The Myxomatous Mitral Valve and Sudden Death

Elliott Chesler, M.D., Richard A. King, M.D., and Jesse E. Edwards, M.D.

SUMMARY. The clinicopathologic features of 14 cases of sudden death attributable to dysrhythmias associated with the myxomatous mitral valve are described. The patients were 14-59 years old (mean 27 ± 11 years). Eleven were female and three male. Of the seven ECGs available, none showed prolongation of the QT interval, but two showed repolarization abnormalities. The material was classified according to the degree of prolapse in the pathologic specimen. When obvious prolapse was found, the expected auscultatory findings had been documented. In three cases there was minimal prolapse, casting some doubt on the hypothesis that traction on the papillary muscles or diastolic dumping of the leaflets may be implicated in the pathogenesis of the dysrhythmias. In one of the cases with minimal prolapse there was a strong family history of sudden death. Endocardial friction lesions were present in 11 cases, including two of the three with minimal prolapse. In five cases there was a thrombotic lesion in the angle between the posterior leaflet and the left atrial wall containing fibrin and platelets. These abnormalities may be important in the pathogenesis of the ventricular dysrhythmias.

Sudden death is a very uncommon complication of the mitral valve prolapse–click syndrome. While there is strong clinical evidence that the cause of sudden death is a ventricular tachyarrhythmia, its pathogenesis is not known. One theory is that the voluminous prolapsing leaflets produce abnormal tension on the papillary muscles, resulting in electrocardiographic abnormalities and dysrhythmias. However, mitral valve prolapse may be associated with other conditions, such as congestive cardiomyopathy and hypertrophic subaortic stenosis, which in their own right may be important determinants of prognosis, including a predisposition to fatal dysrhythmias.

We found 39 reported cases of sudden death attributed to mitral valve prolapse,1–21 including three cases from our laboratory.7 In only 19 of the reported cases were autopsies performed, but even among these cases the information is, in many instances, sparse, so other pathologic conditions cannot be excluded. Because of the important clinical and forensic implications, we report the clinicopathologic findings in 14 cases of sudden death in whom myxomatous change of the mitral valve was the principal identifiable pathologic abnormality.

Materials and Methods

The 14 specimens were referred from various centers during 1973–1981. Complete autopsies in each case identified the cardiac abnormalities as the only possible causes of sudden death. Two cases emanated from county coroners, and no supplementary clinical information was available. The family history was available in 12 cases, clinical information in 10 and ECGs in seven.

The circumstances surrounding cardiac arrest were determined from paramedic, hospital and county coroner records. From these sources, the interval between the onset of cardiac arrest and the cessation of resuscitative measures was estimated.

The specimens of heart were examined macroscopically for evidence of congenital and other cardiac abnormalities. The coronary arteries were sectioned transversely at 3–5-mm intervals, and representative segments were examined microscopically. Multiple blocks of tissue were taken from the free and septal walls of both ventricles for histologic examination. Particular attention was paid to the histology of the papillary muscles. The atrioventricular node and the proximal portion of the bundle branches were examined in two cases by spot check sections. Serial sections were not made. The mitral valve apparatus was examined for chordal thickening and elongation, and the degree of prolapse of the mitral leaflets was graded from I to III. Friction lesions on the endocardium of the left ventricle adjacent to the chordae were sought.

Definition of Grades of Mitral Valve Prolapse

The degrees of prolapse of the mitral valve leaflets are listed in table 1. Grade I was characterized by mild focal degrees of prolapse or interchordal hooding. Recognizing that some hooding may be present in the normal valve, the cases included under this category were considered to exhibit mild degrees of change but in excess of the normal (fig. 1). Histologic evidence supported the diagnosis of myxomatous change in each case in this category (fig. 2A), and in two there were endocardial friction lesions (fig. 2B), as described by Salazar and Edwards.24 Grade II was characterized by moderate redundancy and grade III by severe redundancy of the leaflets (fig. 3).

Results

Among the 14 cases, three showed grade I, eight grade II and three grade III mitral valve prolapse. The clinicopathologic features pertaining to the 14 cases are summarized in table 1. There were 11 female and three male patients, ages 14–59 years (mean 27 ± 11 [± SD]). Two patients had a history of chest pain, four had palpitations and one patient had dizziness.

Family History

A family medical history was available in 12 cases and was significant in two. In case 13, the father was found to have a nonejection click.
In case 3, a family pedigree was available (fig. 4). Case 3 was a 14-year-old girl whose mother died suddenly at age 36 years. The girl had nine siblings, two of whom died suddenly at the ages of 11 and 12 years, respectively. County coroner reports were available on the mother and these two siblings. No pathologic cause of death was found, but the report on the 12-year-old brother noted thickening of the "septal cusp of the mitral valve." Six of the remaining seven siblings and the father were examined. All six siblings had normal ECGs, but three had echocardiographic evidence of mitral valve prolapse. The father had a normal echocardiogram and ECG. The expression is consistent with an autosomal dominant pattern of inheritance in this family.

**Electrocardiogram**

Of the seven cases in whom some electrocardiographic study had been done, ventricular premature complexes were documented in six. In two of these there was bigeminy, but in only one case was the dysrhythmia treated aggressively. This was a 25-year-old woman (case 8) who had complained of increasing...
lightheadedness, one episode of syncope and periodic substernal pain radiating to the shoulders and arms. Electrocardiographic monitoring demonstrated atrial ectopy and protracted runs of ventricular bigeminy. These persisted despite a therapeutic trial of digoxin and quinidine. Because of persistent symptoms, propranolol, 20 mg twice daily, was administered and quinidine discontinued. This abolished the bigeminy but resulted in symptomatic bradycardia, and a demand pacemaker was implanted. The patient remained well for 6 weeks until she suffered sudden unexpected death. One day before death the pacemaker was found to be functioning perfectly.

One other patient (case 9) had one previous episode of atrial fibrillation, successfully treated with i.v. digoxin and propranolol.

Exercise electrocardiography was performed in cases 5, 9 and 13, each with known ventricular ectopy. In two of these, ventricular ectopy was abolished by exercise, and in one ectopy was aggravated. The remaining patient did not have ectopy immediately before, during or after the exercise test, but bigeminy had been observed on several other occasions. The QT interval was measured in seven available tracings and was 0.4 (upper limit of normal for age and sex 0.432), 0.32 (normal 0.347), 0.36 (normal 0.384), 0.37 (normal 0.405), 0.32 (normal 0.36), 0.28 (normal 0.36), 0.32 (normal 0.395), and 0.32 (normal 0.34) second. ST-T-wave changes in the inferior and left precordial leads were observed in two of these tracings.

**Toxicology and Medications**

The medications taken immediately before death are
listed in table 1. Toxicologic studies were negative in cases 4, 5, 8, 9, 10 and 13.

Auscultatory Findings

Among the three cases with grade I prolapse, two were asymptomatic and had not sought medical attention. Case I had a routine physical examination before operation for a prolapsed lumbar disc. The auscultatory findings were normal.

Among the 11 cases with grades II or III prolapse, in two we had no antemortem information. The remaining nine cases had auscultatory evidence of mitral valve prolapse (four with a midystolic click and late systolic murmur, three with holosystolic murmurs and two with a midystolic click only).

Pathologic Findings

The hearts weighed 195–365 g (mean 279 ± 57 g). In none of the specimens was there evidence of cardiomyopathy, myocarditis, significant coronary atherosclerosis or congenital abnormality to account for sudden death.

Grade I Mitral Valve Prolapse (Three Cases)

Mitral valve apparatus. In two cases, both leaflets of the mitral valve were macroscopically thickened; in the other case, only the posterior leaflet was thickened. The chordae tendineae were intact and of normal length but were thickened in two cases. In case 1, microscopic deposits of fibrin and platelets were present at the junction of the left atrium and posterior mitral leaflet.

Endocardial friction lesions. In two cases there was thickening of the mural endocardium of the left ventricle beneath the posterior leaflet.

Coronary arteries. There was no evidence of atherosclerosis.

Conduction system. The conduction system was examined in case 2 and was normal.

Myocardium. Extensive changes in the myocardium were observed in cases 1 and 2. In case 1, there were multifocal areas of acute necrosis, and interspersed among areas of scarring were lesions of intermediate age, characterized by removal of myocardial fibers. The intramyocardial arteries were normal. These changes were considered to be a result of cardiac arrest and prolonged cardiopulmonary resuscitation. This patient had been in ventricular fibrillation for at least 30 minutes before cardioversion was performed by percutaneous personnel. After this, she remained unconscious and was maintained on a respirator for 6 days.

The findings were similar in case 2. Multifocal areas of acute necrosis of muscle were present, and in other areas there were features of muscle removal. Also, there were several arteries within the papillary muscle that showed marked narrowing of the lumen by fibrous intimal thickening. This patient had also been in ventricular fibrillation for at least 15 minutes before cardioversion by paramedical personnel. She did not regain consciousness and died 8 days later despite assisted respiration.

Grades II and III Mitral Valve Prolapse (11 Cases)

Mitral valve apparatus. The leaflets, in particular, the posterior leaflets, were floppy, thickened and redundant with multiple areas of hooding. The chordae were elongated but not ruptured in any instance. Case 12 showed prominent macroscopic abnormalities at the junction of the left atrium and the posterior mitral leaflet. These consisted of a linear array of deposits of fibrin in the angle between the posterior mitral leaflet and the wall of the left atrium (figs. 3B and 5). There were also fibrous nodules just above this angle that involved the left atrial wall and the superior surface of the posterior mitral leaflet at their zone of mutual contact. Sections taken through the posterior mitral leaflet and adjacent portions of the left atrium and left ventricle showed several processes. The base of the mitral valve showed a focus of dense laminated collagen containing elastic tissue deposited along its atrial surface. Opposite this accumulation, the atrial endocardium showed a focus of thickening with collagen in the superficial part in which there were some elastic fibers. On the surface of each of the fibrous nodules there was

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<th>Heart weight (g)</th>
<th>Degree of prolapse</th>
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*FIGURE 4. Family pedigree of case 3. The propositus is patient III-12. MVP = mitral valve prolapse.*
fibrin undergoing organization. This extended downward from each nodule toward the angle between the atrium and the base of the mitral leaflet. The actual angle between the base of the mitral leaflet and the left atrium showed destruction of tissue filled in by incompletely organized fibrin. At the very apex of the lesion there was an accumulation of dense collagen with an island of fibroelastic tissue resembling that of the atrial endocardium. No significant leukocytic infiltrate was evident, nor was there any calcification.

In case 13, the macroscopic findings in the angle between the left atrial wall and the posterior leaflet consisted of a linear array of hemorrhagic lesions. Microscopically, this consisted of aggregates of connective tissue, fibrin, platelets, leukocytes and red cells. No bacteria were observed (fig. 6). A similar lesion was present in case 4. In case 7, fibrin deposits were identified by microscopy.

Endocardial friction lesions. Friction lesions were present in nine of the 10 cases.

Coronary arteries. Abnormalities of the coronary arteries were present in case 9 only. This 29-year-old man had a focal 50% narrowing of the left anterior descending coronary artery 0.5 cm from its origin and a focal 25% atherosclerotic narrowing of the interme-

diate segment of the right coronary artery. The ascending aorta showed minimal atherosclerosis.

Conduction system. The conduction system was examined in case 5 and was normal.

Myocardium. Case 7 had evidence of multifocal acute myocardial necrosis with hypereosinophilia and coagulation necrosis. This 26-year-old woman collapsed because of ventricular fibrillation. After cardiopulmonary resuscitation, she was cardioverted to sinus rhythm and transported to the hospital. She had numerous episodes of ventricular tachycardia and fibrillation requiring repeated cardioversion and died 48 hours later despite assisted respiration.

In cases 8, 9, and 10, some sections showed small focal areas of interstitial fibrosis without cellular infiltrate or loss of myocardial fibers. These findings are occasionally observed in routine autopsies and were considered to be nonspecific and the cause unknown.

Other Pathologic Findings

Cystic medial necrosis of the aorta was present in five cases. In the four cases without stigmata of Marfan's syndrome, the changes were grade II in case 10 and grade I in cases 3, 9 and 12. Case 14 was recognized as having Marfan's syndrome clinically. The

Figure 5. Case 12. (A) Diagram and (B) photomicrograph of the junction of the left atrium (LA) and the posterior mitral leaflet (PM), as well as the related wall of the left ventricle (LV). There is deposition of fibrin (F) in the angle between the posterior mitral leaflet and the left atrial endocardium. Fibrous nodules (FN) are present both above the angle, involving the left atrial wall and below, involving the superior surface of the posterior mitral leaflet. In the photomicrograph, there is also a friction lesion (FL) of the left ventricular endocardium. Elastic tissue stain; magnification × 5.
aortic root was dilated (10 cm in circumference), and there was grade II cystic medial necrosis.

**Discussion**

Considering the frequency of mitral valve prolapse in the general population, cases of sudden death attributable to this syndrome have attracted disproportionate attention. The possibility has been raised that associated coronary artery disease, left ventricular myopathy, or prolongation of the QT interval may be responsible factors. One of the purposes of our study of 14 patients was to ascertain whether some other form of cardiac abnormality may have played a role in the pathogenesis of the fatal cardiac dysrhythmias. In general, most instances of sudden cardiac death can be resolved by pathologic examination into ischemic heart disease, nonatherosclerotic coronary artery disease (e.g., dissecting aneurysms), or left ventricular hypertrophy associated with idiopathic hypertrophic subaortic stenosis or aortic valve stenosis. Other causes, such as congestive cardiomyopathy, severe pulmonary hypertension, myocarditis and sarcoidosis, are also readily identifiable. All of these were excluded from this study. Also, there was no evidence that drug toxicity or medications caused sudden death in our patients. (An additional case of sudden death and mitral valve prolapse in our collection was excluded because of a strong suspicion of quinidine toxicity.)

Three of our cases had evidence of multifocal myocardial necrosis. These changes are attributed to inadequate coronary blood flow as a result of prolonged circulatory arrest and the protracted resuscitation that followed the dysrhythmia. Experimental studies in dogs have demonstrated lack of coronary blood flow during closed-chest resuscitation. None of the specimens showed evidence of “contraction band necrosis” suggestive of acute myocardial ischemia, as found in sudden coronary death. The myxomatous mitral valve and secondary changes in adjacent structures were thus the only important pathologic abnormalities. Five cases showed evidence of aortic cystic medial necrosis, one of which had all the clinical features of Marfan’s syndrome, which is associated with the myxomatous mitral valve.

In his review of 25 cases of sudden death associated with mitral valve prolapse, Jeresaty identified the potential victim as having the following features: A 40-year-old woman with a history of syncope who has a late systolic murmur preceded by a click, or a pansystolic murmur with late systolic accentuation. The ECG shows inferolateral ST-T changes and frequent premature ventricular systoles. Left ventriculography demonstrates obvious mitral valve prolapse and minimal-to-moderate mitral regurgitation. Patients with “silent” mitral valve prolapse or an isolated click do not appear to be susceptible. A family history of sudden death is an added risk factor. Traction on the papillary muscle is favored as the mechanism for the repolarization changes and dysrhythmias.

Our material was classified according to the degree of prolapse of the myxomatous valves in the pathologic specimens. In patients with grade II and III prolapse,
the findings conform in general with the clinical description of Jeresaty, in that the expected auscultatory findings were present. However, only two of the seven ECGs showed repolarization changes.

In the patients with grade I prolapse, the findings are of particular interest. Case 1 had been examined before lumbar disc surgery, and no abnormal auscultatory findings were recorded. The ECG was normal except for frequent ventricular ectopy.

The family history of case 3 is germane in that sudden death afflicted a mother and three of her children, none of whom had sought medical attention. The occurrence of sudden death in such asymptomatic patients with minimal prolapse may refute the hypothesis that either traction on the papillary muscle or "diastolic dumping" by voluminous leaflets may produce endocardial or papillary muscle irritability and dysrhythmias. Additionally, the degree of prolapse demonstrated in these patients at autopsy is unlikely to be demonstrable by angiography or echocardiography.

The cause of the dysrhythmias in subjects with the myxomatous mitral valve remains an enigma. Endocardial friction lesions were present in 12 of the 14 cases (86%), including two of the three cases with grade I prolapse. These lesions arise as a result of friction between chordae and the left ventricular mural endocardium which, in some instances, may lead to marked fibrosis of the mural endocardium. Mechanical stimulation of the endocardium by the thickened chordae could be responsible for the ventricular dysrhythmias and the repolarization changes. In those cases wherein repolarization changes are permanent, the endocardial scarring may be responsible. In five other specimens (36%), there was a lesion in the angle between the posterior leaflet of the mitral valve and the left atrial wall. These contained aggregates of platelets and fibrin. Embolism from these deposits could lead to transient cerebral ischemic attacks and, more important relative to sudden death, to small coronary emboli, the latter causing dysrhythmias. Actual emboli were not detected in our material, possibly because of spontaneous lysis. Their sequelae may be difficult to demonstrate microscopically. Such embolism may also perhaps account for electrocardiographic evidence of myocardial infarction reported in patients with mitral valve prolapse in whom the coronary arteries are normal angiographically. In another study from this laboratory, which included 102 cases of myxomatous valves not associated with sudden death, endocardial friction lesions were present in 77 instances (77%) and fibrin deposits between the posterior mitral leaflet and left atrial wall were found in four instances (4%).

Ventricular fibrillation has been reported as a complication in those cases of mitral valve prolapse with prolongation of the electrocardiographic QT interval. The latter abnormality was not evident in this study, and the true frequency of this finding is uncertain. In our material the major portions of the conduction system were examined in only two cases, and there were no abnormalities. Bharati et al.

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