo trace, which showed the steepest slope during systole and early diastole, was digitized, displayed on a video-screen and accepted if well outlined. A left ventricular diameter time curve was obtained by calculating the instantaneous distance between the interventricular septum and left ventricular posterior wall. Nine point least square smoothing and differentiation formulas were used to compute instantaneous values for VCF. The left ventricular diameter time curve, the VCF curve, the ECG and phonocardiogram were plotted on a Calcomp X-Y plotter (fig. 2). The computer method will be reported in
2. In the tilt study, the following values were determined:

1. Left ventricular end-diastolic (maximal) diameter in cm. The temporal relationship between the QRS complex and the maximal left ventricular diameter was variable in individual patients. The average delay between the onset of QRS and the maximal diameter was 39 ± 22 msec for all patients studied in the supine position, 51 ± 23 msec with tilt and 37 ± 25 msec after amyl nitrate inhalation.

2. Left ventricular diameter at the time of mid-systolic click (click diameter) in cm.

3. Maximal endocardial velocity of circumferential fiber shortening (max \( V_{CF} \)) in circ/sec. Endocardial \( V_{CF} \) was calculated as the first derivative of the instantaneous left ventricular diameter divided by the left ventricular end-diastolic diameter.\(^{17} \) \( V_{CF} \) was corrected for end-diastolic dimensions in order to eliminate its preload dependence.\(^{18} \) Normalized \( V_{CF} \) is only affected by afterload and/or contractility.\(^{19, 20} \) Therefore, by normalizing \( V_{CF} \), the left ventricular end-diastolic diameter and max \( V_{CF} \) became two independent parameters. Max \( V_{CF} \) was used to characterize acute changes in afterload and/or contractility, whereas the end-diastolic diameter was used to indicate alterations in preload. Max \( V_{CF} \) always occurred in the preprolapse period, an average of 85 ± 17 msec before the mid-systolic click. Beat-to-beat variation of max \( V_{CF} \) in six consecutive beats was less than 11% (unpublished data).

4. The time between the first heart sound and the mid-systolic click \( S_1-X \) in msec. Individual values represent an average of 2–6 beats. Control values in the supine position were compared with values after tilt and after amyl nitrate administration using Student’s paired \( t \)-test to determine statistical significance. The value \( P < 0.05 \) was considered statistically significant.

Results

The individual data are summarized in table 2. In six patients, tilt and amyl nitrate data were compared with control values; in eight patients, recordings of only one maneuver, either tilt or amyl, were considered adequate for evaluation. The typical response to these maneuvers is illustrated for an individual patient in figure 3.

Shortening of \( S_1-X \) and Reduction of the End-diastolic Diameter with Tilt

The effect of tilt was studied in ten patients. On an average, changes from supine to 40–60° head-up tilt resulted in shortening of the \( S_1-X \) interval by 44 msec, from 226 to 182 msec. At the same time, the end-diastolic diameter decreased from 5.05 to 4.50 cm. However, this maneuver did not alter the click diameter which averaged 3.40 cm supine and 3.37 cm with tilt. In eight of the ten patients, max \( V_{CF} \) did not change with tilting. No change in heart rate was noted.

Figure 4 demonstrates that the click diameter remained virtually constant in the presence of marked changes in the end-diastolic diameter induced by tilt.

Figure 5A illustrates the relationship between \( S_1-X \) and the end-diastolic diameter before and after tilt. It shows that a reduction of the end-diastolic diameter resulted in shortening of the \( S_1-X \) interval. Patients 2 and 14 are not included in this figure, as max \( V_{CF} \) changed with tilting in these patients.

In patient 14, \( S_1-X \) did not change with tilt despite a reduction in the end-diastolic diameter. However, max \( V_{CF} \) decreased, outweighing the reduction in end-diastolic diameter. The decrease of max \( V_{CF} \) may represent an inappropriate response to tilt in this patient with significant coronary artery disease.

Shortening of \( S_1-X \) and Increase of max \( V_{CF} \) with Amyl Nitrite

In ten patients, the effects of amyl nitrate were studied. Within 15 seconds after amyl nitrite administration, the mean \( S_1-X \) interval shortened by 87 msec. No significant decrease in the mean end-diastolic diameter had occurred up to this time (5.10 vs 4.99 cm), although a tendency to decrease was noted in some patients, particularly patients 3 and 10. The average rise in heart rate was 36 beats/minute. As with tilt, no significant change of the mean click diameter (3.47 vs. 3.40 cm) was observed after amyl nitrite inhalation. However, max \( V_{CF} \) had increased by 42% from 2.15 to 3.06 circ/sec.

Figure 5B demonstrates that in all patients shortening of \( S_1-X \) immediately after amyl nitrite administration was associated with an increase in max \( V_{CF} \).

Discussion

A mid-systolic click which occurs earlier in systole with upright posture or amyl nitrite administration is diagnostic of mitral valve prolapse. Therefore, these maneuvers have become useful tools of clinical examination and phonocardiography in detecting this most common form of mitral valve abnormality. Occasionally, neither click nor murmur is heard at rest, and only these provocative tests will reveal the typical auscultatory findings.

In previous studies it was found that the mid-systolic click occurs at the time of mitral valve prolapse.\(^{3, 4} \) This was confirmed in a recent echo and phonocardiographic study by Winkle et al.,\(^{3, 4} \) who established a good correlation between the time of systolic click and the onset of echocardiographic prolapse. These authors were also able to demonstrate that after amyl nitrite administration, both click and prolapse move earlier in systole, thus maintaining their close temporal relationship. It can be concluded from their study that a movement of the systolic click reflects a change in the onset of mitral valve prolapse.

The present study demonstrates that — even in the face of markedly altered hemodynamics — the left ventricular diameter at the time of mid-systolic click is virtually constant in an individual patient. A significant decrease in preload, as occurred with tilt, was shown to have essentially no influence on the click diameter. Amyl nitrite, which is known to reduce venous return and afterload,\(^{18} \) also did not affect the click diameter. This leads to the conclusion that, in a given heart, mitral valve prolapse occurs at a critical left ventricular chamber size.

A constant click diameter may be explained by the fixed length of the fibrous, noncompliant chordae and mitral valve leaflets. In early systole, the left ventricular diameter usually exceeds the critical diameter at which the prolapse occurs,
and the chordae are taut and still able to hold the mitral leaflets in a proper position. When the critical diameter is reached in mid-systole, they become redundant; and when there is further shortening of the left ventricular diameter, the excessive leaflet tissue can no longer be retained and prolapses into the left atrium.

The constancy of the click diameter implies that two factors, namely the left ventricular end-diastolic diameter and the velocity of circumferential fiber shortening in the preprolapse period, determine the time of the onset of mitral valve prolapse, each of them contributing to a more or less important degree. The end-diastolic diameter controls the

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**Figure 2.** The principle of the computerized method used to analyze the echo and phonocardiographic recordings is illustrated. Septal and posterior wall endocardial echoes of the original recording (A) were digitized, adequately smoothed, and plotted (B). From the digitized echoes, the left ventricular diameter time curve was calculated (C), representing the instantaneous distance between septal and posterior wall endocardium. $V_{cf}$ was calculated as the first derivative of this diameter time curve divided by the end-diastolic diameter and plotted as well. In addition to these plots, a printout of all instantaneous values and the automatically determined values of the end-diastolic diameter, the click diameter, max $V_{cf}$, and $S_1-X$ were obtained. $PCG$ = phonocardiogram; $V_{cf}$ = velocity of circumferential fiber shortening; $LVD$ = left ventricular diameter.

**Figure 3.** Typical recordings of the echocardiogram, phonocardiogram, and electrocardiogram and their corresponding computer plots in an individual patient (85) studied supine, with tilt, and 8 sec after amyl nitrite administration. It is apparent from all three plots that max $V_{cf}$ (labelled by arrow in the first beat) occurs well before the mid-systolic click. Change from supine to tilt resulted in shortening of the $S_1-X$ interval by 24 msec and a decrease of the end-diastolic diameter from 4.85 to 4.34 cm with no change in max $V_{cf}$. Eight seconds after amyl nitrite administration, $S_1-X$ shortened by 101 msec due to the increase in max $V_{cf}$ with only a minor decrease of the end-diastolic diameter by 1.1 mm. $PCG$ = phonocardiogram; $LV$ = left ventricle; $V_{cf}$ = velocity of circumferential fiber shortening; $LVD$ = left ventricular diameter.
Table 2. Summary of Individual Data

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<th>Patient</th>
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<th>EDD (cm)</th>
<th>DX (cm)</th>
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<th>S1-X (msec)</th>
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Mean ± SD

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*P < 0.05
**P < 0.01
***P < 0.001

Abbreviations: EDD = left ventricular end-diastolic diameter; DX = click diameter; max Vcf = maximal velocity of circumferential fiber shortening; S1-X = time interval between first heart sound and systolic click.
The click diameter is plotted against the end-diastolic diameter. The arrows represent changes of these parameters induced by tilt. The end-diastolic diameter decreased markedly with tilt, whereas the click diameter remained more or less unchanged. This indicates that the left ventricular diameter at which the prolapse occurs is constant in an individual patient.

The onset of prolapse, as it requires more time to achieve a constant click diameter from larger than from smaller end-diastolic dimensions. A larger end-diastolic diameter, therefore, would result in later prolapse, a smaller end-diastolic diameter in earlier prolapse. This, however, only holds true under the condition that VCF in the preprolapse period remains unchanged. Max VCF can be regarded as a good estimate of this initial velocity of fiber shortening, as it was found to be a reproducible parameter, which always occurred in the preprolapse period. An increase in max VCF obviously would result in earlier attainment of the click diameter and, therefore, earlier prolapse. Accordingly, a decrease in max VCF would be accompanied by later prolapse. These considerations were verified by our study.

With tilt, the earlier prolapse was due to a decrease in end-diastolic diameter, as no significant change in max VCF was observed. Immediately after amyl nitrite, earlier prolapse was due to an increase in max VCF, as no significant change in end-diastolic diameter had occurred at this time. Figure 6 illustrates in an individual patient that at a later time after amyl nitrite administration, both elevated max VCF and diminished end-diastolic diameter contributed to the earlier onset of prolapse. In this patient, shortening of S1-X from 226 to 147 msec 12 seconds after amyl nitrite was associated only with an increase in max VCF from 2.16 to 3.46 circ/sec. Additional shortening of S1-X, from 147 to 101 msec, occurred when the end-diastolic diameter had maximally decreased from 5.19 to 4.37 cm 32 seconds after amyl nitrite inhalation, with max VCF remaining at its elevated level. The combined effect of both factors explains why S1-X was much shorter after amyl nitrite administration than with tilt, although the decrease in the end-diastolic diameter was similar with both interventions. The S1-X interval in this patient could be predicted (dashed line) from the end-diastolic diameter and max VCF using bidimensional linear regression (r = 0.81). The good prediction makes it likely that these variables alone determine the onset of mitral valve prolapse.

Another example concerns the effect of a premature ventricular complex on the S1-X interval (fig. 7). The first two beats in normal sinus rhythm show a mid-systolic click 218 and 216 msec after the first heart sound. The click is followed by a late-systolic murmur. The following premature ventricular beat has a markedly diminished end-diastolic diameter (3.34 cm). At the time of the first heart sound the left ventricular diameter is already shorter than the click diameter and, therefore, this beat results in a holosystolic prolapse and murmur. The postextrasystolic beat shows earlier prolapse as well. In this beat, however, the
end-diastolic diameter remains unchanged and only the increase in max \( V_{CF} \) accounts for the earlier onset of prolongation.

The present study demonstrates that mitral valve prolapse occurs at a critical left ventricular chamber size. The onset of the prolapse is determined by left ventricular end-diastolic dimensions and the velocity of circumferential fiber shortening during the preprolapse period.

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