"To observations which ourselves we make, we grow more partial for the observers sake."

Alexander Pope
Moral Essays

The relation among the late systolic murmur, nonejection click, and prolapse of the mitral valve was established by Barlow and Pocock in 1963.1 In the past decade, 1,545 articles have discussed various aspects of this form of mitral regurgitation. How much this literature has added to our knowledge and to patient care is debatable.

The pathology of the myxomatous mitral valve and related complications have been described with elegance and precision.2–4 Myxomatous replacement of the fibrosa weakens the involved mitral leaflet. Under the influence of left ventricular pressure, the leaflets and chordae become stretched—a process variously called “billowing,” “ballooning,” “prolapse,” or “floppy” mitral valve but most often clinically referred to as mitral valve prolapse (MVP). Clinical observations have delineated the auscultatory characteristics of the nonejection click and the associated regurgitant murmur.5 Also, the electrocardiographic, cineangiographic, and echocardiographic findings in the typical case have been well documented.6–8

However, the waters have become muddied by reports associating the myxomatous mitral valve with various conditions, including sudden death and neuroendocrine disorders. These associations may be purely coincidental or a bias of sample selection. In particular, symptoms encountered among patients with the so-called “MVP syndrome” are more likely a result of psychogenically induced anxiety or comorbidity than neuroendocrine dysfunction. This point of view is elaborated on.

Associated Conditions

It is established that the myxomatous valve may be complicated by varying degrees of mitral regurgitation and infective endocarditis.9–14 Also, there is a pathological basis for less causally established complications such as stroke and coronary embolism in the form of aggregations of platelets in the angle between the posterior mitral leaflet and the left atrial wall and on the leaflets themselves.15–18 There is a definite association with other inherited connective tissue abnormalities such as Marfan’s and the Ehlers-Danlos syndromes, pectus excavatum, and pseudoxanthoma elasticum.19–21 Other associations are questionable.

MVP detected by echocardiography does not necessarily imply that the valve is myxomatous. Often, the distinction in the literature between normal, myxomatous, “billowing,” “prolapsing,” “floppy,” and “hooded” leaflets is hazy, and interpretation of information may therefore be difficult. Also, there is considerable interobserver and intraobserver variation in interpreting echocardiograms; this introduces sampling bias into both patient and control populations. In atrial septal defect and hypertrophic obstructive cardiomyopathy, prolapse of normal leaflets may occur when there is a disproportion between the volume of the left ventricle and the size of the mitral annulus.22 Similarly, prolapse of normal leaflets may occur in inferior myocardial infarction and other myocardial diseases such as myocarditis and cardiomyopathy because of failure of chordal systolic tension.23 This finding has also been reported in approximately 10% of trained athletes by Lewis et al.24 Markiewicz et al25 found a similar incidence in 100 nonathletic young women, although this series may have been biased because the subjects were volunteers who responded to advertisement. In these cases, the leaflets appear thin and do not have the thickness and redundancy of the myxomatous valve.

Consequently, attempts by echocardiographers to identify minor degrees of prolapse of normal leaflets beyond the plane of the annulus appear to be inappropriate. In support of this view, some interchordal hooding is present in the normal mitral valve, and even a skilled pathologist may have to rely on histology to support a diagnosis of minor degrees of change in excess of the normal. Identifying minor degrees of prolapse of the mitral leaflets simply increases the “background prevalence” and the chances of finding a coincidental association with another condition.
Obviously, fortuitous concurrence of a truly myxomatous valve with other cardiac abnormalities must happen. MVP is identified in approximately 4% of the population, and coincidental association will be most likely when some other condition, whether cardiac or noncardiac, occurs (e.g., migraine or mitral annular calcification). For example, it is not surprising that MVP has been described in association with mitral annular calcification in women in their 70s as three fourths of them have been found to have some degree of calcification at autopsy (J.E. Edwards, personal communication). Similarly, a pathological study found a high incidence (18%) of myxomatous valves among patients with ventricular septal defect, but careful comparison with other information in that report suggested that they were unrelated occurrences.

Zullo et al. have clearly illustrated the effect of patient selection and ascertainment bias in the case of the purported association between MVP and hyperthyroidism. By studying the prevalence of all types of thyroid disorders among family members with and without MVP, they were unable to demonstrate a statistically valid link between hyperthyroidism and symptomatic subjects with MVP. Such noncausal associations are likely to be identified in populations who share multiple symptoms. In MVP and hyperthyroidism, the outstanding common symptom is palpitation, and this leads to ascertainment bias.

**Sudden Death**

Sudden unexpected death resulting from dysrhythmia among young people has been reported as a complication of MVP. However, adequate clinical details, electrocardiographic recordings of the final events, and detailed pathological findings are rare, so it is difficult to determine how definite this association is. In 1983, one of us reviewed 39 reported cases of sudden death attributed to myxomatous mitral valves. Autopsies were performed in only 19, and in many, the information was so sparse that other pathological abnormalities could not be excluded with certainty. Undoubtedly, some cases of sudden death that had been attributed to the myxomatous mitral valve were results of drug toxicity, electrolyte disturbances, or other unrecognized and unrelated cardiac pathologies such as cardiomyopathy. In their long and careful follow-up of patients with MVP, Pocock and Barlow encountered only one patient who died suddenly. This young woman had been treated for multifocal ventricular extrasystoles, and a myxomatous mitral valve was the only finding at autopsy; ventricular fibrillation was the presumed cause of death. More recently, Nishimura et al. reported six sudden deaths among 237 asymptomatic or minimally symptomatic patients with MVP who had been followed for a mean of 6.2 years. Similarly, Duren et al. performed a prospective follow-up of 300 patients (mean follow-up, 6.1 years) and encountered three cases of sudden death. Unfortunately, autopsies were not available in either series. Duren et al. pointed out that their data may have been biased because their patients had been referred to a cardiac center for evaluation and that their results did not necessarily reflect on the natural history in the general population.

Of our 14 patients with sudden death, in whom we documented that the myxomatous valve was the only pathological finding, there was no recording of the final dysrhythmia in five patients. Because premature ventricular complexes had been documented at some time, the final event was presumed to be ventricular dysrhythmia. It was postulated that the mechanism for the dysrhythmia could be related to mechanical friction on the endocardium by the thickened chordae. Evidence for this friction is the presence of fibrous endocardial lesions, which when confluent and calcified may be detectable by angiography and echocardiography. Alternatively, there is experimental evidence that traction on the papillary muscles may produce ventricular ectopy. This observation is supported by those rare patients with hemodynamically mild mitral regurgitation associated with repeated syncope and ventricular tachycardia in whom valvuloplasty of voluminous leaflets abolished the dysrhythmia (J.B. Barlow, personal communication).

These findings in so few cases must be reconciled with other evidence. In the Framingham Study, dysrhythmias were detected with similar frequency by resting 12-lead, exercise, and 1-hour ambulatory electrocardiography in subjects with and without MVP. The Framingham Study was population based and avoided the selection bias evident in other studies from tertiary referral centers that reported life-threatening cardiac dysrhythmias. The effect of selection bias was clearly demonstrated by Kramer et al., who compared patients with MVP with similarly asymptomatic controls: Patients with MVP did not have an excessive prevalence of dysrhythmias. Also, electrophysiological studies have not contributed to defining the role of ventricular ectopy. Among patients with MVP and high-grade ventricular ectopy, some studies have demonstrated normal intracardiac conduction and refractoriness. Others have pointed out that programmed ventricular stimulation may induce polymorphic ventricular tachycardia that could be simply a nonspecific response to aggressive stimulation protocols.

Episodes of sudden death among the population at large are not usually recorded by ambulatory electrocardiography. Ventricular tachycardia and fibrillation are the usual findings and complicate ischemic heart disease. However, occasional cases of asystolic cardiac arrest have also been documented. Recently, Milstein et al. reported their findings in six survivors of cardiac arrest. None of these young patients had detectable heart disease. A hypotensive-bradycardic response with syncope reproduced in the survivors by passive orthostatic tilt was thought to be neurally mediated via mechanoreceptors in the left ventricle.
Cardiac asystole could explain those cases in pathological and forensic literature in which sudden death in young people has not been associated with demonstrable cardiac abnormality and the conduction system was normal.\textsuperscript{49,50} It also raises the question of whether some sudden deaths have been erroneously attributed to the myxomatous mitral valve when the actual causes were neurally mediated hypotension cardiac asystole. This association has been documented by Leichtman et al,\textsuperscript{51} who described 11 members of a family with a high prevalence of MVP and syncope; orthostatic tilt reproduced the symptoms coincident with hypotension and marked bradycardia. Similar findings were reported by Santos et al\textsuperscript{52} in 12 of 86 patients with MVP, but there were no controls in this study, so the association could be a result of selection bias. Thus, the causal relation between the myxomatous mitral valve and sudden death remains unclear. What is clear is that in the absence of severe mitral regurgitation and left ventricular dysfunction, the risk of sudden death in young people without ventricular dysrhythmias, syncope, or presyncope is so remote that patients should not be told of the possibility.

**Mitral Valve Prolapse Syndrome**

When a diagnosis of MVP is made clinically and no other conditions or symptoms are present, such patients have been considered to have “primary” or idiopathic MVP. The term “billowing mitral leaflet syndrome” was introduced by Barlow and Pocock\textsuperscript{53} when symptoms such as fatigue, anxiety, weakness, and palpitation were associated with MVP. Recently, the term “mitral valve prolapse syndrome” was used by Boudoulas et al\textsuperscript{20} to categorize symptomatic patients whom they believe had neuroendocrine or autonomic dysfunction with a “hyperadrenergic” state. They proposed that MVP may be a marker for autonomic dysfunction.\textsuperscript{54} Several studies have reported autonomic dysfunction among patients with MVP prolapse. Pasternac et al\textsuperscript{55} studied 15 symptomatic patients. They measured plasma norepinephrine levels, heart rate, and supine and standing systolic and diastolic blood pressures. Total plasma catecholamine and norepinephrine levels were significantly increased in patients in both positions, and the heart rate was lower than normal in patients in the supine position but returned to normal in patients in the upright position. These investigators believed that this “hyperadrenergic” and vagotonic state could explain many of the manifestations of the MVP syndrome. These observations are supported by Coghlan et al\textsuperscript{56} but somewhat at variance with those of Gaffney et al,\textsuperscript{57} who found diminished vagal response to the diving reflex and to phenylephrine infusion. Boudoulas et al\textsuperscript{58} found increased 24-hour urinary norepinephrine and epinephrine excretion in symptomatic patients with MVP. Also, isoproterenol infusion produced a dose-related increase in heart rate in MVP patients that was greater than that in controls. They thought that MVP may be a specific marker in certain people “for the constitutional, neuroendocrine-cardiovascular process that is currently designated as the MVP syndrome.”\textsuperscript{59} Other studies have reported decreased epinephrine excretion and increased vagal tone in patients with MVP.\textsuperscript{60} We believe that these conflicting findings are a result of several factors. First, many study populations have been small, symptomatic, and mostly female, and not all control populations have been clearly defined. Second, MVP has not always been excluded by echocardiography in controls.\textsuperscript{55,57,58} Third, some studies have drawn conclusions from measuring catecholamines at rest or during passive standing.\textsuperscript{56,58} It is preferable to study changes in circulating catecholamines during orthostatic stress and isometric exercise. We have shown that among 11 consecutive patients with myxomatous valves encountered in hospital practice who were evenly matched with controls for age and sex, there was no significant difference between plasma norepinephrine levels, heart rates, and blood pressures in response to orthostatic tilt. Also, psychological testing for anxiety neurosis demonstrated no difference between the two groups.\textsuperscript{54} These findings have been amply confirmed. In a comparison of patients who have neurocirculatory asthenia with normal controls, Mantysaari\textsuperscript{62} reported no significant difference in response to hyperventilation, orthostatic tilt, Valsalva maneuver, cold pressor test, or isometric handgrip. Similarly, Lenders et al\textsuperscript{53} found no differences in neurohumoral responses to orthostatic tilt of symptomatic and asymptomatic patients with MVP. Recently, Taylor et al\textsuperscript{64} studied normal controls, asymptomatic patients with MVP, and patients with MVP who had symptoms suggestive of autonomic dysfunction. The autonomic responses to ice water immersion and the administration of isoproterenol, phenylephrine, and tyramine were the same in patients with similar symptoms and did not distinguish between those who did and those who did not have MVP. These authors reported that the autonomic responses to physiological maneuvers and agonist drugs in controls and in patients with MVP are heterogeneous and may be partially responsible for the divergent findings reported in the literature; bias in patient selection and small sample size could favor one abnormality over the other.

The symptoms associated with MVP are indistinguishable from those occurring in Da Costas syndrome and neurocirculatory asthenia and were thought by Wood\textsuperscript{65} to be the result of a psychiatric disorder (anxiety state). In modern terminology, they are classified as “panic disorder with somatization”\textsuperscript{66} and occur in 2–5% of the general population,\textsuperscript{67} 6–10% of patients attending primary care clinics,\textsuperscript{68} and 10–14% of patients in cardiology practice.\textsuperscript{65} The problem of how to reconcile the occurrence of similar auscultatory, echocardiographic, and electrocardiographic features in patients with and without symptoms was clearly recognized by Barlow and Pocock.\textsuperscript{7} They emphasized that patients with marked prolapse...
are not necessarily symptomatic, yet those with mild prolapse may have numerous symptoms. The obvious question is what is the mystique peculiar to the myxomatous mitral valve compared with other causes of mitral regurgitation that predisposes to these symptoms and associated autonomic dysfunction? There probably is none.

The contention of Leatham and Brigden69 that "isolated disease of the mitral valve causing mild or moderate reflux seldom causes symptoms other than those of iatrogenic anxiety" is buttressed by considerable evidence. Psychiatric studies have shown that scores for symptoms of anxiety and neurosis in patients with MVP were not different from those in patients with other cardiac diseases.70–72 In their extensive review, Margraf et al73 concluded that there was no functional relation between MVP and panic disorders and that comorbidity in highly symptomatic individuals was the likely explanation. Thus, the weight of evidence does not support the notion that myxomatous change in the mitral valve has any causal relation with psychiatric disorder. We do not doubt that there are some patients who may be "hyperadrenergic," but we feel that this could be a result of superimposed anxiety in a select group of individuals subjected to a host of maneuvers, tests, and studies in attempts to elucidate and make observations on additional facets of a "new disease."

We conclude that when all of the maladies attributed to the myxomatous mitral valve have been considered, only mitral regurgitation of varying degrees of severity, rupture of the chordae, infective endocarditis, and stroke will be importantly associated. Only in a minute subset of patients with complex ventricular ectopy and syncope or presyncope is there a risk for sudden death.

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