Denton A. Cooley's 50th Anniversary in Medicine

The Cumulative Risks of Prolapsing Mitral Valve

40 Years of Follow-up

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Prolapsing mitral valve is a common cardiac condition, occurring in approximately 16 million people in the United States alone. Primary prolapsing mitral valve may be familial or nonfamilial and may be associated with myxomatous degeneration of the mitral valve leaflets, such as occurs in Marfan syndrome and other connective tissue disorders. Secondary forms may be associated with such entities as rheumatic fever (especially after commissurotomy) and coronary artery disease (in the presence of ruptured chordae tendineae), and with such congenital conditions as interatrial defect and primary cardiomyopathy with outflow tract obstruction.

Prolapsing mitral valve is characterized by late systolic murmur, mid-systolic click, or both. Arrhythmias occur in the form of benign premature atrial contraction, premature nodal contraction, and paroxysmal atrial tachycardia. As the patient ages, atrial flutter and atrial fibrillation tend to develop. In some chronic cases, especially those involving atrial fibrillation, systemic emboli may occur. Rare premature ventricular contractions may be largely benign, whereas more frequent premature ventricular contractions may lead to severe arrhythmic complexes such as ventricular tachycardia or ventricular fibrillation. With advancing age, atrioventricular conduction defects of varying degrees or sick sinus syndrome may necessitate a pacemaker installation. About one quarter of prolapsing mitral valve cases progress, with increasing mitral insufficiency and increasing enlargement of the left atrium and left ventricle, which at times leads to congestive heart failure. Coronary artery disease may occur with the severity commensurate with the patient's age group.

About three quarters of patients with prolapsing mitral valve syndrome lead normal lives. ***(Texas Heart Institute Journal 1994;21:267-71)***

In the course of our treatment of numerous patients with prolapsing mitral valve, we have had the unusual good fortune to observe 250 patients whose average follow-up equals 40 years. What follows is an informal overview of the disease and its cumulative risks, which draws upon our personal experience and that of other clinicians.

Key words: *Echocardiography, Doppler; heart valve diseases/diagnosis; mitral valve insufficiency/diagnosis; mitral valve prolapse*

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Prevalence and Causation

There are approximately 16 million individuals with prolapsing mitral valve in the United States.* Estimates of the percentage of the general population that might be involved have varied from 4.4%[1] to 6.3%.[2]

Prolapsing mitral valve is relatively uncommon before the growth spurt of adolescence. There is a greater prevalence in women, and a heavy genetic infiltration in young girls (under the age of 16 to 20). After the age of 20, the disease affects men and women about equally, regardless of familial traits; and after the age of 50, there is a higher rate of advanced disease in the male.

Primary prolapsing mitral valve may be familial or nonfamilial and may be associated with myxomatous degeneration of the mitral valve leaflets, such as occurs in Marfan syndrome and other connective tissue disorders. In about two thirds of cases, the predominant involvement is in the posterior cusp, and in about one third it is in the anterior cusp or both cusps.[3] Secondary forms may be associated with such entities as rheumatic fever (especially after commissurotomy) and coronary artery disease (in the presence of ruptured chordae tendineae), and with such congenital conditions as interatrial defect and primary cardiomyopathy with outflow tract obstruction.

*Harvey WP. Personal communication.

Diagnosis

In 1935, Sam Levine and William P. Thompson[4] noted a late systolic murmur in a good many of their patients, but were uncertain of the cause. It was not until the 1960s that the basis of the auscultatory findings of prolapsing mitral valve was confirmed by Reid[3] and Barlow,[5,6] working independently of one another. The late systolic murmur behaves like mitral regurgitation, decreasing with the administration of amyl nitrite and increasing with the infusion of phenylephrine hydrochloride. Reid and Barlow visualized mitral regurgitation angiographically in patients with a late systolic murmur. Moreover, they recorded both the midsystolic click and late systolic murmur in the left atrium by means of intracardiac phonocardiography: they passed a phonocatheter through the lumen of a transseptal catheter.

Auscultation. In our experience, early diagnosis of mitral valve prolapse was helped greatly by detection of late systolic murmur and midsystolic click. The murmur[7] may be increased by placing the patient in a standing (vertical) position or by using Valsalva's maneuver. The vertical position may produce systolic murmurs that increase in intensity moving anteriorly toward the sternum and the 1st heart sound. The murmur may be prolonged. The systolic click also moves anteriorly toward the 1st heart sound.

Squatting may incline the heart towards a horizontal position, which may cause posterior movement toward the 2nd heart sound and may shorten the systolic click and move it closer to the 2nd heart sound.[8-10] Bradycardia or propranolol may produce the effect of squatting.

Detection of the late systolic murmur is best by using a diaphragm stethoscope while performing a Valsalva maneuver. In the rare case, so-called systolic "honk" may replace the murmur itself.[9]

Echocardiography. Another invaluable aid to diagnosis is the positive echocardiogram. Diagnosis of the prolapsing mitral valve is established when there is an abrupt middle-to-late systolic posterior displacement of part of the initial closure to at least the closure line, 2 mm below the line joining the point of valvular closure.[11,12] The M-mode echocardiogram reveals the sagging of the prolapsing cusps,[10] but is less accurate than the 2-dimensional echocardiogram, which delineates the area of mitral regurgitation, the valvular movement, and the chamber size of the left atrium and ventricle. The 2-dimensional echocardiogram helps to establish the severity of prolapse. Two-dimensional echocardiographic findings are often accompanied by similar auscultatory findings of a non-ejection midsystolic click and a late systolic mitral murmur.[10] If the Doppler is added in a contrast color,[13] it may reveal evidence of regurgitation from the left ventricle to the left atrium, and may further delineate the severity of the underlying mitral regurgitation.

Electrocardiography. During the 1st 2 decades of life, the electrocardiogram may be entirely normal or may show bursts of paroxysmal atrial tachycardia and premature atrial contraction. In about 10% of prolapsing mitral valves, ST segment sagging changes will be seen in leads II, III, aVF, and V4, V5, and V6. Along with this, there will frequently be a QT prolongation.[14] With increasing age (late 40s), paroxysmal atrial fibrillation and flutter,[15] sick sinus syndrome,[16] and atrioventricular block[14] may occur.

During treadmill testing, the false positive rate is about 50% in individuals whose ST segments are abnormal. As a result, we may use thallium-201 to attempt to determine the degree and area of involvement. If the thallium-201 test is positive, we may go ahead with selective coronary cineangiography and left ventriculography to evaluate the possible severity of the mitral regurgitation and the degree of coronary artery involvement.

Radiographic Imaging. Early radiographs (in the young patient) may show some gross skeletal abnormalities, such as pectus excavatum, pigeon breast, straight-back syndrome, scoliosis, or kyphoscoliosis, but the heart size is usually normal at those times. Beginning at about 50 years of age and on into each subsequent decade, about one third of the patients that I saw progressed with cardiac enlargement. If there had been a significant rupture of the chordae tendineae, mitral regurgitation was prone to come early. If the patient was showing increasing evidence of mitral regurgitation, obviously the left atrial radiographic image would begin to increase in size. As a result of posterior displacement of the esophagus, left atrial enlargement could be visualized indirectly.

In older patients about to undergo valvular surgery, and in surgical candidates with symptoms suggestive of angina, selective coronary cineangiography is performed to determine whether angioplasty or coronary artery bypass might be necessary, in addition to the valvular surgery.

Ergonovine Testing. In the younger age groups, somewhat atypical left lateral chest pain may be present. It is less likely than the typical pain of angina found in older patients. If the electrocardiogram and thallium-201 tests are negative, we occasionally use ergonovine maleate intravenously, which may suggest coronary spasm alone. However, we may resort to selective coronary arteriography and cineangiography in this situation.

Progression of the Disease

After more than 40 years of observation, I can say that approximately three fourths of our patients had a largely benign course. However, in the early years of our practice, before a wide range of therapies

became available, many of these patients were quite symptomatic, especially those with fatigue, atypical chest pain, palpitations, and abnormal respiratory symptoms such as hyperventilation and long sighing respirations, which were not uncommon.

Younger Patients. The patient may be largely asymptomatic during the 1st 30 to 40 years of life. However, some patients develop the symptoms of fatigue, deep sighing respiration, hyperventilation, and palpitation mentioned above. The palpitation is secondary to premature atrial or ventricular contractions. Occasionally, this anxious condition is accompanied by very brief episodes of syncope and by a rather unpredictable, atypical chest pain that is centered about the apex and is frequently short and stabbing.

In some younger individuals, the onset of the arrhythmias is largely benign. In addition to premature atrial contractions, these arrhythmias may consist of nodal premature contractions and paroxysmal atrial tachycardia. Paroxysmal atrial tachycardia is seen frequently and has a tendency to recur, but usually is easy to control.

Older Patients. Most of the severe complications occur after 50 years of age (Table I), and even then only about one fourth involve the mitral valve. Moderate symptoms occur earlier in men, in a ratio of about 2:1.

In the 5th and 6th decades and thereafter, paroxysmal atrial fibrillation,[16] flutter, and more frequent premature ventricular contractions begin to appear. Atrial fibrillation and flutter (the former being much more common) increase in frequency as the patient ages. In the patient's 50s, sick sinus syndrome or increasing atrioventricular heart block may develop (with heart rates down in the 30s or 40s), and may necessitate the installation of a pacemaker.[14]

If the atrial fibrillation is chronic, progressive enlargement of the left atrium may be accompanied by clotting and may result in embolic phenomena. Em-

TABLE I. Complications and Treatment of Prolapsing Mitral Valve in 3 Age Groups, from 51-80 Years

Age	Number of Patients	Complications	Treatment
51-60	38 (21 M & 17 F)	Angina with 1-3 ventricular septal defect=3	Angioplasty Mitral valve replacement & coronary artery bypass=3
		Congestive heart failure=5	Mitral valve replacement=5
		Cerebral embolism=5	Anticoagulants (later)
		Sick sinus syndrome=1	Pacemaker
		Coronary artery spasm=1	Diltiazem
61-70	40 (25 M & 15 F)	Congestive heart failure=14	Mitral valve replacement=14
		Sick sinus syndrome=6	Pacemaker=6
		Subacute bacterial endocarditis=2	Antibiotics
		Emboli=2	Anticoagulants (later)
71-80	17 (10 M & 7 F)	Congestive heart failure with 4+ mitral regurgitation=8	Mitral valve replacement=14
		with coronary artery disease=2	Coronary artery bypass=2
		Embolus=1	Anticoagulants (later)
		Subacute bacterial endocarditis=4	Antibiotics
		Atrial fibrillation=12	Medical

Note: Mitral valve complications occur as a result of increasing severity of regurgitation and of left atrial and left ventricular hypertrophy, which often results in congestive heart failure. Rhythm disturbances and conduction defects may be encountered. Associated coronary artery disease may be seen with the severity and frequency commonly encountered in the patient's age group. Systemic emboli and bacterial endocarditis are rare.

boli are most prone to go to the brain, but may go elsewhere.

Sudden death reportedly occurs in about 1% of all patients with mitral prolapse.[17] This is likely to happen when excess ventricular irritability is present and when ventricular tachycardia degenerates into ventricular fibrillation. On 2 occasions, we have found it necessary to defibrillate patients with mitral prolapse, and they recovered satisfactorily.

Bacterial endocarditis, either acute or subacute, occurs in about 3% to 6.5% of all individuals who have prolapsing mitral valve.[16,18] If there is associated acute bacterial endocarditis, especially if the pathogen is a staphylococcus (*S. aureus* or *S. epidermis*) superimposed on the mitral valve, congestive heart failure is much more prone to occur. *Streptococcus viridans* may occur in 3% to 7% of subacute bacterial endocarditis cases, but is more benign and does not destroy the valve as a staphylococcus does. Those who have been infected with streptococcus frequently get through the episode without any severe valvular damage.

Some patients, independent of endocarditis, have progressive enlargement of the left atrium and left ventricle, and may necessitate valvular surgery for congestive heart failure.

Treatment

Arrhythmias. Arrhythmias may be assessed with the aid of a treadmill stress test or 24-hour electrocardiographic monitoring. Because premature atrial contraction and premature nodal contraction are usually benign, they may not require treatment. Premature atrial tachycardia, the onset of which may occur at any age, is easily controlled with propranolol, which is more effective in the treatment of supraventricular arrhythmias than ventricular arrhythmias. Premature ventricular contractions rarely require treatment when they occur infrequently; but when they occur often, ventricular arrhythmias are likely to develop, and premature ventricular tachycardia may progress to ventricular fibrillation. Frequent ventricular contractions may be controlled with quinidine sulfate, procainamide, or (for less tractable cases) amiodarone. Atrial flutter or atrial fibrillation may appear in the patient's 50s; atrial fibrillation can be reversed with medical or electrical cardioversion. In a significant percentage of patients with mitral valve prolapse, evidence of a sick sinus syndrome or prolonged atrioventricular conduction may necessitate the placement of a pacemaker.

Coronary Artery Spasm. In the event of coronary artery spasm, we frequently get good relief with the administration of a calcium channel blocker, such as Cardizem.

Cerebral Embolism. When cerebral embolism occurs as a result of left atrial enlargement and clotting, we allow the condition to stabilize and then usually start a long-term anticoagulant, such as Coumadin. We find long-term anticoagulants more satisfactory than aspirin or Persantine.

Endocarditis. Antibiotics may be used prophylactically, on a short-term basis, if the patient is at immediate risk of endocarditis. When streptococcal endocarditis occurs, it frequently responds well to penicillin, without additional severe damage. However, when *S. aureus* or *S. epidermis* is the pathogen, the greater tendency towards severe valvular damage increases the likelihood of surgery. As a rule, in patients with staphylococcus bacterial endocarditis, we attempt to treat with antibiotics for at least 2 to 3 weeks prior to surgery and use various types of prostheses, sometimes a mechanical valve and sometimes a porcine valve, the latter if we expect the patient's longevity to be less than 8 to 10 years. At times, the use of a Carpentier fibroelastic ring[19,20] has been quite satisfactory; and in some patients, sculpting of the native valve may be of help. Cooley has had extensive experience in mitral valve surgery with porcine and mechanical valves, as well as with Carpentier fibroelastic rings.[21,22] If left untreated, severe mitral valve damage may ultimately lead to congestive heart failure.

Other Conditions. In the early stage of prolapsing mitral valve, simple reassurance can do much to control a patient's anxiety; and antidepressants are of course useful in treating depressed patients of any age. The patient can be taught to control hyperventilation by using a paper sack or by closing off the nose and mouth. In general, exercise should be allowed, but should be monitored when patients begin to get progressive cardiac enlargement.

Summary

Diagnosis of prolapsing mitral valve may be established by echocardiograms revealing abrupt middle-to-late systolic posterior displacement of part of the initial closure to at least the closure line (2 mm below the line joining the point of valvular closure). Two-dimensional echocardiography helps to establish the severity of the mitral prolapse. The 2-dimensional echocardiographic findings may be accompanied by a non-ejection midsystolic click and a late systolic mitral murmur. Approximately three fourths of the individuals involved can live their entire lives on medical treatment alone, but after the age of 50 about one fourth will undergo some form of surgical therapy, which might include the implantation of a porcine valve, a mechanical valve, or a fibroelastic ring. In recent years, there has been renewed interest in surgical reconstruction of the native valve to correct mitral insufficiency. Such corrections are observed to be increasingly applicable

and durable, and relatively free from complication. The results are equal to those obtained after prosthetic mitral valve placement.

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