Long-Term Follow-Up of Idiopathic Mitral Valve Prolapse in 300 Patients: A Prospective Study

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A prospective long-term follow-up study was made of 300 patients with *idiopathic* mitral valve prolapse, diagnosed by clinical, cineangiographic and echocardiographic criteria. There were 136 male and 164 female patients, ranging in age from 10 to 87 years (mean 42.2). The study included all patients with primary mitral valve prolapse, irrespective of clinical condition at the onset, and excluded only those patients with "secondary" mitral valve prolapse attributable to an accompanying established disorder. The average follow-up period was 6.1 years (range 6 months to 20 years).

Two patients died of a noncardiac cause. The clinical condition of 153 patients remained stable. In 27 patients a supraventricular tachycardia occurred that was readily controlled with medication and caused no serious clinical complications. In 20 patients signs of mitral regurgitation appeared, but the patients remained clinically asymptomatic.

Serious complications developed in 100 patients. Sudden death, most likely due to ventricular fibrillation, occurred in three patients; documented ventricular fibrillation was seen in two. Ventricular tachycardia developed in 56 patients, but in all instances the rhythm disorder was managed effectively and durably with medication. Infective endocarditis occurred in 18 patients, 4 of whom died during treatment and 6 of whom needed mitral valve replacement. The remaining eight patients suffer from severe mitral regurgitation that will require surgery in the near future. Twenty-eight patients underwent mitral valve operation because of progressive regurgitation. Cerebrovascular accidents occurred in 11 patients, but lifelong treatment with coumarin derivatives or antiplatelet aggregation agents was not considered necessary.

Because all patients had been referred to a cardiology center for further evaluation, the results may be biased and do not necessarily represent the natural history of mitral valve prolapse in the general population. Nevertheless, for this particular subset, the results strongly suggest that *idiopathic* mitral valve prolapse is not a benign disorder.

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The long-term prognosis of patients with idiopathic mitral valve prolapse is generally considered favorable, but a critical survey of published data reveals that this conclusion is less well founded than might be expected. In fact, almost all communications that deal specifically with the follow-up of patients with mitral valve prolapse either have included a heterogeneous patient population or have appeared in abstract form only, lacking the necessary details (1–7). Two reports (8,9) that we are aware of document a benign nature of mitral valve prolapse. One of these (8) relates specifically to children and young adults. The second report (9) docu-

ments the long-term prognosis for patients with mitral valve prolapse diagnosed by echocardiography and defines a high risk group on the basis of echocardiographic criteria.

The present study documents the long-term prognosis of 300 patients with idiopathic mitral valve prolapse, all referred to a cardiology center, in an attempt to contribute to a better understanding of the natural history of the condition and, hence, its clinical management.

Methods

Study patients. From April 1963 through April 1983, 300 patients were seen with idiopathic mitral valve prolapse. There were 164 female and 136 male patients, ranging in age between 10 and 87 years (average 42.2). The diagnosis was made on the basis of cineangiographic or echocardiographic criteria, or both. Patients with mitral valve prolapse were excluded from the study if they had a history of rheumatic

fever, ischemic heart disease, perimyocarditis, primary or secondary cardiomyopathy, congenital heart defect, right ventricular dysplasia, Marfan's syndrome, hypertension, cardiac trauma, increased QT interval or electrocardiographic (ECG) signs of pre-excitation. All patients underwent a general physical examination, a 12 lead ECG study at rest and after exercise, continuous Holter ECG monitoring for a period of 24 h (or longer when deemed necessary) and a roentgenographic study.

The average follow-up period for these 300 patients was 6.1 years (range 6 months to 20 years). The severity of complaints or symptoms determined whether or not the patients were seen in the outpatient clinics at intervals of 3, 6 or 12 months. Each patient was seen once yearly by one of us (D.R.D), whether or not the patient had initially been referred from another hospital.

Causes for referral. Patient complaint was the main reason for referral in 197 (65%) of the 300 patients. The symptoms varied considerably and some patients had more than one complaint. Chest pain was the most common condition, occurring in 124 patients (62.9%). Other reasons for referral were palpitation (99 patients), dyspnea (69 patients), fatigue (80 patients), dizziness (34 patients), syncope (31 patients) and cerebrovascular accident (11 patients). In the remaining patients reasons for referral included, among others, unusual auscultatory findings, ECG abnormalities and an abnormal chest roentgenogram.

Physical examination. Of the 300 patients, 124 had a late systolic click, 97 had a late systolic click together with a late systolic murmur and 10 had a pansystolic murmur with a late systolic click. Sixty-nine patients had no click. Forty-three of these patients had a pansystolic murmur and 26 had a late systolic murmur. In each patient the characteristic of the murmur was confirmed by phonocardiography.

In 127 of the 300 patients, the diagnosis of mitral valve prolapse was first established by cineangiography (10,11), either because echocardiography was not yet available as a routine procedure or because the echocardiographic diagnosis was made but it was believed justifiable at the time to have the diagnosis confirmed by angiocardiography. All underwent left and right heart catheterization with cineangiography.

In all 300 patients the diagnosis of mitral valve prolapse was confirmed by echocardiography (12–15). A late or pansystolic movement >2 mm below the line of coaptation of the mitral valve leaflets during systole (the CD line) was considered diagnostic. Two-dimensional scans, in both the apical four chamber and long-axis views, were considered diagnostic when during systole one or both valve leaflets bulged into the left atrium beyond the plane of the mitral valve ring.

Between 1963 and 1973 the diagnosis of mitral valve prolapse was made in all patients on the basis of cineangiography alone. In all of these patients the diagnosis was

Table 1. Long-Term Follow-Up of 300 Patients With Idiopathic Mitral Valve Prolapse*

Noncardiac death	2
(1 with previous ventricular tachycardia)	
(1 in stable condition)	
Without serious complications	
Stable clinical condition	153
Change in auscultation	20
(clinically insignificant mitral regurgitation)	
Supraventricular tachycardia	27
(clinically without complications)	
With serious complications	
Sudden death	3
Ventricular fibrillation	2
Ventricular tachycardia	56
(4 developed endocarditis)	
(1 died of cause unrelated to mitral valve prolapse)	
(7 were operated on because of progressive mitral regurgitation)	
Endocarditis of mitral valve	18
(6 were operated on)	
Mitral valve operation	28
(6 after endocarditis)	
(7 had a previous history of ventricular tachycardia)	
Cerebrovascular accident	11

*Nineteen patients were classified in more than one category.

confirmed at a later stage by echocardiography. From 1973 to 1978 the diagnosis was based on M-mode echocardiography alone, and from 1978 on each patient was also studied with two-dimensional echocardiography. In all patients whose diagnosis initially was based solely on M-mode echocardiography, two-dimensional echocardiography at a later stage confirmed the diagnosis.

Results

On the basis of the follow-up findings in these 300 patients, two main groups were identified, those without and those with serious complications (Table 1).

During the follow-up period two patients died of a noncardiac cause. One patient was in a stable cardiac condition, but died of disseminated bronchial carcinoma. One patient died of staphylococcal pneumonia complicating Guillain-Barré disease; this patient previously had ventricular tachycardia that responded well to medication.

Patients Without Serious Complications

During the follow-up period the clinical cardiac condition of 153 of the 300 patients remained stable (Table 1).

Murmur of mitral regurgitation. In another 20 patients a change, indicative of mitral regurgitation appeared on auscultation. A late systolic murmur developed in 14 patients whose initial examination had revealed only a late systolic
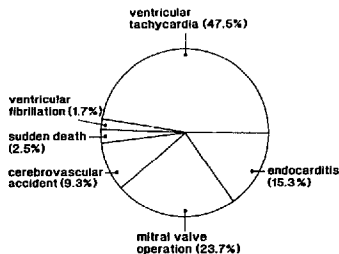
Figure 1. Percent distribution of 118 serious complications in 100 of 300 patients with idiopathic mitral valve prolapse.

click. The other six patients developed a pansystolic murmur, although initially a click and late systolic murmur were present. Further investigations in these 20 patients revealed no abnormalities other than a slight increase in diameter of the left atrium as determined echocardiographically. One may argue that these patients should be considered to have had a serious complication, but throughout the study their cardiac condition remained stable and further aggravation of their mitral regurgitation did not occur. For these reasons they were included in the group without serious complications.

Supraventricular tachycardia. This arrhythmia occurred in 27 of the 300 patients. The arrhythmia responded well to a beta-receptor blocker (10 patients) or verapamil (17 patients). Six patients had a recurrence of their supraventricular tachycardia, but in each a higher dose of medication abolished this complication. There were no serious complications such as presyncope, syncope or pulmonary congestion among these patients. One patient eventually died of the complications of Guillain-Barré disease.

Patients With Serious Complications

Of the 300 patients, 100 developed a serious complication. Because 19 patients had more than one such complication, the total number of major complications was 118 (Table 1). The percent distribution of the 118 complications among these 100 patients is shown in Figure 1.

Sudden death. Three patients died suddenly: two men, 27 and 70 years of age, respectively, and one woman, 53 years of age. The 27 year old patient suddenly and unexpectedly collapsed as a result of ventricular fibrillation. After successful defibrillation he was referred to our unit. Extensive examinations revealed a late systolic click and mitral valve

prolapse. A 24 h Holter ECG recording revealed short episodes of ventricular tachycardia. The coronary angiogram was normal. The patient was treated with alprenolol and diphenylhydantoin. Repeated Holter monitoring showed no further ventricular tachycardia. He died suddenly 6 months after the initial episode. In retrospect, it appeared that he had not taken his medication for weeks. There was no autopsy.

In the second patient to die suddenly, the 53 year old woman, the diagnosis of mitral valve prolapse with mild regurgitation was established in 1963 at age 36. In 1973 the late systolic murmur, preceded by a click, had changed to a pansystolic murmur. In 1980 the patient complained of fatigue and episodes of tachycardia. Cardiac catheterization revealed mitral valve prolapse with severe regurgitation but normal pressures at rest and during exercise. The coronary angiogram was normal. The 24 h Holter ECG recording showed frequent ventricular premature beats. Before medication could be started the patient died suddenly, there was no autopsy.

The third patient, the 70 year old man, was known to have had isolated mitral valve prolapse and regurgitation for 12 years. He was admitted with complaints of dyspnea. Echocardiography revealed mitral valve prolapse with dilation of both the left atrium and the left ventricle. He was treated with diuretics with an initial good result. Two years later he died suddenly; there was no autopsy.

Ventricular fibrillation. This arrhythmia was recorded in two patients. The first patient, who died suddenly, was discussed earlier. The second patient was a 34 year old man who underwent successful defibrillation. Extensive investigations revealed mitral valve prolapse, without mitral regurgitation, and paroxysmal ventricular tachycardia. The patient was treated with alprenolol and diphenylhydantoin, and, during a period of 12 years, had no further episodes of serious ventricular tachycardia, although short runs of clinically asymptomatic ventricular tachycardia were occasionally detected on follow-up Holter recordings. Over the years, however, moderate mitral regurgitation gradually developed, at present, the patient is still in stable condition.

Ventricular tachycardia. Ventricular tachycardia, defined as three or more premature ventricular complexes in sequence with a heart rate of 140 to 200 beats/min (16), was detected among 56 patients; in 42 of these, the duration of the tachycardia was >10 s. Forty-eight patients were treated successfully with alprenolol, with or without diphenylhydantoin. The remaining eight patients needed a different antiarrhythmic medication.

Although the ventricular tachycardia was well controlled, other complications of the prolapsing mitral valve occurred in 11 of these 56 patients. Progressive mitral regurgitation eventually necessitated surgery in seven patients and mitral valve endocarditis developed in four. One patient died of bronchial carcinoma while in a stable condition.
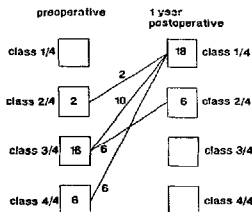
Figure 2. Preoperative and 1 year postoperative functional class (New York Heart Association) of 24 patients who survived mitral valve surgery.

Endocarditis. Twenty-four episodes of infectious endocarditis of the mitral valve were recorded among 18 patients; in the vast majority, the endocarditis was caused by *Streptococcus viridans*. In seven patients it developed after a dental procedure performed without antibiotic prophylaxis. Four patients died during treatment for their infection and six patients needed valve replacement; in these 10 patients the diagnosis "floppy mitral valve" was confirmed. The remaining eight patients all suffer from severe mitral regurgitation.

Mitral valve operation. Twenty-eight patients were operated on because of hemodynamically significant mitral valve regurgitation with left heart failure. Six of them needed surgery because of previous mitral valve endocarditis. There were 17 men, aged 36 to 66 years (average 49.3), and 11 women, aged 33 to 70 years (average 58.8). In 15 patients the mitral valve was replaced by a mechanical prosthesis. Two patients received a bioprosthesis and 11 patients underwent a reconstructive procedure. The diagnosis of floppy mitral valve was confirmed at operation and at pathologic examination. Chordal rupture was present in all resected valves.

Four patients died of cardiogenic shock during the postoperative stage. The remaining 24 patients showed good improvement in their clinical condition (Fig. 2). The follow-up period of these patients was between 6 months and 9 years (average 4.5 years). During this period, two patients died. One patient succumbed to progressive left heart failure and one patient, with a mechanical valve prosthesis, died of cerebrovascular complications.

Cerebrovascular accidents. A cerebrovascular accident occurred among 11 patients, 7 female and 4 male, ranging in age between 23 and 62 years (average 40). None of these patients had apparent coagulation disorders or paroxysmal atrial fibrillation. None of the women used oral contraceptives.

In six patients the diagnosis of encephalomalacia was made and considered to be caused by cerebral emboli. These

patients were treated with coumarin derivatives. The remaining five patients presented with recurrent transient ischemic attacks. These patients were treated with antiplatelet aggregation drugs. In each of the 11 patients the medication was stopped after approximately 1 year. During the subsequent follow-up period of 2 to 6 years (average 3) all patients remained free of symptoms.

Discussion

The present study documents the long-term follow-up of 300 patients with idiopathic mitral valve prolapse. There were only two patients who died of a cause unrelated to mitral valve prolapse. It appears that 200 of the 300 patients stayed well during the follow-up period and developed no severe complications. This finding may be interpreted as supporting the generally quoted view that the natural history of mitral valve prolapse is basically benign. A close survey of published studies, however, reveals that this conclusion is not necessarily supported by data. Several studies have included patients with congenital and acquired cardiac malformations (1,6,7,17–19), and others have included patients who, during follow-up, appeared to have no mitral valve prolapse (17,20). A number of reports (2–5,17), moreover, have appeared only in abstract form, but as far as we are aware have not been published in full in the international literature.

Comparison with previous studies. To our knowledge, there are two studies (8,9) that justify conclusions regarding the natural history of mitral valve prolapse. Bisset et al. (8) documented a favorable course in 119 children and young adults, ranging in age from 2.5 to 22.2 years, with a mean follow-up interval of 6.9 years. They concluded that mitral valve prolapse has a benign nature. Their findings, however, may be biased by the young age of their patients; a consideration based on the fact that not a single patient was observed with progression of mitral valve regurgitation and sudden death. In our experience and that of others, this is most unusual. Nishimura et al. (9) recently reported the long-term follow-up (mean 6.2 years) of 237 patients with mitral valve prolapse documented by echocardiography. They found a low incidence rate (4.2%) of complications and concluded that the natural history is benign. However, they studied only patients who were minimally symptomatic or asymptomatic. In other words, they excluded from study all patients who at the onset already had severe mitral regurgitation, either class III or IV according to the criteria of the New York Heart Association, or signified by a markedly enlarged left ventricle with a diastolic dimension >70 mm. They also excluded patients >70 years of age. These exclusion criteria may have had a significant effect on the eventual outcome.

The present study included all patients with idiopathic mitral valve prolapse, irrespective of initial clinical presen-

tation. In other words, patients were excluded only because of abnormalities known to cause secondary mitral valve prolapse. All patients had abnormal auscultatory findings, represented either by a click or by a late or pansystolic murmur with or without a click. This implies that no patients were studied with so-called silent mitral valve prolapse. On the basis of our own experience we question whether silent mitral valve prolapse, known also as "echo only" mitral valve prolapse (21), has true clinical significance. In the series of Nishimura et al. (9), 20 patients were in this category and none presented any complications over the follow-up period.

On the other hand, all patients in our study were seen in a cardiology referral center. Hence, our findings in this selected group of individuals do not necessarily describe the natural history of mitral valve prolapse as it may occur in the general population.

Complications. Although 200 patients showed no complications during the follow-up period, the remaining 100 patients had serious effects (Fig. 1). Three patients died suddenly, that is, within 1 h after onset of the acute episode. Ventricular fibrillation is considered the most likely cause of death in these patients, one of whom had previously undergone successful defibrillation after a previous episode of this arrhythmia. The ECG was normal in one patient and in the other two patients it showed nonspecific ST-T wave abnormalities in the anterolateral and inferior leads, respectively. There were no differences in the ECG patterns between patients who developed serious complications and those who did not. The low incidence of sudden death among patients with idiopathic mitral valve prolapse is in accordance with the findings of other investigators (9,20,22-25).

Previous reports (25-29) often cite life-threatening ventricular tachycardia as a complication of mitral valve prolapse. The present study confirms the high incidence of rhythm disorders. In our experience, however, even serious ventricular tachycardia can be effectively and durably treated with a beta-receptor blocker, alone or in combination with diphenylhydantoin. All patients with documented ventricular tachycardia were taking medication and none of them died in the follow-up period.

Infective endocarditis occurred in 18 of the 300 patients, a relatively high incidence. This is particularly unexpected because previous reports (2,5,9,23,30,31) usually refer to endocarditis as a rare complication in patients with mitral valve prolapse. Our findings seem to support those obtained by Mills et al. (20). The significance of this complication is emphasized by the fact that 4 of the 18 patients with infective endocarditis eventually died and another 6 patients needed mitral valve replacement. The remaining eight patients, all of whom are currently "bacterially healed," suffer from severe mitral regurgitation that undoubtedly will necessitate mitral valve replacement in the near future.

Mitral regurgitation appeared to be a major problem among patients with idiopathic mitral valve prolapse. One could argue that this finding is inherent in the inclusion criteria because a high percentage of patients manifested mitral regurgitation when first seen. In fact, on entry into the study 123 patients (40.9%) had a late systolic murmur and only 53 (17.6%) had a pansystolic murmur. The latter group should be considered as presenting with clinically important regurgitation, a conclusion supported also by the fact that 226 patients (75.3%) when first seen had a normal-sized heart in anteroposterior and oblique projections on chest X-ray film. Nevertheless, the presence of mitral regurgitation of even minimal degree at the onset of this follow-up study may have promoted mitral regurgitation as a frequent and serious complication.

It is worthwhile to reiterate that 20 of the 200 patients *without* serious complications developed signs of mitral regurgitation during the follow-up period although they were clinically asymptomatic. The findings suggest that the development of symptomatic mitral regurgitation appears to be a matter of time. This conclusion is deduced from the history of the patients and the age distribution of those who eventually needed operation. Pathologic studies in these patients revealed a "floppy valve" with ruptured chordae (32).

It has been suggested that patients with idiopathic mitral valve prolapse are at risk of having a cerebrovascular accident (33-37). This complication affected 11 patients. In none of these patients could the cause of the cerebral complication be established with certainty. Thrombi originating at the angle between the mitral valve and the left atrium have been suspected (22), but there are no conclusive data in our study to substantiate this hypothesis. At present, it remains uncertain whether there is a direct relation between idiopathic mitral valve prolapse and cerebrovascular accidents. The present study suggests that long-term treatment with coumarin derivatives or antiplatelet aggregation agents is not justified, but further experience with a larger number of patients is mandatory to substantiate this important facet.

Mitral valve prolapse: a benign condition? Because 100 of the 300 patients with idiopathic mitral valve prolapse presented some form of serious complication during the follow-up period, we do not consider this condition benign. Our difference of opinion with other investigators may relate to factors such as criteria for inclusion and, in particular, criteria for exclusion. In the series documented by Nishimura et al. (9), for instance, patients with severe mitral regurgitation or enlarged left ventricular dimensions on admission were not included in the follow-up study. The authors correctly point out that their study applies only to patients who are minimally symptomatic or asymptomatic. Hence, their conclusion that mitral valve prolapse is a benign condition cannot be applied in a general sense.

Moreover, all full-length studies that we are aware of have been retrospective rather than prospective. This is one reason that they have often included patients who eventually

appear to have conditions affecting mitral valve function other than idiopathic mitral valve prolapse. Our series is the first prospective study to include all patients with mitral valve prolapse, except those with secondary prolapse and—by necessity—those with silent mitral valve prolapse.

The present study is based on individuals with mitral valve prolapse who for one or another reason were referred to a cardiology center, and our results should be considered carefully from this standpoint. As mentioned previously, the relatively high incidence of patients who first presented with a murmur consistent with mitral regurgitation may have had a negative effect on the final outcome. Therefore, the conclusions reached in our study, like those in previous studies, also cannot be applied in a general sense. The physician responsible for the welfare of a patient with idiopathic mitral valve prolapse should, once this diagnosis is firmly established, be aware that the clinical decision-making process with respect to prognosis is biased by various selection criteria, but that it surely is an oversimplification to consider the condition benign.

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