

## Prevalence and Severity of Mitral Regurgitation in the Mitral Valve Prolapse Syndrome: A Doppler Echocardiographic Study of 80 Patients

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Doppler echocardiography was performed in 80 consecutive patients (22 men, 58 women), aged  $38 \pm 16$  years, who had mitral valve prolapse diagnosed by two-dimensional echocardiography. Of the 80 patients, 16 (20%) were asymptomatic and 11 (14%) had a normal physical examination (no click or murmur). The M-mode echocardiogram was negative for mitral valve prolapse in 11 patients (14%) and equivocal or nondiagnostic in 19 patients (24%). Mitral regurgitation was evaluated using pulsed mode Doppler echocardiography and was quantified by the mapping technique as minimal or mild when a holosystolic regurgitant jet was recorded just below the mitral valve into the left atrium, and as moderate or severe when the jet was detected at the mid- or distal left atrium.

Mitral regurgitation was found in 55 (69%) of the 80 patients and it was minimal or mild in 47 patients (59%) and moderate or severe in 8 (10%). In 20 (36%) of the 55 patients with mitral regurgitation by Doppler tech-

nique, a systolic murmur was not detected and each of the 20 had only mild mitral regurgitation. Left atrial and left ventricular size were significantly smaller in patients with mild or no regurgitation as compared with the eight patients with moderate or severe regurgitation. These eight patients were all men (six over 50 years of age) who usually presented with dyspnea and a holosystolic murmur; the mitral valve prolapse was holosystolic by M-mode and involved both leaflets by two-dimensional echocardiography.

In conclusion: 1) Mitral regurgitation as assessed by Doppler echocardiography was common in patients with mitral valve prolapse, but was usually mild and not always associated with an audible murmur. 2) Significant mitral regurgitation was rare (10%) and usually occurred in men with mitral valve prolapse who were more than 50 years old.

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Mitral valve prolapse is increasingly recognized as a common cause of severe pure mitral regurgitation in patients requiring mitral valve replacement (1-3). Progression of mitral valve prolapse to spontaneous rupture of chordae tendineae and severe mitral regurgitation has been documented in several cases (2-4). In some patients, infective endocarditis may be the cause of significant mitral regurgitation or worsening of existing mild mitral regurgitation, whereas in others, progressively increasing regurgitation without chordal rupture or endocarditis can develop (3,5). The overall prevalence of mitral regurgitation in the mitral valve prolapse syndrome is not known, as most patients are

asymptomatic or mildly symptomatic and cardiac catheterization is only rarely performed. In addition, specific groups of patients with mitral valve prolapse who are prone to development of significant mitral regurgitation and may need mitral valve replacement have not been identified.

Doppler echocardiography is reliable and sensitive in detecting even mild degrees of mitral regurgitation and in semiquantifying its severity (6,7). In this prospective study, we assessed the prevalence and severity of mitral regurgitation in a large number of patients with mitral valve prolapse using Doppler echocardiography. In addition, we describe characteristic clinical and echocardiographic findings in patients with mitral valve prolapse and significant mitral regurgitation.

### Methods

**Study patients.** Eighty consecutive patients who were referred to the echocardiography laboratory by their primary

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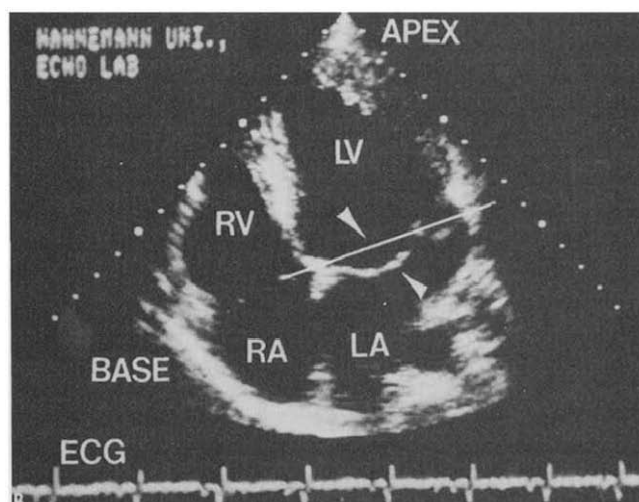
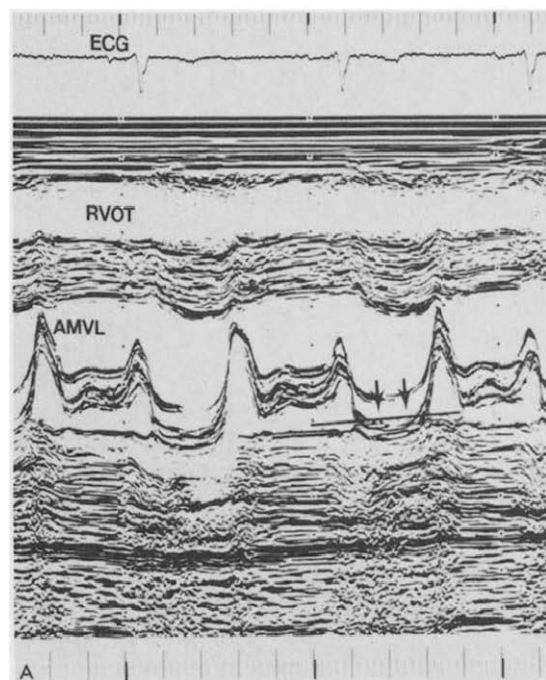
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physician because of symptoms or physical signs suggestive of mitral valve prolapse and who were confirmed to have this condition by two-dimensional echocardiography were studied. There were 22 men and 58 women, aged 15 to 79 years (mean  $\pm$  SD  $38 \pm 16$ ). These patients were referred for an echocardiographic study because of symptoms (chest pain, palpitation, shortness of breath or dizziness) or physical signs (mid- or late systolic click, late systolic murmur, or both) suggestive of mitral valve prolapse. Of these patients, only those with definite prolapse on two-dimensional echocardiography (defined as a bowing motion of the anterior or posterior mitral leaflets, or both, through the plane of the mitral valve annulus into the left atrium during systole) as agreed on by two experienced echocardiographers were included in the study (8). Patients with potential causes of secondary mitral valve prolapse, such as rheumatic mitral valve disease, atrial septal defect, coronary artery disease with prior myocardial infarction, significant pericardial effusion or cardiomyopathy were excluded. All patients were examined by two cardiologists before performance of the echocardiographic study, and the echocardiographic data were analyzed without knowledge of symptoms or physical signs.

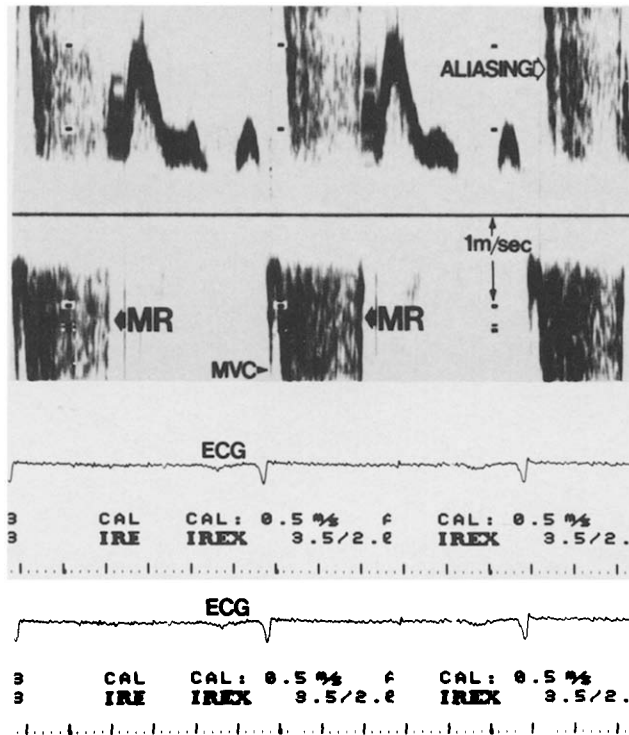
**Echocardiography.** M-mode, two-dimensional and Doppler echocardiographic studies were performed with the Irex-Meridian phased array system. Derived M-mode echocardiograms of the left atrium and left ventricle were obtained from the left parasternal window. The size of the left atrium and ventricle in end-diastole (in centimeters) was determined according to the recommendations of the American Society of Echocardiography. Mitral valve prolapse on an M-mode echocardiogram was defined as a mid- to late systolic or holosystolic displacement of one or both mitral leaflets at least 3 mm below the line joining the point of valve closure in systole and the point of valve opening in diastole (9) (Fig. 1A). The M-mode echocardiograms were classified as negative for mitral valve prolapse, and as equivocal or nondiagnostic when the two observers did not agree about the diagnosis or the findings were of borderline significance. Mitral valve prolapse was distinguished as holosystolic or late systolic. On two-dimensional echocardiography, the parasternal long-axis and apical four chamber views were used for the assessment of mitral valve prolapse (8) (Fig. 1B). The severity of prolapse as well as the involvement of one or both mitral leaflets was noted. The presence of tricuspid valve prolapse was assessed using the right ventricular inflow-outflow view or the apical four chamber view. Criteria similar to those applied to mitral valve prolapse were applied to tricuspid valve prolapse, which was defined as a posterior displacement of one or more tricuspid valve leaflets toward the right atrium in systole (8).

**Doppler echocardiography** was performed utilizing the pulsed mode technique and a 2.5 MHz simultaneous two-dimensional and Doppler imaging transducer. The sample



**Figure 1.** A, M-mode echocardiogram from a patient with mitral valve prolapse showing significant holosystolic posterior buckling of the mitral valve (**arrows**). B, Two-dimensional echocardiogram (apical four chamber view) demonstrating prolapse of both mitral valve leaflets (**arrows**). AMVL = anterior mitral valve leaflet; ECG = electrocardiogram; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; RVOT = right ventricular outflow tract.

volume of the pulsed mode was initially placed below the mitral valve in the apical four chamber view, and the presence of mitral regurgitation, defined as a clear-cut holosystolic regurgitant jet, was interrogated (Fig. 2). Semiquantitation of mitral regurgitation was attempted using the technique of mapping the regurgitant jet into the left atrium (6,7). Mitral regurgitation was defined as minimal or mild when the regurgitant spectral signal was recorded just below the mitral valve or less than 2 cm from the mitral valve into the left atrium. Significant mitral regurgitation was consid-

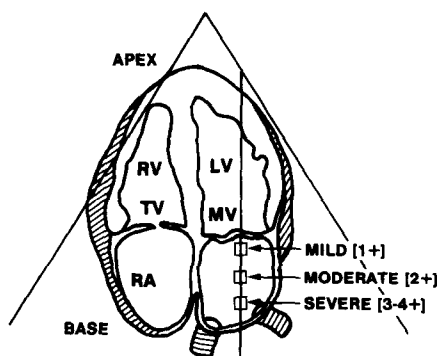


**Figure 2.** Example of mitral regurgitation (MR) spectral signal as obtained by sampling by pulsed mode Doppler technique inside the left atrium (LA). Aliasing develops because of the high velocity of the regurgitant jet. ECG = electrocardiogram; MVC = mitral valve closure.

ered to be present when the regurgitant jet was recorded in the mid- (moderate) or distal (severe) left atrial cavity (Fig. 3).

*Patients were then classified into three groups.* Group I included patients with mitral valve prolapse and no mitral regurgitation by Doppler technique; Group II, patients with insignificant (minimal or mild) mitral regurgitation; and Group

**Figure 3.** Schematic diagram of the two-dimensional apical four chamber view illustrating the mapping technique of semiquantifying mitral regurgitation by pulsed mode Doppler echocardiography. The sampling sites inside the left atrium and the corresponding degree of mitral regurgitation are shown (arrows). MV = mitral valve; TV = tricuspid valve; other abbreviations as in Figure 1.



III, patients with significant (moderate or severe) mitral regurgitation. Tricuspid regurgitation was quantified by pulsed mode Doppler technique in a similar fashion, utilizing the apical four chamber view and mapping of the regurgitant jet into the right atrial cavity (7,10).

**Statistical analysis.** All measurements in the text and tables are expressed as mean  $\pm$  SD or range. Linear regression analysis was used for the correlation between left atrial and left ventricular size by M-mode echocardiography, and the severity of mitral regurgitation by Doppler echocardiography. Comparison among the three groups of patients for different clinical and echocardiographic features was carried out with analysis of variance using Tukey's or Bonferroni's *t* test correction for multiple *t* testing and the chi-square test where appropriate. A probability (*p*) value of less than 0.05 is considered statistically significant.

## Results

**Symptoms (Table 1).** Of the 80 patients, 16 (20%) were asymptomatic. The most frequent complaints of the other patients included chest pain (43 patients), shortness of breath (28 patients), palpitation (22 patients) and dizziness or near-syncope (12 patients); 33 patients (41%) complained of more than one symptom. Palpitation was more common in women than men. Otherwise, symptoms were not significantly different in men and women and in patients over or under 50 years old.

**Physical examination.** Examination was negative (no systolic click or murmur) by both examiners in 11 (14%) of 80 patients. A mid- or late systolic click was present in 38 (47%) and a late systolic or holosystolic murmur in 43 (54%) of the patients; 17 patients (21%) had both a systolic click and murmur, as agreed on by the two examiners. They also agreed about the presence or absence of a click in 68 (85%) of the patients and about the presence or absence of a systolic murmur in 69 (86%). During the time of the echocardiographic studies, only 2 (3%) of the 80 patients had atrial fibrillation; all others had normal sinus rhythm.

**M-mode echocardiography.** The recording was negative for mitral valve prolapse in 11 (14%) and equivocal or nondiagnostic in 19 (24%) of the 80 patients. Of the remaining 50 patients with an M-mode echocardiogram diagnostic for mitral valve prolapse, 25 had holosystolic and 25 had late systolic prolapse. The type of mitral valve prolapse diagnosed by M-mode technique (holosystolic or late systolic) was not associated with any particular symptom or physical sign. Left atrial size measured  $3.4 \pm 0.7$  cm (range 2.5 to 5.8) and left ventricular size in end-diastole measured  $4.7 \pm 0.6$  cm (range 3.5 to 6.8).

**Two-dimensional echocardiography.** Mitral valve prolapse was detected in all 80 patients by two-dimensional echocardiography. Prolapse of both anterior and posterior mitral leaflets in any of the views used was seen in 35 patients (44%); in the remaining 45, only the anterior leaflet

**Table 1.** Comparison Among Patients With Mitral Valve Prolapse and No Mitral Regurgitation (Group I), Mild (Group II) and Significant (Group III) Mitral Regurgitation by Doppler Echocardiography for Various Clinical and Echocardiographic Variables

	All Patients	Group I (no MR)	Group II (mild MR)	Group III (significant MR)
Number of patients	80	25	47	8
Age (yr)	38 ± 16	30 ± 12	40 ± 14†	51 ± 22
Men/women	22/58	6/19	8/39	8/0*
Symptoms				
None	16	5	11	0
Chest pain	43	18	22	3
Palpitation	22	9	12	1
SOB	28	9	13	6*
Dizziness	12	2	8	2
Physical examination (agreed by both examiners)				
Negative	11	4	7	0
Click	38	10	27	1*
Systolic murmur	43	8	27	8*
Both	17	1	15	1
Atrial fibrillation	2	0	0	2
M-mode echocardiogram				
Negative	11	3	8	0
Equivocal or nondiagnostic	19	7	12	0
Holosystolic MVP	25	7	12	6
Late systolic MVP	25	8	15	2
LA size (cm)	3.4 ± 0.7	3.2 ± 0.6	3.4 ± 0.4	4.6 ± 1.0*
LV size (end-diastolic) (cm)	4.7 ± 0.6	4.6 ± 0.4	4.6 ± 0.6	5.7 ± 0.8*
2D echocardiogram				
MVP				
Both leaflets	35	7	20	8*
Anterior leaflet	45	18	27	0*
View				
Apical four chamber	24	7	17	0
Parasternal long-axis	5	2	3	0
Both	51	16	27	8*
TVP	7	2	3	2

\*p < 0.05 vs. Groups I and II; †p < 0.05 vs. Group I. LA = left atrial; LV = left ventricular; MR = mitral regurgitation; MVP = mitral valve prolapse; SOB = shortness of breath; TVP = tricuspid valve prolapse; 2D = two-dimensional.

was involved. The diagnosis of mitral valve prolapse was made in the apical four chamber view in 24 patients, in the parasternal long-axis view in 5 and in both views in 51 (64%) of the 80 patients. Tricuspid valve prolapse, usually of mild degree, was observed in 7 (9%) of the 80 patients.

**Doppler echocardiography.** Mitral regurgitation was found by pulsed mode Doppler technique in 55 (69%) of the 80 patients; it was minimal or mild in 47 patients (59%) and moderate or severe in 8 (10%). A systolic murmur was heard on auscultation in 8 (32%) of the 25 patients with no mitral regurgitation by Doppler technique. It was not detected in 20 (36%) of the 55 patients with mitral regurgitation by Doppler technique, and all 20 had only minimal or mild regurgitation. There was a weak but statistically significant correlation ( $p = 0.0001$ ) between the severity of mitral regurgitation by Doppler study and left ventricular

( $r = 0.43$ ) and left atrial size ( $r = 0.59$ ) by M-mode echocardiography. Overall, men and patients more than 50 years old had a larger left atrial and left ventricular size and higher degrees of mitral regurgitation by Doppler technique than did women and patients less than 50 years old.

**Patients with significant mitral regurgitation.** The clinical and echocardiographic characteristics of the three groups of patients with mitral valve prolapse and 1) no mitral regurgitation, 2) insignificant (minimal or mild) regurgitation, and 3) significant (moderate or severe) regurgitation are shown in Table 1. Compared with the other two groups, the eight patients with significant mitral regurgitation by Doppler study (Group III) were older, with a mean age of  $51 \pm 22$  years (five were over 50 years) and all were men. They most commonly presented with shortness of breath and they all had a holosystolic grade 3 to 4/6 murmur; a definite mid-systolic click was detected in only one of them.

By M-mode echocardiography, six of the eight patients had holosystolic mitral valve prolapse, and the left atrium and ventricle were significantly larger than in the other two groups of patients. On two-dimensional echocardiography, severe prolapse of both mitral leaflets was seen in both the apical four chamber and parasternal long-axis views in all eight patients, and tricuspid valve prolapse was present in two of them. A flail mitral valve, however, was not evident by M-mode or two-dimensional echocardiography in any patient. Because the degree of mitral regurgitation by Doppler echocardiography was considered to be only moderate in five of the eight patients, and as most of them were only mildly symptomatic (New York Heart Association functional class II), cardiac catheterization and subsequent mitral valve replacement were required in only two patients who were more symptomatic and had severe (3 to 4+) mitral regurgitation by left ventriculography. The mitral valve appeared myxomatous during surgery in both patients; in one of them, a flail mitral valve due to ruptured chordae tendineae was found. The other six patients are being managed medically (Table 2).

### Discussion

#### Diagnostic standard for mitral valve prolapse.

Establishing the diagnosis of mitral valve prolapse is often difficult and at times confusing, because no diagnostic standard for this entity is available. Many physicians will consider this diagnosis in a patient with a mid- or late systolic nonejection click with or without a late systolic murmur, regardless of the patient's symptoms (11). Others (8) will accept the echocardiographic diagnosis of mitral valve prolapse by M-mode or, preferably, by two-dimensional echocardiography. Negative M-mode studies have been reported in 8 to 25% of patients with two-dimensional echocardi-

grams diagnostic for mitral valve prolapse (8). In our study, we used derived M-mode echocardiograms, and found negative studies in 14% and equivocal or nondiagnostic studies in 24% of the patients. Using a combination of echocardiographic signs, a high sensitivity and specificity of M-mode and two-dimensional echocardiography have been reported (12) in diagnosing mitral valve prolapse when the physical findings were considered as the diagnostic standard. An isolated click, however, is not uncommon in normal subjects and in a significant percent of patients it is caused by entities other than mitral valve prolapse (11). In addition, patients with an echocardiographic diagnosis of mitral valve prolapse may have an entirely normal physical examination (13,14). In the general population sample included in the Framingham study (13), only 9% of the patients with mitral valve prolapse by M-mode echocardiography had a systolic click or murmur on auscultation. Other investigators (14) found a 17% incidence of normal cardiac examination in patients with echocardiographic mitral valve prolapse. In our study, 20% of patients had a normal physical examination despite the presence of prolapse by two-dimensional echocardiography. On the other hand, the echocardiographic criteria for the diagnosis of mitral valve prolapse are not uniform, are subject to a significant inter- and intraobserver variability and can be affected by transducer position and angulation. Thus, the diagnosis of mitral valve prolapse may be difficult, particularly in borderline or mild cases (15).

In our study of 80 consecutive patients referred to the echocardiographic laboratory by their primary physician because of physical findings (systolic click or murmur) or symptoms suggestive of mitral valve prolapse, we included only patients with a definite diagnosis of prolapse by two-dimensional echocardiography. The diagnosis was agreed on by two experienced echocardiographers (Fig. 1B). Only two patients, not included in this study, had physical find-

**Table 2.** Clinical and Echocardiographic Findings in Eight Male Patients With Mitral Valve Prolapse and Significant Mitral Regurgitation by Doppler Echocardiography

Case	Age (yr)	Symptoms	NYHA Class	Physical Examination			MVP	M-Mode		2D Echo		Doppler		Cath.	Outcome
				Click	Holosyst Murmur	Rhythm		LA Size	LV Size	MVP	TVP	MR	TR		
1	54	SOB	II	-	+	NSR	Holosyst	3.9	5.2	Both	-	Mod	-	ND	Med Rx
2	65	CP	II	+	+	NSR	Late syst	4.7	6.1	Both	-	Mod	-	ND	Med Rx
3	18	CP, SOB	II	-	+	NSR	Holosyst	5.3	6.8	Both	-	Mod	-	ND	Med Rx
4	18	Syncope	I	-	+	NSR	Holosyst	3.0	4.8	Both	-	Mod	-	ND	Med Rx
5	79	SOB	III	-	+	AF	Holosyst	5.7	5.0	Both	+	Sev	Mild	ND	Med Rx
6	64	SOB	II	-	+	NSR	Holosyst	4.0	5.0	Both	-	Mod	-	ND	Med Rx
7	59	SOB	III	-	+	AF	Holosyst	5.8	6.8	Both	+	Sev	Mild	3 to 4+ MR	MVR
8	54	SOB, CP	III	-	+	NSR	Late syst	4.5	5.8	Both	-	Sev	-	3+MR	MVR

AF = atrial fibrillation; Cath. = cardiac catheterization; CP = chest pain; Holosyst = holosystolic; Med Rx = medical treatment; Mod = moderate; MVR = mitral valve replacement; ND = not done; NSR = normal sinus rhythm; NYHA Class = New York Heart Association functional class; Sev = severe; Syst = systolic; TR = tricuspid regurgitation; 2D Echo = two-dimensional echocardiogram; + = present; - = absent, other abbreviations as in Table 1.

ings (systolic click and murmur) suggestive of mitral valve prolapse but a negative two-dimensional echocardiogram.

**Mitral regurgitation in mitral valve prolapse.** The late systolic murmur in mitral valve prolapse is probably due to mitral regurgitation and is usually associated with a systolic click. The exact prevalence and severity of mitral regurgitation, however, as well as the specific groups of patients with mitral valve prolapse who may develop significant mitral regurgitation, are not known. A high prevalence rate (50 to 65%) of mitral regurgitation by angiography has been reported in a select population of patients with mitral valve prolapse (14). Most patients with this syndrome, however, are asymptomatic or mildly symptomatic and rarely require invasive studies.

An abnormal mid- to late systolic flow signal was found by Doppler echocardiography in a significant percent of patients with mitral valve prolapse, most of whom did not have clinical or angiographic evidence of mitral regurgitation (16). On the other hand, an early systolic backward flow coinciding with the mitral valve closure signal and not exceeding the first half of systole has been observed in normal persons. The prevalence of mitral regurgitation by Doppler echocardiography in apparently normal individuals may increase with advancing age (17). The presence of a more prolonged holosystolic regurgitant flow signal was required in our study to define mitral regurgitation by Doppler technique. Using a semiquantitative technique of mapping the regurgitant jet into the left atrium, mitral regurgitation was classified as mild, moderate or severe (6,7) (Fig. 3). Mitral regurgitation was found in 55 (69%) of the 80 patients with mitral valve prolapse; it was minimal or mild in 47 (59%) and moderate or severe in 8 (10%). A systolic murmur of mitral regurgitation was not detected in 20 (36%) of the 55 patients with evidence of mitral regurgitation by Doppler echocardiography and all 20 had only minimal or mild regurgitation. On the other hand, in eight patients with a systolic murmur on auscultation, mitral regurgitation was not detected.

All eight patients in our study with mitral valve prolapse and significant mitral regurgitation were men, and six of them were more than 50 years old (18). Common characteristics in these patients included clinical presentation with shortness of breath, a holosystolic grade 3 to 4/6 murmur (without click) and holosystolic mitral valve prolapse by M-mode and severe prolapse of both leaflets by two-dimensional echocardiography (Table 1). The left atrium and ventricle were significantly larger in these eight patients. Most of them, however, were only mildly symptomatic (functional class II) and only two required mitral valve replacement (Table 2). Although a flail mitral valve was not found by echocardiography in any of them, it was present at surgery in one patient. In contrast to previous pathologic, angiographic and echocardiographic studies which found tricuspid valve prolapse in 21 to 52% of patients with mitral

valve prolapse (8), we found only seven such patients (8%) by two-dimensional echocardiography, and two of them had significant mitral regurgitation by Doppler study. Tricuspid regurgitation, usually minimal or mild, was detected in five of these seven patients. Using contrast echocardiography, Morganroth et al. (8) reported a 40% incidence of tricuspid regurgitation in patients with tricuspid valve prolapse.

Our findings are in agreement with previous studies (2,3,5,18,19) which report that older men with mitral valve prolapse develop severe mitral regurgitation requiring mitral valve replacement more often than women. Epidemiologic studies (20) show that the prevalence of mitral valve prolapse in women decreases progressively with advancing age from 17% in those between 20 and 30 years old to less than 2% in those over 70 years old. In contrast, the prevalence in men is similar in all age groups and ranges between 2 and 4.4%. It has been proposed that the usually clinically silent echocardiographic prolapse in young women may be a different entity from the severe prolapse of older men which often leads to severe mitral regurgitation and mitral valve replacement (21). Severe mitral regurgitation in the mitral valve prolapse syndrome may result from spontaneous rupture of the chordae tendineae, or from endocarditis, but is relatively rare (22,23). In some patients, however, progressive mitral regurgitation without chordal rupture may occur. The mechanism of the development and progression of mitral regurgitation in these patients is unknown, but it may relate to further redundancy of myxomatous cusps exposed to left ventricular pressure and gradual dilation of the mitral anulus with advancing age (24). Chronic unbalanced stress on the valve tension and closure apparatus resulting in degeneration of the connective tissues and insufficient chordal support, especially in older patients, may lead to significant mitral regurgitation and eventual rupture of chordae tendineae (25.) Papillary muscle dysfunction, probably caused by the chronic and chaotic chordal "tugging" of floppy leaflets, may be another contributing factor (26). Other associated conditions more prevalent in older patients, such as coronary artery disease and mitral anular calcification, may also contribute to disturbed function of the mitral valve apparatus, but were not evident in any of our patients.

**Clinical implications.** Our study group included patients who were referred to the echocardiography laboratory by their primary physicians because of symptoms or clinical signs suggestive of mitral valve prolapse and were found to have definite prolapse by two-dimensional echocardiography. Such a group may not be representative of the larger number of individuals with mitral valve prolapse detected by screening a general population (24). Mitral regurgitation by Doppler echocardiography was a common finding in our study patients, but it was usually mild, and in about one-third of them it was not associated with a systolic murmur. In our series, significant mitral regurgitation was rare (10%)

and usually occurred in men with mitral valve prolapse who were more than 50 years old. Although only two of these patients required mitral valve replacement, patients with mitral valve prolapse and significant mitral regurgitation by Doppler echocardiography should be followed up more closely. Previous studies (27,28) have suggested that individuals with mitral valve prolapse and evidence of mitral regurgitation are at higher risk of developing complex atrial and ventricular arrhythmias. In regard to endocarditis prophylaxis, most authorities recommend limiting its application to patients with mitral valve prolapse associated with a definite audible systolic murmur on auscultation (29-32). Whether patients with mitral valve prolapse not associated with an audible murmur but with evidence of mitral regurgitation by Doppler echocardiography should be given antibiotic prophylaxis before dental or surgical procedures remains to be determined.

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