MEDICAL GRAND ROUNDS

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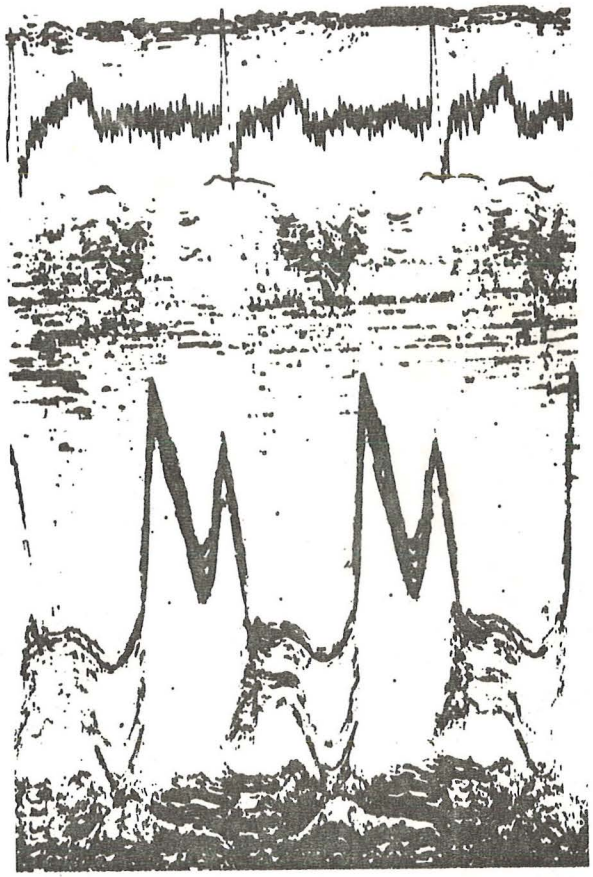
MITRAL VALVE PROLAPSE



All our actions take their hue from the complexion of the heart, as landscapes their variety from light.

Francis Bacon

Introduction

Mitral valve prolapse (MVP) is a disorder of the mitral apparatus in which chordae tendineae of excessive length allow enlarged mitral leaflets to prolapse into the left atrium during ventricular systole. The prolapse is manifest to the examining physician classically as a mid-systolic click followed by a systolic murmur of mitral regurgitation.

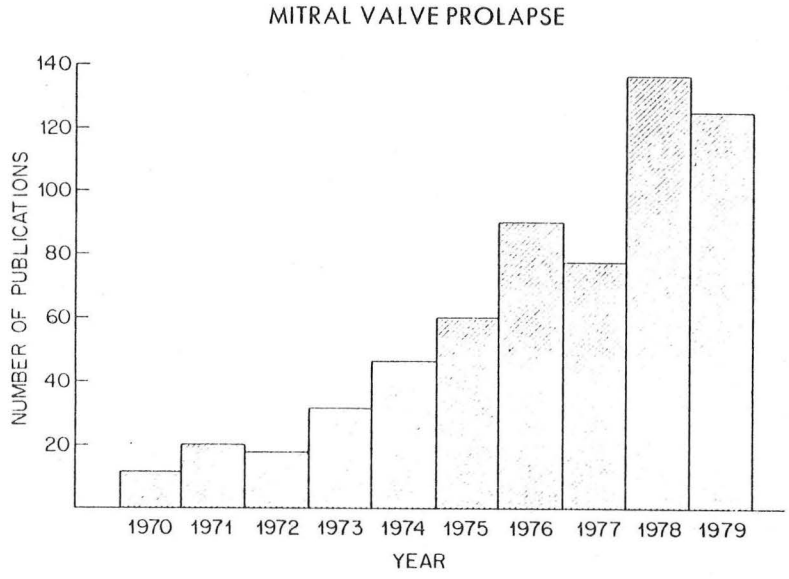


Figure 1 shows the number of publications on Mitral Valve Prolapse for each year since 1970.

MVP is probably the most common human cardiac disorder. Its widespread prevalence has resulted in a staggering amount of investigative and descriptive literature (see Figure 1). Recognition of these voluminous efforts was obtained in 1978 when Index Medicus assigned MVP its own separate heading. Yet, despite all of the investigative work in MVP, there is probably more confusion today than when the condition was first described by Barlow in 1963. We will present evidence that MVP is a common cardiac finding with a variety of causes and no more diagnostic specificity than a third or fourth heart sound. In contrast, Mitral Valve Prolapse Syndrome is a distinct disorder with involvement of multiple organ systems leading to a confusing array of symptoms. Yet, the syndrome has a precise pathophysiological basis. The purpose of this paper is 1) to review the current knowledge of MVP 2) to organize that information on the basis of pathophysiology and 3) to provide some suggestions for patient management.

History

The first description of a patient with mitral valve prolapse was by Osler.

> J.W., aged 12, a well nourished young girl was sent to me in May, 1880, by Dr. Buller (the first Professor of Ophthalmology at McGill University) who had noticed a remarkable whistling sound, while examining her eyes. The mother stated she had been a healthy child though never robust....Auscultation-As she sits upright in the chair the heart sounds at the apex and the base are clear; no murmur. When she stands a loud systolic murmur is heard at the apex, high-pitched, somewhat musical, of maximum intensity in fifth interspace; it varies a good deal being loud for three or four beats and then faint for one or two succeeding ones, due to the influence of respiration. On removal of the ear from the chest wall, the murmur can be heard at a distance of several inches. It disappeared quite suddenly and could not be detected on most careful examination. She was then asked to run about the room and up and down stairs. On sitting down, after this, the heart's action was very forcible, but the heart sounds were clear. The child then suggested that she heard it most frequently when in the stooping posture; and on causing her to lean forward and relax the chest, the murmur was at once heard, and with greatly increased intensity. It was distinctly audible at a distance of three feet two inches by measurement and could be heard at any point on the chest and top of the head. On July 13, I saw her again at her home and failed after prolonged examination to hear the murmur. She stated that she had not heard it herself for some time. But on July 21, there was no constancy in the variations. The rhythm is distinctive systolic, the first sound of the heart is not effaced by it though not so sharp as in its absence. During an examination extending over 20 minutes the murmur was present only 4 or 5 times and for a brief interval only less than a minute each time... I am not prepared to suggest an explanation of the cause of the murmur in this instance, and [He adds that his patient] ...was delicately built and nervous.

Gallavardin described a "bruit de galop mésosystolique" in 1887 but, like Osler, believed it to be extra-cardiac in origin; in this case due to pleuropericardial adhesions. This explanation for clicks and murmurs was generally accepted during the next 74 years, although Paul Dudley White did note in the 1932 edition of his textbook that tensing of the chordae tendineae

might be causing the mid-systolic clicks. Barlow (1963) identified the mitral origin of the click-murmur complex. Hancock and Cohn described the mid systolic click - late systolic murmur Syndrome in 1966. A similar study describing the findings in 90 patients with the syndrome was published by Barlow and Pocock (1968). These two studies are remarkable for their keenness of observation and completeness. They remain superb sources of clinical information on MVP syndrome.

The subsequent availability of cardiac catheterization and echocardiography has led to widespread recognition of the syndrome and several other observations on large series of patients have been published. (Jeresaty 1971, 32 cases; Pocock and Barlow 1971, an additional 130 cases; Scampardonis 1973, 87 cases) This led to a rather confusing lack of agreement on nomenclature which has yet to be settled. (Abrams, 1976; Jeresaty, 1978) The various names used to describe MVP and MVP Syndrome over the past 15 years are listed in Table 1.

Click syndrome	Prolapsing mitral leaflet syndrome
Click murmur syndrome	Mitral valve prolapse
Systolic click-late systolic mumur syndrome	Idiopathic mitral valve prolapse
Billowing posterior leaflet syndrome	Mitral valve prolapse syndrome
Ballooning of the mitral valve leaflets	Mitral valve prolapse-click syndrome
Overshooting mitral leaflets	Auscultatory-electrocardiographic syndrome
Barlow's syndrome	"Floppy" valve syndrome
	"Click chick" syndrome

Although there is still no general agreement, the term "Mitral Valve Prolapse" adequately describes the abnormal valvular action, while the term "Mitral Valve Prolapse Syndrome" should be used only when the clinical constellation surrounding MVP is present. This terminology will be utilized here. Jeresaty (1979) has further recommended that "Floppy Mitral Valve" should be reserved for the advanced forms of the syndrome accompanied by severe mitral insufficiency, but there is no evidence that his suggestion is being followed (Barlow, 1979).

Pathology

Read's (1965) report on six patients with mitral valve prolapse syndrome who were operated on for severe mitral regurgitation was one of the first published descriptions of the pathology associated with MVP. This and subsequent reports (Pomerance, 1969; Shappell, 1973; Ranganathan, 1973; McKay, 1973; Davies, 1978; Baehrel, 1978; Ross, 1978; Kay, 1979; Malcolm, 1979) have provided a clear picture of MVPS in operated or autopsied cases.

The findings are:

1) Voluminous, redundant, scalloped and thickened leaflets
2) Mitral annular dilatation
3) Myxomatous transformation of the valve substance
4) Absence of inflammatory changes or valvular calcification
5) Absence of large or small coronary artery disease
6) Small foci of endocardial and papillary muscle fibrosis

Gross Pathology

Mitral Annulus: In mitral regurgitation of rheumatic or ischemic causes, there is no dilatation of the mitral annulus in distinction to MVP where marked enlargement is common (Carpentier, 1978; Kay, 1979). Myxomatous degeneration is responsible for this annular dilatation.

Leaflets and Chordae Tendineae: The leaflets are enlarged and redundant, with extensive infolding. The chordae are thin and elongated. When distended the leaflets balloon back into the left atrium and, when viewed from that chamber, appear domed and wrinkled. There is usually thickening of the leaflets and often of the chordae, also. This is thought to be a result of trauma from hitting the endocardial surfaces during the opening and closing of the valve (Guthrie and Edwards, 1976). Appropriately-placed endocardial scars support this concept (Pomerance, 1969), but rather severe valvular changes have also been reported in a 4-month-old infant. This suggests that years of trauma are not needed to produce such changes (Roberts, 1976).

Myocardium: Scarring and subendocardial fibrosis of the papillary muscles have also been noted (Pomerance, 1969; Salazar and Edwards, 1970; Cobbs, 1977; Ross, 1978), although no one has reported evidence of either acute or healed infarction.

Microscopical Pathology: Normal mitral leaflets are composed of two layers, the fibrosa auricularis and the fibrosa ventricularis of the atrial and ventricular surfaces, respectively. Between these fibrous layers lies the spongiosa. The fibrosae are composed of dense collagen material while the spongiosa is, as its name implies, a loose connective tissue with a large amount of ground substance.

Myxomatous Degeneration: is the process responsible for the changes in the collagen structures. There is an increase in ground substance with large accumulations of acid mucopolysaccharide material that is composed of hyaluronic and chondroitin sulfates in the spongiosa. This material can be seen when stained with PAS or Alcian blue (Marshall and Shappell, 1974). The increase in ground substance is associated with a loss of integrity in the outer fibrous layers. These are continuous with the chordae and the annulus and stretching and thinning of these structures occurs. No abnormal periodicity of the collagen structure itself has been found (Davies, 1978) and the

etiology of the degeneration is not known.

There are a number of findings that allow differentiation of mitral valve prolapse from rheumatic mitral disease. These are listed in Table 2.

Mucoid degeneration	*Chronic rheumatic valve disease*
Degenerative process	Inflammatory process
Fibrosa affected only	All valve layers involved
Cusp expands (loss of density)	Cusp contracts (fibrosis following inflammation)
Commissures not adherent	Usually commissural adhesions
No calcification (apart from any coexistent mitral ring deposits)	Often calcified
Chordae thin, or showing friction changes only	Chordae usually thick, fused, contracted
Cusp anatomical layers remain distinct microscopically	Fibrous disorganization of cusp architecture microscopically
No vascularization	Vascularized cusps usual

In summary, the entire mitral apparatus is affected in MVPS: the leaflets, chordae tendineae, papillary muscles, annulus and subjacent endocardium. It is no surprise that the mitral apparatus fails to function properly in this syndrome.

Mechanics of Mitral Valve Prolapse

All components of the mitral apparatus must function properly for competent closure of the mitral valve (Roberts, 1973). As the ventricle contracts during systole, it shortens longitudinally. The papillary muscles contract simultaneously, keeping tension on the chordae tendineae that provide support for the mitral leaflets. In MVP, the leaflets are relatively too large for the annulus and ventricle and tend to balloon back into the left atrium during systole. Poor apposition of the leaflets then allows regurgitation. Elongation of the chordae tendineae, mitral annular dilatation, and dyskinetic (i.e. chaotic or disorganized) left ventricular contraction, especially inferiorly or inferolaterally, all contribute toward improper coaptation and leakage of the valve.

Fontana (1970) noted, as did Osler, that the click and murmur of MVP were markedly affected by changes in position. Standing causes the click to move closer to the first heart sound (S_1) and the murmur to become louder and longer. A similar response was provided by amyl nitrite inhalation, (Epstein and Coulshed, 1973; Winkle, 1975), head-up tilting, (Towne, 1978), and right atrial pacing (Towne, 1975). All of these maneuvers diminish left ventricular end-diastolic volume and exaggerate the mismatch between LV chamber size and leaflet and chordal architecture. Maneuvers or positions which increase LV

volume, such as isometric handgrip exercise or a supine position, can be used to diminish the degree of prolapse.

Mathey (1976) used a combination of echocardiographic and phonocardiographic techniques to demonstrate that the prolapse and the click occurred at a reproducible, constant left ventricular volume for a given patient. The above mentioned maneuvers merely hasten or delay the point in systole at which the critical prolapse volume is reached.

The click has been recorded in the area of the mitral valve using intracardiac microphones, and is generally believed to be produced by tensing of the chordae tendineae (Ronan, 1965). The click occurs simultaneously with the systolic retraction noted on the apex cardiogram, an event which heralds the onset of mitral regurgitation (when present). As with other heart sounds, it is not clear whether the click is due to actual vibration of the chordae, the mitral valve leaflets, both structures, or perhaps turbulence from flow reversal. Sometimes the maneuvers do not produce the expected result; the click and murmur might be heard better supine than standing, amyl nitrite inhalation can cause both click and murmur to disappear, etc. These paradoxical responses are probably the result of a complex interaction of altered left ventricular volume and contractility. Both factors (volume and contractility) affect mitral valve function and can have opposite effects. The complexity and variability in the interaction of these factors may explain the sometimes intermittent nature of the click-murmur complex.

Clinical Presentation

The majority of patients with MVPS complain of atypical, non anginal chest pain, palpitations, shortness of breath, dyspnea, fatigue, lightheadedness, or syncope. The reported incidence of such symptoms among MVPS patients varies considerably from one series to the next, but these complaints constitute the overwhelming majority of those encountered in clinical practice. Table 3 lists the percentage of patients with each complaint drawn from patient data of several large series.

SYMPTOMS IN MVPS

	NUMBER OF PATIENTS	CHEST PAIN %	DYSPNEA %	PALPITATIONS %	SYNCOPE %	FATIGUE %
HANCOCK AND COHN 1966	40	35	30	48	10	12
MALCOLM 1976	85	72	"MANY"	49	14	"MANY"
JERESATY 1973	100	61	18	46	4	22
COGHLAN 1979	44	30	"COMMON"	8	4	?

A majority of patients with symptomatic MVPS are female, despite an autosomal dominant mode of inheritance for the disorder. (Table 4)

Sex Ratio In Mitral Valve Prolapse

Author	Year	# Patients	% Women
Barlow	1968	90	65
Pocock and Barlow	1971	130	72
Jeresaty	1973	100	64
Malcolm	1976	85	58
Hancock and Cohn	1966	45	58
McLaren	1976	168	65
Chandraratna	1977	74	64
Coghlan	1979	44	70
DeMaria	1974	33	66
		769	65

Typically, the women will be in their twenties or thirties. They are often nervous and high-strung individuals (Hancock and Cohn, 1966), and can frequently be recognized in the waiting area. They are usually tall and thin and some have a Marfanoid habitus, although other characteristics of that syndrome are absent (wrist and thumb signs, ectopia lentis, arachnodactyly). Skeletal abnormalities are common (Salomon, 1975; Bon Tempo, 1975). Up to 70% of patients will have some minor deformity such as straight back, dorsal scoliosis, or pectus excavatum. We have examined a group of women with MVP, with and without MVP syndrome, and have found them to be taller than the average for the US population, and to have an increased arm span to height ratio, a narrow AP chest diameter and smaller calf and thigh circumferences (Schutte, 1980). Udoshi (1979) studied 76 male and 4 female patients selected for the presence of skeletal abnormalities. Thirty-one per cent had evidence of MVP by echocardiography. Thus one can have a high index of suspicion of MVP based on physical characteristics even before the patient is examined. Consistent with these generalized developmental abnormalities is the finding of unusual fingerprint patterns in MVP patients (Swartz, 1976).

Other complaints from our MVPS patients include poor sleep habits, and a "cold-natured" feeling associated with cold hands and feet. Raynaud's phenomena has not been seen in MVP. Orthostatic intolerance is surprisingly

common and manifests itself as lightheadedness or near-syncope when arising in the morning or when changing position suddenly. Blood pressure is eventually maintained but with marked vaso-constriction, high heart rate, and a narrow pulse pressure.

These symptoms may have a life-long duration, but generally fit into two patterns. Our experience suggests that one group will have been aware of their symptoms since sometime after puberty. This group will have generally ignored their symptoms until an event such as syncope or the observation of frequent PVC's during a routine exam results in a referral for cardiac evaluation. A second group will have a distinct, definable onset of symptoms, often to an exact date. These patients will describe themselves as previously healthy and well-functioning and, although there are often signs of pre-existing emotional and/or cardiovascular problems, they were usually coping adequately until the onset of current symptoms. These latter patients are the ones who report severe chest pain, weakness, fatigue, palpitations in the absence of serious arrhythmias, and poor exercise capacity. Panic attacks are also common in this group. Not surprisingly, these are the ones who are most often diagnosed as neurotics. It is important to recognize, however, that both groups - those with significant arrhythmias found serendipitously and those with these "neurotic" complaints -are very typical of MVPS and it should be suspected in both situations. MVP and MVPS are seldom found in the elderly. Most of the patients seen in Cardiology at this institution are more than 50 years of age, but most of those diagnosed with MVP are usually under age 40. The disease appears to "cure" itself with time.

Physical Exam

Despite a multiplicity of available diagnostic modalities in cardiology, mitral valve prolapse remains an auscultatory syndrome. A sharp, crisp, mid-systolic click followed by an apical systolic murmur of mitral regurgitation is the hallmark of this syndrome. The click and murmur may occur together or separately. Auscultatory findings are as follows:

1) Mid-systolic click followed by a late-systolic murmur
2) Isolated (non-ejection) early, mid or late systolic click(s)
3) Isolated late or pan-systolic apical murmur of mitral regurgitation
4) Precordial "Honk" or "Whoop"

Jeresaty (1979) has tabulated the auscultatory findings in 350 patients followed by himself and his associates. Experience at this institution shows a similar distribution of findings. (Table 5)

Isolated mid to late systolic click	186	(53.1%)
Early click	4	(1.1%)
Midsystolic click and late systolic murmur	60	(17.2%)
Late systolic murmur	7	(2.0%)
Precordial honk	4	(1. %)
Pansystolic murmur	30	(8.6%)
"Silent" MVP	59	(16.9%)
Total	350	(100%)

The click and murmur can come or go in an individual patient depending on the circumstances at that moment. This can be used to advantage by the physician to bring out the click and murmur in MVPS patients. The simplest method is to examine the patient first while she is squatting and then while standing. This may seem a bit strange to those trained to auscultate the mitral valve with the patient in the left lateral decubitus position, but results can sometimes be dramatic. In fact, the so called "whoop" or mitral "honk" are almost never heard in any position but standing. Several of these "honks" have been so loud that they could be heard several feet from the patient (Osler, 1880; Hancock and Cohn, 1966; Segall, 1976; Young, 1977).

Amyl nitrite inhalation produces a similar decrease in left ventricular end diastolic volume by peripheral vasodilatation, but also gives a significant tachycardia. The strain phase of the Valsalva maneuver reduces venous return and left ventricular end diastolic volume. These maneuvers cause the onset of prolapse to occur earlier in systole. The click will appear to move closer to S_1 but actually systole shortens and S_1 moves closer to the click (Winkle, 1975; Towne, 1978). The murmur will become longer and often louder under circumstances of diminished ventricular volume. Of all the maneuvers and interventions, we have found auscultation with squatting and standing to be the most useful. Phonocardiograms can be taken in these positions and with amyl nitrite to confirm the examiner's findings, if necessary. Other findings on physical exam related to skeletal abnormalities have already been mentioned in the previous section.

Since a variety of cardiac and non-cardiac conditions (e.g. ischemic heart disease, cardiomyopathy, and thyrotoxicosis) can present with symptoms similar to mitral valve prolapse syndrome, the above suggestions for examination should only compliment, and not substitute for, an otherwise thorough physical examination.

Diagnostics

There are a variety of tests available to the physician that will aid in diagnosing mitral valve prolapse. These will be discussed in order of usefulness.

Phonocardiogram

A typical mitral valve prolapse phonocardiogram is shown in Figure 2. There may be multiple clicks (Desser and Benchimol, 1972) that are not appreciated on auscultation. Simultaneous carotid pulse tracing or apex cardiograms can help differentiate an early mitral click from ejection sounds. Ejection sounds tend to occur during the first 80 msec of systole and do not move toward or away from the first heart sound with changes in left ventricular volume. With early severe prolapse, clicks may occur during the first 80 msec of systole, but these are unusual (Hutter, 1971; Feldman, 1972; Chandraratna, 1977).

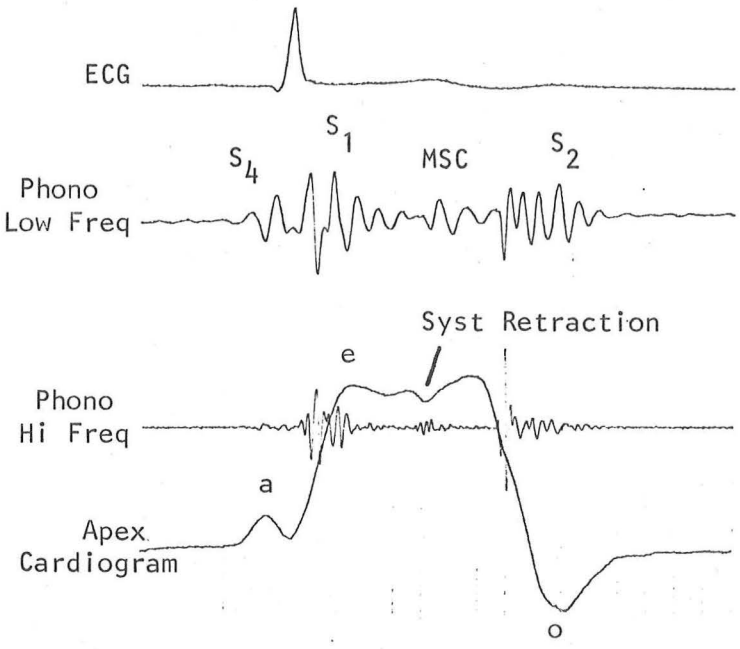


Figure 2 shows an ECG, phonocardiogram and apexcardiogram from a 25 year old woman with MVP syndrome.

The carotid pulse tracing and the apexcardiogram often show a notching at the point in systole at which the click occurs. Simultaneous echo and phonocardiographic studies have confirmed the click and systolic apical retraction occur at the onset of prolapse of the mitral leaflets. Presumably, the prolapse causes a transient decrease in LV ejection, resulting in a palpable dip in the apical impulse and a recordable notch in the carotid pulse. Echo tracings of the aortic leaflets provide collaboration for this explanation (Howard, 1977).

A number of authors have reported the presence of a proto-diastolic click in MVP (Bonner, 1976, Cheng, 1977; Aintablian, 1978; Genda, 1978). Simultaneous echo and phono tracings show it to occur at the onset of left ventricular posterior wall relaxation and mitral valve opening. It occurs before the usual "opening snap" of mitral stenosis, but at a time when ventricular blood flow is changing direction, contraction is ending, and the mitral valve is beginning to open. The exact etiology of this sound is unknown, but its presence could lead to an erroneous diagnosis of rheumatic heart disease in an MVP patient on the basis of mitral regurgitation and an opening snap. A systolic click and murmur which move in the typical fashion with changes in ventricular volume and an absence of mitral stenosis on echocardiography will allow differentiation of these two disorders.

Electrocardiogram

The electrocardiogram is often abnormal in MVPS patients. Bowers (1961) called attention to inferior ST and T wave changes in 7 of 55 patients with mitral valve prolapse in the Marfan syndrome. Two of these seven patients had pathological confirmation of the presence of the typical "floppy" mitral valve. Barlow (1968) detailed findings in 90 patients with prolapse; 54 had normal electrocardiograms, and 22 were abnormal secondary to coexisting ischemia, hypertensive or congenital heart disease. The remaining 14 had evidence of infero-posterior ischemia or infarction. The typical pattern consisted of small Q waves in leads II, III, and AVF with elevated ST segments and inverted T waves in the same leads. Similar changes were also seen in lateral leads V_5 and V_6 suggesting involvement in that area as well. An occasional patient had Q waves across the precordium with tall peaked T waves and some ST elevation. (see Figure 3).

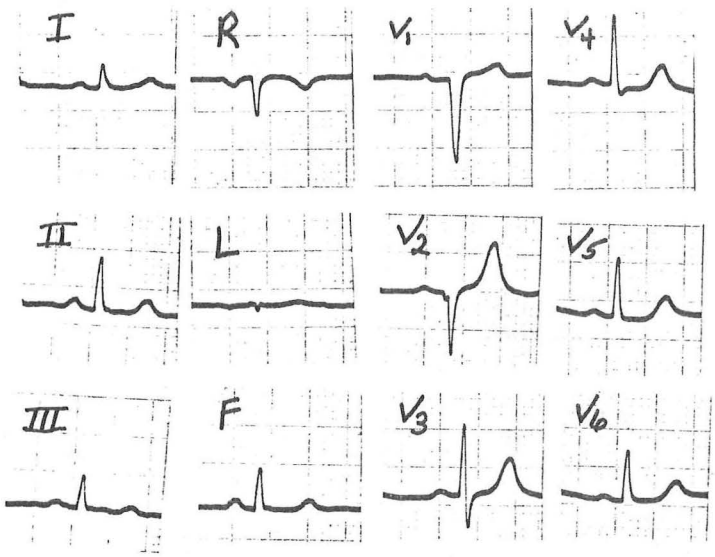


Figure 3 shows an ECG from a 42-year-old woman with MVP syndrome. She has normal coronary arteries despite the QS pattern in leads V_{1-2} which are consistent with an old anterior myocardial infarction.

Even with what is now known about ST and T changes in particularly fit individuals and so called "Athletes Heart" (Blomqvist, 1979), it would be very difficult for one to read anything but an old infarction in many of these cases. Cardiograms repeated biannually in 11 of these 14 patients revealed PVC's in 5, and a prolonged PR interval (1° heart block) in two. Three additional patients, under age 40, with normal resting cardiograms, had paroxysmal atrial fibrillation. Since Barlow's description of the electrocardiographic changes in MVP, numerous studies have documented the absence of

any coexisting coronary artery disease to explain these abnormalities (Lobstein, 1973). Jeresaty (1973) noted a 42% incidence of inferior T wave changes in his series of 100 patients. Barlow and Pockock (1975) reviewed 144 cases and found a 37% incidence of abnormal ECG's, 22% being the typical inferior T wave flattening and inversion. Probably the largest study of ECG's in MVP patients who were catheterized to rule out other cardiac disease was that of Lerdani and his colleagues at the Cleveland Clinic in 1976. They retrospectively reviewed 125 cases of angio-diagnosed MVP. There were 68 men and 57 women, mean age 43 years. Patients with other forms of cardiac disease were not included and all in the series had normal coronary arteries. Thirty-six percent had inferior T wave inversion. There was no correlation between the severity of the prolapse and the presence or absence of ECG abnormalities.

While the incidence of ST and T changes among patient populations is about 1/3, it is much lower in general surveys where asymptomatic MVP as well as MVP syndrome are studied. Markiewicz (1976) found only 18% abnormal ECG's while Procacci's (1976) much larger survey of 1169 women found a 15% incidence. Any series of catheterized patients will probably have a high incidence of "ischemic" ECG patterns, in that those findings with chest pain often result in cardiac catheterization, particularly in older patients at higher risk of coronary artery disease. The significance and possible etiology of these ECG changes, as well as the association of MVP with Wolff-Parkinson-White syndrome, QT prolongation, and various arrhythmias will be discussed in subsequent sections.

Exercise Testing

As one might anticipate from the previous section on resting electrocardiographic abnormalities, the interpretation of the stress electrocardiogram is a difficult matter. There are about 25 publications on ECG abnormalities in MVP patients, but very few papers study the exercise response in mitral valve prolapse. DelRio (1971) discussed abnormal post-exercise ECG's in 10 women with MVPS and normal coronary arteries. These all had typical ST and T abnormalities present before, during and after exercise. Malcolm (1976) reported 44 patients with MVPS, 39 of these with cath proven normal coronary arteries. Eighteen stopped exercise prior to reaching target heart rate. Reasons for stopping included: chest pain (5), fatigue (7), ventricular arrhythmias (4), dizziness (1), and ST depression (1). There were 12 of 39 with a "positive" ST response to exercise, that is $\geq$ 1 mm ST depression for at least 80 msec. Six others had non-diagnostic ECG changes. These authors felt that the responses differed from true ischemic changes in that they either disappeared immediately after stopping exercise or they persisted for more than 10 minutes. A subsequent paper by the same authors gave a further breakdown of these ST changes in a larger series. Only two patients had typical ST changes and both were later found to have coronary artery disease. Other patients had long-lasting ST depression atypical of exercise-induced ischemia. We have studied twelve patients with MVPS (Gaffney, 1978). Patients over 35 years of age had been catheterized for other indications

prior to the study. Three of the 12 women had "ischemic" responses to exercise; one of these 3 had left main coronary artery disease and the other 2 had abnormal resting ECG's.

Diagnostic accuracy of the exercise electrocardiogram is extremely poor and unreliable in the presence of resting ECG abnormalities involving the ST and T waves. In evaluating studies of MVPS patients' responses to exercise, one must know whether the resting ECG's were normal or not. An abnormal resting ECG is often the reason many of these patients were exercised in the first place. The solution of this problem would require a study in which MVP patients with normal resting ECG's are exercised. This has not been done.

For these reasons, patients in our laboratory are not stressed for diagnostic purposes as much as for determination of functional capacity. As noted in the section on "Clinical Presentation", patients with MVPS often have atypical chest pain, fatigue, poor exercise capacity, shortness of breath and dyspnea. An exercise test provides the physician with an objective assessment of the patient's complaints. Crowe (1979) and colleagues at Iowa have used exercise stress testing to separate patients with such "neurotic"-type complaints into two groups: those with and those without impaired exercise capacity. In 20 patients with a psychiatric diagnosis of "anxiety neurosis," 8 with impaired exercise performance were found to have mitral valve prolapse by echocardiography and physical exam without significant mitral regurgitation. Those without mitral valve prolapse had normal exercise tolerance despite their history of diminished capacity. The full importance of these findings in respect to the pathophysiology of MVPS patients complaints remains to be determined but it does suggest the need of a thorough, objective evaluation of MVPS patients.

In order to differentiate symptoms caused by coronary artery disease from those present in mitral valve prolapse syndrome several groups have utilized myocardial perfusion scintigraphy during exercise (Gaffney, 1978; Massie, 1978; Klein, 1978). These authors have found that patients with mitral valve prolapse syndrome and normal coronaries do not have perfusion defects on scintigraphy, regardless of the presence or absence of electrocardiographic changes or arrhythmias. This test should help the clinician evaluate the older patient who has prolapse, but also has a history somewhat suggestive of coronary artery disease. An abstract by Tresch (1978) suggested that the majority of patients with mitral valve prolapse have thallium perfusion defects during exercise and at rest. However, these authors found no correlation between symptoms, electrocardiographic abnormalities, the presence of perfusion defects or their location. These findings obtained without quantitative scintigraphic data require verification. Extensive investigation of wall motion by scintigraphy has not been carried out in mitral valve prolapse but contraction abnormalities have been documented by angiography in a number of centers. One would expect the same abnormalities to be seen with this nuclear technique. For this reason, one would anticipate nuclear wall motion studies to be of no use in differentiating mitral valve prolapse from coronary artery disease. These studies may have value as

a semiquantitative method of estimating regurgitant fraction. They may also be useful as a research tool for evaluating the effect of various drug interventions on LV function in MVP.

Echocardiography

M-Mode echocardiography can be useful when there is still a question of mitral valve prolapse after the history and physical examination have been completed. Shah and Gramiak (1970) were among the first to describe the two main patterns of mitral valve prolapse on echocardiography: mid-systolic buckling and pan-systolic bowing. An additional 40 to 50 publications have appeared since that time, but none has settled the major question of what constitutes prolapse on echocardiography.

A number of authors have published criteria for interpreting the echo but the lack of a "gold standard" has doomed their efforts from the start. Markiewicz (1976) published an elaborate set of outlines for the diagnosis of MVP. (see Figure 4).

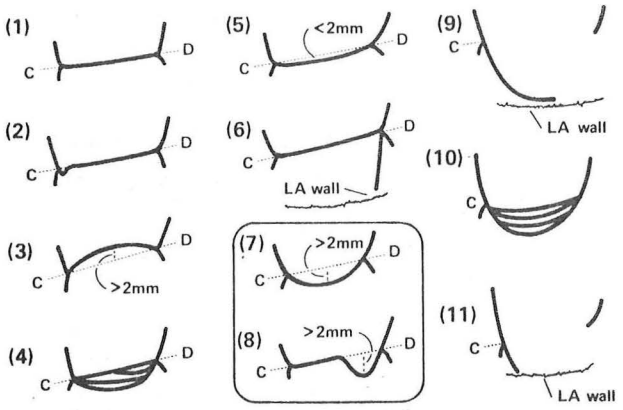


FIGURE 4. *Diagrammatic schema used to classify echocardiographic patterns of mitral valve systolic motion. Patterns 7 and 8 are those previously reported in association with mitral valve prolapse.* C = *apparent point of coaption of anterior and posterior mitral leaflets.* D = *point of apparent leaflet separation. Pattern 1) Predominant echo extending directly along* CD *line. Pattern 2) abrupt early posterior motion (20–80 msec). Pattern 3) predominant echo curvilinear and anteriorly convex deviating more than 2 mm from a drawn* CD *line. Pattern 4) predominant pattern 1 with addition echoes posterior to the CD line. Pattern 5) smooth pansystolic anteriorly concave (hammock shaped) echo deviating less than 2 mm from the drawn* CD *line. Pattern 6) a low-intensity echo extending from the left atrial wall and merging with the anterior mitral leaflet in early diastole. Pattern 7) smooth pansystolic anteriorly concave (hammock shaped) echo deviating more than 2 mm from the drawn* CD *line. Pattern 8) late systolic posterior motion extending more than 2 mm posterior to the drawn* CD *line. Pattern 9) marked posterior motion of the leaflet echo close to the left atrial wall and visible more than 50% of systole. Pattern 10) multiple smooth pansystolic anteriorly concave (hammock shaped) echoes without clearly defined* D *point. Pattern 11) marked posterior motion of the leaflet echo merging with the left atrial wall echo in early systole.*

Although his suggestions are not widely accepted, we have found them useful, but perhaps too selective and often not applicable. DeMaria has two publications on the diagnostic criteria of MVP, (1974 and 1977). The first specifically addresses "the variable spectrum of MVP" and used angiography as the standard for diagnosis. The illustrations are clear-cut examples of either mid-systolic buckling or pan-systolic bowing and present no diagnostic challenge even to the most naive observer. The 1977 paper repeats the 1974 observations and, in fact, uses the same echocardiograms as examples. It

does not tell the reader what to do with less than classical echoes.

There are a number of inherent limitations, in diagnosing mitral valve prolapse, some specific to the disease and others specific to echocardiography itself. First, prolapse is a dynamic lesion and may not be present when the echocardiogram is taken, although specific studies similar to those done with phonocardiography have not been carried out. Winkle (1974, 1976) determined that propranolol had no effect on the timing of prolapse as observed on echocardiogram. Amyl nitrite inhalation converted a few patients from mid- to pan-systolic prolapse on echo, but this was an inconstant finding. He concluded that the differences between the two studies were due to the more pronounced changes in LV volume produced by the amyl nitrite. Sahn (1977) has shown that the pattern of prolapse is somewhat dependent on the position of the transducer, providing another reason why Winkle was not able to find differences in timing of the prolapse on echo; Winkle's studies utilizing amyl nitrite were done acutely, while those with propranolol were accomplished with observations obtained over a period of several weeks. A much greater variability in transducer position is likely for the latter study. A second problem is that the prolapse patients often have chest wall deformities and midline hearts that make the echo technically very difficult to obtain. Third, prolapse may occur in a direction which is parallel to the echo beam and thus not detectable by single crystal M-Mode echocardiography. Finally, there are a number of transducer positions, particularly those from superior intercostal interspaces, which can give a false-positive picture of mitral valve prolapse in up to 50% of the patients examined. To avoid technically-induced false-positive echocardiograms, one must position the transducer perpendicularly or inferiorly to the mitral valve. One must also record both the anterior and posterior leaflets and the closing "C" and opening "D" points. Echoes which do not meet these technical criteria are difficult, if not impossible, to interpret accurately. Large pericardial effusions with a swinging heart can produce a picture similar to MVP so caution is to be exercised in that situation (Levisman, 1976).

Putting all of these problems aside (not an easy task) one can examine the echo's relative diagnostic sensitivity against either phonocardiographic or angiocardiographic standards. Markiewicz (1977) in his survey of 100 presumably healthy women at Stanford found a 17% incidence of MVP by phono, a 21% incidence by echo, but only 10% had both phono and echo positive. Procacci (1976) found that, of the women with prolapse, 92% had either a click or a click and murmur, while 81% had a diagnostic echo. Differences between the two studies probably relate to the different criteria used for diagnosis. Malcolm (1976) found an 80% sensitivity for echo when compared with phono, DeMaria 90%, and Jeresaty estimates 80%.

Comparisons of echocardiographic with angiographic studies show far less agreement. Boughner (1975) found an overall agreement of 54%, No phonocardiographic data were given, however and the two techniques may well be identifying patients with different "diseases". Ruwitch (1977) reported

twelve cases of MVP in which the echo was definitely positive in only one and probably positive in another two. None of these patients had the classic mid-systolic click, late systolic murmur complex on auscultation. Subsequent letters to the editor debated the appropriateness of the authors' angiographic criteria for MVP but this controversy was not resolved. It seems that angio will identify a large segment of the population with MVP who have neither physical nor clinical findings of MVPS.

In summary, if one has a patient with a persistent mid-systolic click - late systolic murmur complex, chances are 80-90% that an echo will confirm prolapse, but the diagnosis has already been made by auscultation. In the presence of an early or intermediate click on an isolated mitral murmur, echocardiographic sensitivity is diminished, but can still be helpful if a clearly diagnostic pattern is present. The clinical significance of MVP on echo without auscultatory findings is not clear, although it is an important diagnostic category to some investigators. Jeresaty's (1979) "Silent" prolapse is exceedingly rare at this institution despite an avalanche of patients referred for echocardiography with a "diagnosis" of R/O MVP.

Two-Dimensional Echocardiography

Two-dimensional echocardiography has been available for about three years and was immediately applied to the diagnosis of mitral valve prolapse (Gilbert, 1976; Sahn, 1977; Terasawa, 1978). These authors have utilized two-dimensional echocardiography to explain why M-mode echo sometimes fails to record mitral valve prolapse and why it produces false positives under certain circumstances. Two-dimensional echocardiography did not initially appear to offer substantial advantages over M-mode, but this is changing as researchers gain more experience with the new technique. Two-dimensional echocardiography gives the examiner the ability to assess left ventricular function with particular emphasis on wall motion in the posterior inferior aspect of the heart, where abnormalities often occur in patients with prolapse. The size of the mitral valve can be appreciated more easily with two-dimensional echo. Finally the 2D echo allows one to pick precise locations for recording M-mode tracings. It is expected that studies with this new tool will lead to a more useful and inclusive scheme for diagnosing prolapse, including such items as left ventricular wall motion abnormalities in the area of the mitral annulus and the size of the mitral valve, as well as the more traditional recordings of prolapse itself.

Angiography

Although Humphries and Mckusick utilized angiography to document mitral valve prolapse in the Marfan syndrome, the first angiographic report in a patient with mitral valve prolapse syndrome was by Ross and Criley (1962). Barlow published 4 additional cases in 1966, and termed it "aneurysmal protrusion of the posterior leaflet of the mitral valve". A pair of papers by Grossman (1968) and Ehlers (1970) gave angiographic and clinical data on 6

young women, 5 with mitral valve prolapse syndrome and 1 with the Marfan syndrome. Ranganathan (1973) reported 16 patients with angio confirmed MVP. Eleven of these had severe mitral regurgitation. He noted triscalloped bulging of the posterior leaflet into the left atrium and identified these scallops anatomically. (see Figure 5).

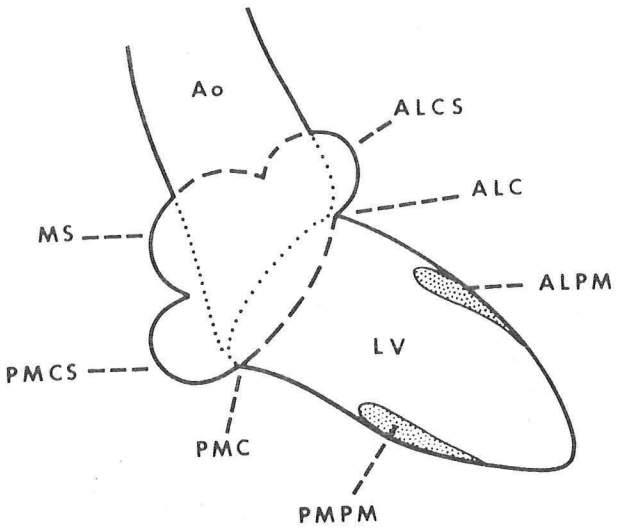


Figure 5.

Line diagram of a left ventriculogram in the RAO projection. The upper continuous and barred line extending from the posteromedial (PMC) to the anterolateral commissure (ALC) outlines the prolapsed scallops of the posterior leaflet of the mitral valve. (PMCS = posteromedial commissural scallop; MS = middle scallop; ALCS = anterolateral commissural scallop of the posterior leaflet). For orientation the locations of the posteromedial (PMPM) and anterolateral (ALPM) papillary muscles have been outlined in the left ventricle (LV). Their apices usually point toward the respective commissures. Also included is the location of the normal mitral valve ring shown by the lower dotted and barred lines forming a circle. The barred line represents the posterior mitral ring. Note that the anterior part of the mitral ring (dotted line) has a common attachment with the aortic root (AO).

Pathological examination of valves obtained at surgery showed the typical changes seen in MVPS. Interestingly, none of the patients had serious involvement of the anterior leaflet, which perhaps explains why no anterior leaflet prolapse was found by echo in this study.

Jeresaty (1979) discusses this point at length in his text on MVP. In a series of 40 patients with MVP, he found 27 with isolated posterior leaflet prolapse, pure anterior leaflet prolapse in 1, and combined disease in 12. A subsequent paper by Ranganathan (1976) found isolated posterior leaflet prolapse in 42 patients, both leaflets prolapsed in 17, and isolated anterior leaflet prolapse occurred in none of the patients. (It should be noted that the latter study included the cases from his 1973 publication.)

A further angiographic sign described by Jeresaty (1979) is the so-called "doughnut" pattern, seen with prolapse of both leaflets and often with annular dilatation as well. The latter has also been responsible for causing the angiographic mitral valve outline to appear unaltered in both systole and diastole.

In addition to the abnormalities of the mitral apparatus itself, numerous authors have called attention to the abnormal patterns of contraction seen in mitral valve prolapse. The most common pattern has been called the

"ballerina's foot" or the "hour-glass" because of contraction in the central portion of the left ventricle with anterior and inferobasal dyskinesis (Gooch, 1972; Scampardonis, 1973; Liedtke, 1973; Cobbs, 1977).

Despite the almost universal agreement that LV contraction abnormalities are common in MVP (see DeMaria, 1975 for an exception) there is little agreement on why the pattern exists. Some authors have described hyperkinetic changes (Scampardonis, 1973), others hypokinetic changes (Liedtke, 1973), and dyskinesis (Gooch, 1972; Gulotta, 1974). Probably the one thing that can be said with certainty is that the majority of MVPS patients will have some left ventricular contraction pattern abnormality and that the inferobasal and anterior regions subjacent to the papillary muscles are most likely involved. Cobbs (1978) reported improved LV contraction in some but not all patients following mitral valve replacement.

As with echocardiography, there is substantial disagreement as to what constitutes MVP on the angiogram. DeMaria (1977) asked 20 trained cardiologists to review 13 "clear cut" angiograms and got no agreement in diagnosing the films. The confusion is nowhere more evident than in the papers dealing with the subject of coronary artery disease and MVP. Raizada (1977) reviewed echocardiograms and angiograms from 25 patients with angina and coronary artery disease. Sixty percent had prolapse of the posterior leaflet by angiography, 5 had positive echoes. There was a reasonable correlation of prolapse with the severity of coronary artery disease, leading these authors to conclude that: 1) coexisting mitral valve prolapse and coronary artery disease are usually associated with triple vessel disease, 2) Inferior ischemia is an important correlate, and 3) Echo is positive in only about 1/3 of the cases. Jeresaty (1977) immediately criticized the quality of the echoes and angios used in this paper. The authors responded with further data to support their premise. However, their criteria for diagnosing prolapse by echo and angio are not clear and are probably not generally accepted. Verani (1976) reported angio data on 130 patients, 15 of 92 with coronary artery disease had MVP, and 5 of 28 with normal coronaries also had MVP. There were no correlations between the extent of coronary artery disease, LV segmental contraction abnormalities, and MVP. Two patients with "clear-cut" MVP and coronary artery disease were later shown to have normal mitral valves at autopsy. Smith (1977) reported that, of 358 patients examined angiographically, 40% had MVP. Six patients had clinical MVPS and of these all had positive angios and echoes. The rest did not. Thus, coronary artery disease can induce MVP, probably as the result of papillary muscle dysfunction, but it does <u>not</u> produce MVPS.

In 1979 Cohen, Shaw, and Spindola-Franco published an excellent series of angiographic and echocardiographic correlations in MVPS. These authors reviewed 860 angiographic cases performed between 1973 and 1977. Utilizing the criteria for diagnosis of MVP derived from these 860 patients, another 1022 angiographic studies were analyzed prospectively between 1975 and 1979. Four types of diastolic ventricular configurations were described, each with

the mitral valve fulcrum in a different location. (see Figure 6).

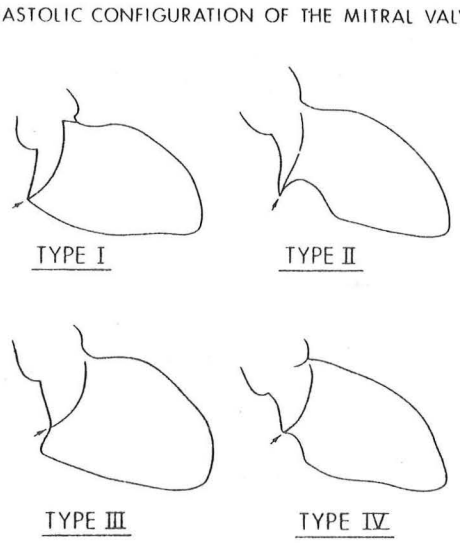
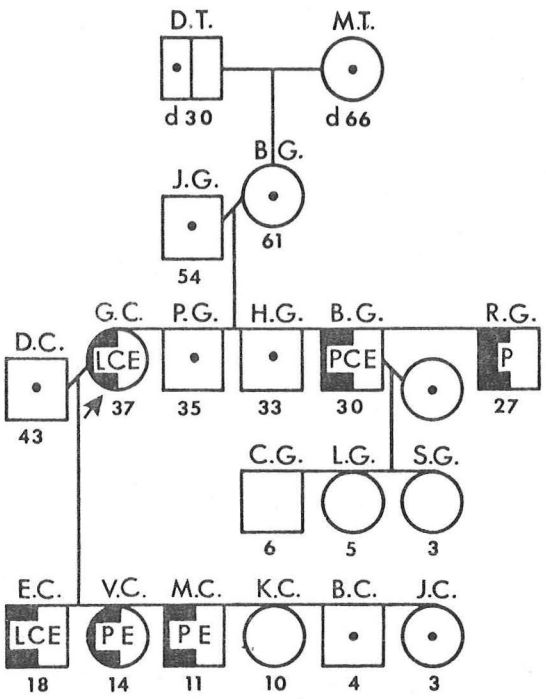


Fig. 6. Sketches of diastolic frames of left ventriculograms demonstrating the four mitral valve configurations. The arrows identify the mitral valve fulcrums. Types I and II have low fulcrums, but Type II has a notched fornix. Types III and IV both have high fulcrums, and the fornix is also notched in Type IV.

Prolapse was diagnosed as present when the leaflets protruded inferiorly and posteriorly in relation to this fulcrum. Twenty one patients, or 1.9% of the adults catheterized in these series, had angiographic MVP which met their criteria. All had an echocardiographic diagnosis of MVP, also. Three other patients with echo MVP in this series had normal ventriculograms. Overall diagnostic agreement was approximately 88%. By their method, the frequencies of angiographic, echocardiographic, and clinically diagnosed MVP were not significantly different. Rigid adherence to the criteria suggested by these authors for interpretation of the angiogram would diminish the confusion surrounding the angiographical diagnosis of MVP.

Inheritance

Mitral valve prolapse is an inherited trait transmitted as an autosomal dominant. A large number of family studies has been published documenting this inheritance pattern. The pedigree of a family with mitral valve prolapse reported by Shell (1969) is shown in Figure 7. There are three case reports involving twins. Girard and Girard (1977) reported MVP in themselves and in their 74-year old mother. Vuthoori and Beard (1979) reported two 20-year-old female identical twins, both with palpitations, histories of infantile pyloric obstruction requiring surgery, and skeletal abnormalities. Rizzon (1973) reported two twins with MVP, associated with straight back, pectus excavatum, and high, arched palates.



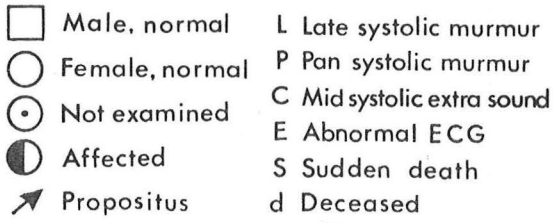


Figure 7.

The pedigree of the G.C. family (family 1), showing that six of 10 individuals examined had a mid-systolic extra sound, a late systolic murmur, a pansystolic murmur, an abnormal electrocardiogram, or some combination of these findings.

Prevalence

One of the more puzzling aspects of MVP has been the surprisingly high prevalence of the condition in otherwise normal individuals. Rizzon (1973) found a 0.33% prevalence in 1009 women studied. Brown (1975) examined and performed echo and phonocardiograms in 700 asymptomatic volunteers, 120 men and 580 women. One man (0.5%) and 29 women (16%) had MVP by echo. Twenty three of the echo-positive women had a non-ejection systolic click and/or apical murmur documented by phono. An additional 10 men and 32 women had clicks or murmurs on phono but these were not categorized as typical of MVP. A summary of prevalence data, presented by sex, is shown in Table 6.

In examining these papers, one must be aware of a number of problems associated with the study designs. First, any survey of "asymptomatic" individuals should not advertise "free heart tests" as a method of soliciting volunteers. Markiewiez (1977) used such advertisements in the Stanford Daily to recruit his volunteers. Forty-nine percent of the women answering these ads had murmurs, 53 a history of syncope, and 60 were regularly taking oral contraceptives or other medications. Hence, the population was anything but asymptomatic and unselected. As a result, his estimate of MVP prevalence

remains the highest in the literature.

A second problem concerns the method of diagnosis of MVP. Echocardiographic studies find a much higher prevalence of MVP than that seen in either phono or autopsy series. Ideally, one would like to have a non-invasive method which detects persons who have true myxomatous degeneration of the mitral valve. The data presented in Table 6 suggest that the combined echo/phono studies come closest to that goal if autopsy series are the "gold standard."

Prevalence of MVP

	Author	Year	Number Examined	% with MVP	Comments
Male					
	Brown	1975	120	0.5	General Population
	Sbarbaro	1979	100	4	Echo only; Medical Students
	Dorsee	1979	107	6	MSC-LSM, (+) Echo 1 Symptomatic
	Davies	1978	1111	3.9	Autopsy Series
	Longo	1977	900	1.5	Air Force Air Crewmen (Highly Selected)
Female					
	Procacci	1976	1169	6.3	Air Force Dependents
	Markiewicz	1977	100	17.0	Stanford Coeds
	Brown	1975	520	1.4	General Population
	Rizzon	1973	1009	0.33	
	Davies	1978	873	5.2	Autopsy Series
Male and Female					
	Pomerance	1969	3083	1	Autopsy Series
	McLaren	1976	12050	1.4	School Children
	Block	1976	136	4.4	

The major question with prevalence studies, in the general population as well as in families, is that of an apparent difference in the sex ratio. There is a higher prevalence of clinically observed MVP among women, although this is not seen in the autopsy series. The latter suggest that, pathologically, MVP affects both sexes equally, as would be expected in a condition with an autosomal dominant inheritance. Yet, despite an equal prevalence pathologically, women seem more likely to have clicks, murmurs, positive

echoes, and symptoms from MVP. Jeresaty (1979) explains this genetically as "incomplete penetrance and reduced expressivity in the male and the young..."

A more precise question is why is the condition more manifest in adult women than in men or in children of either sex? McLaren's (1976) study of MVP in children reported a 1.4% incidence. Although it is uncommon to find MVP clinically in children, it does occur (Sahn, 1977). An alternate to Jeresaty's explanation deals with the dynamic nature of the lesion itself. Cardiovascular sex differences appear mainly at puberty. Causes are complex and not completely understood, but women have higher resting heart rates and lower ventricular volumes, both end-systolic and end-diastolic. It may be that these differences in ventricular configuration cause prolapse to be more manifest in post-pubertal women who have a less favorable ventricular-valvular relationship than in children and men. Proof for this theory is lacking, but it does explain the known facts, without the complicated and somewhat implausible genetic scheme invoked by Jeresaty. It is of interest that in our practice there is a virtual absence of well-trained, highly fit women with mitral valve prolapse. Training produces decreases in resting and submaximal heart rates with corresponding increases in stroke volume and end-diastolic volume. A pilot project, currently underway, examines the effects of conditioning on both symptoms and physical findings of MVPS.

Associated Conditions

A number of cardiac and connective tissue disorders occur so frequently in patients with mitral valve prolapse that some non-coincidental association with MVP seems likely. These disorders will be discussed individually and then a more general discussion will follow.

Skeletal Defects

Skeletal defects have been mentioned in the section on "Clinical Presentation" and have been reported in up to two-thirds of MVP patients (Ehlers, 1970; BonTemop, 1975; Salomon, 1975; Gaffney, 1979; Udoshi, 1979). These abnormalities consist of pectus excavatum, scoliosis, straight back, and a high arched palate. We recently examined a family in which the mother had mild scoliosis and mitral valve prolapse, one daughter had pectus excavatum, another had mild scoliosis but neither had mitral valve prolapse. The link between these skeletal abnormalities and MVP is not known, but it is of interest that both conditions involve defects in connective tissue structures that share a common time of embryological development.

Ehlers-Danlos Syndrome

Cabeen (1977) reported a 51-year-old man with a life-long history of hyperextensible skin and joints with multiple joint dislocations. A strong family history of type III Ehlers-Danlos was present. Classic MVP with a mid-systolic click - late systolic murmur was present on physical exam. Echo-

cardiography showed a pan-systolic bowing pattern of mitral valve prolapse and a dilated aortic root. This man had conduction system disease consisting of complete right bundle-branch block and left posterior hemi-block. The author presents a fine discussion of conduction defects and cardiac disorders associated with Ehlers-Danlos. Brandt (1975) reported a 47-year-old man with a similar history of Ehlers-Danlos. This patient also had paroxysmal atrial tachycardia and a daughter with mitral valve prolapse and paroxysmal atrial tachycardia. Echo in the patient showed pan-systolic mitral valve prolapse and a dilated aortic root. We have seen two patients with Ehlers-Danlos, both with classic physical findings for mitral valve prolapse. Pan-systolic bowing and marked aortic root dilatation were present on echocardiography. There were no symptoms of mitral valve prolapse present. Aortic dilatation, rather than MVP, is not usual cause of morbidity in these patients. Ehlers-Danlos patients have myxomatous degeneration of the mitral valve. The link between these two disorders appears to be a common defect in connective tissue that affects skin, tendons, and cardiac valves.

Marfan Syndrome

Virtually all patients with the Marfan syndrome will exhibit mitral valve prolapse during physical exam or echocardiography on the basis of myxomatous degeneration of the mitral valve. Aortic dilatation is also common in this setting, as with Ehlers-Danlos (Shanker, 1967; Ehlers, 1970; Sahn, 1976; Gruber, 1978). Both mitral and aortic disease can lead to significant morbidity and mortality. MVP can be the mode of presentation for the Marfan syndrome. Any patient with a click and murmur and a Marfanoid habitus should be examined for other signs of the syndrome, including ectopia lentis, wrist sign, thumb sign, family history of sudden death, etc. A common, genetically determined connective tissue defect is responsible for the coexistence of these two disorders.

Although virtually all of the patients with the Marfan syndrome will have mitral valve prolapse, virtually none will have mitral valve prolapse syndrome, i.e. chest pain, palpitations, fatigability, syncope, etc. Although some authors have suggested that MVP is a "forme fruste" of the Marfan syndrome (Read, 1965), this is probably not the case because aortic valve disease is extremely rare in mitral valve prolapse syndrome, ectopia lentis does not occur, etc.

Neurofibromatosis

A single case of neurofibromatosis and MVP has been reported by Etches (1978). It is not clear whether this finding is coincidental or not. The lack of similar cases suggests a coincidence, although careful studies have not been performed.

Osteogenesis Imperfecta

Wood (1973) described two men with osteogenesis imperfecta who had mitral valve prolapse with severe mitral regurgitation. Both required surgery, at which time pathological confirmation of myxomatous degeneration of the mitral valve was obtained. Similar severe valvular and annular degeneration have been reported by others (Criscitiello, 1965; Hill, 1974; Waters, 1977). As with the Marfan syndrome such patients have MVP and may require mitral and aortic valve replacement. They do not have the mitral valve prolapse syndrome.

Tricuspid Valve Prolapse

Tricuspid prolapse appears to occur frequently in the presence of mitral valve prolapse, but difficulties of noninvasive diagnosis make it impossible to determine the precise incidence of this associated finding. Baehrel (1978) reported 10 of 70 patients operated for mitral regurgitation had tricuspid involvement producing tricuspid regurgitation. Eight of these had tricuspid annular dilatation, a common finding in right-sided heart failure, but only 2 had tricuspid valve prolapse itself. Gooch (1972) reported that 6 of 13 patients with MVP also had tricuspid valve prolapse, as documented by right ventricular angiography. Only one of these six had tricuspid regurgitation and it was clinically insignificant. Ten of these patients were women. Ten had skeletal abnormalities including 8 with narrow AP chest diameter and 2 with scoliosis. We have seen one case of definite tricuspid valve prolapse documented by right ventricular angiography in an 8-year-old boy referred to us for an evaluation of skeletal defects and a cardiac murmur. MVP was also present, and was the cause of the murmur. Tricuspid valve prolapse and tricuspid regurgitation do not seem to be a common problem in MVP. Why the tricuspid valve should be involved part of the time without aortic or pulmonary involvement is not clear; nor, for that matter, is it clear why the mitral valve should be affected more than the others. Of the four cardiac valves, the mitral valve is subjected to the highest pressures and the greatest stresses. Its involvement in MVP may be on a basis similar to that which makes it the primary site of rheumatic involvement.

A second category of associated diseases includes a variety of myopathies.

IHSS

Idiopathic Hypertrophic Subaortic Stenosis is a myopathic cardiac disorder characterized by asymetrical hypertrophy of the interventricular septum (ASH). Mitral regurgitation is often present, but clicks are rare. Numerous investigators have noted an occurrence of MVP in patients with IHSS or ASH. Barlow observed IHSS in one of ninety patients in his 1968 series. Gerbaux (1970) reported seven cases of coexisting IHSS and MVP. Jeresaty (1971), in an editorial on the etiology of mitral valve prolapse, noted that 68% of the

twenty-two patients with IHSS in his series also had MVP. Chandraratna (1977) reviewed 190 consecutive cases of "Echocardiographic" mitral valve prolapse (with or without the syndrome) and found 16 with IHSS. Six had a history of syncope or near-syncope, unassociated with arrhythmias.

It should be emphasized that patients with IHSS and echo or angiographic mitral valve prolapse do not have MVP syndrome, and there is no evidence that myxomatous degeneration of the mitral valve is generally present. There is a single case report of a 69-year-old man with severe mitral regurgitation, myxomatous mitral degeneration, and classical IHSS. There was nothing to suggest mitral valve prolapse syndrome in this man (Guthrie, 1976).

X-linked Muscular Dystrophy

X-linked Muscular Dystrophy of both the Duchenne type (6/22 cases) and the Becker (benign) type have been associated with mitral valve prolapse (Biddison, 1979). A strong relationship of MVP with either the disease or the carrier state was observed in four family pedigrees. Narrow AP chest diameters were seen in all three female patients with clicks in Family 1. Three men had MVP in Family 2; the two men with clicks also had severe kyphoscoliosis. Myxomatous degeneration of the valve leaflets in two patients was found at autopsy. Similar patterns of coexisting mid-systolic clicks and skeletal abnormalities were found in two other families.

Sanyal (1979) reported results from evaluations of 20 boys with biopsy, biochemical and electromyographic evidence of Duchenne progressive muscular dystrophy. Systolic clicks and scoliosis were present in the seven who had MVP by echocardiography. Another 4 boys with MVP on echo did not have clicks, murmurs, or scoliosis. ECG changes typical of Duchenne cardiomyopathy were present in 6, but the inferior-lateral ST changes of MVP were not found. The exact etiologic relationship of MVP with muscular dystrophy was not determined. Valve involvement was not reported prior to the report cited above. In fact, there is substantial evidence that the mitral valve is not involved in muscular dystrophy (Perloff, 1967; Frankel, 1976). Further clinico-pathological studies are required.

Myotonic Dystrophy

Myotonic dystrophy characterized by myotonia, weakness, frontal baldness, cataracts, and cardiovascular involvement including conduction defects and congestive heart failure, has been found to be associated with mitral valve prolapse. Valvular heart disease had not been previously noted in myotonic dystrophy. Winters (1976) reported a kindred with mitral valve prolapse and myotonic dystrophy. Twenty-five relatives were studied, 10 with myotonic dystrophy. Eight of those ten had MVP on echo, and half had clicks or murmurs. The incidence of skeletal abnormalities was not given, and no pathological data were available. The strong association of MVP with myotonic dystrophy in this kindred suggests genetic linkage. The precise

nature of this linkage and the role of myotonic dystrophy in MVP under these circumstances is not known. Symptoms of MVP were absent from Winters' patients and their ECG abnormalities were typical of myotonic dystrophy but not of MVP. Cook (1978) reported a 55-year-old man with myotonic dystrophy and a harsh apical murmur. Echo showed mitral valve prolapse and autopsy revealed a cupped and thickened mitral valve with myxomatous degeneration of the posterior leaflet. This report suggests some link between the connective tissue defect in MVP and myotonic dystrophy, although the association in this one case could have been coincidental.

Atrial Septal Defects

There is an increased incidence of ostium secundum ASD's in mitral valve prolapse and vice versa. Reports by Barlow and Pocock (1968) and Hancock and Cohn (1966) included cases of MVP and ostium secundum ASD's. By 1975, Barlow and Pocock had seen 36 patients with an ASD and a click or murmur of MVP. The ECGs of their patients were typical of ASD's, and only 6 had the inferior T wave changes of MVP. Left axis deviation, as reported by Victorica (1974), was not seen, and probably represents an ostium primum defect with associated mitral valve abnormalities. Of 54 patients with ostium secundum ASD's, Betriu (1975) identified 20 with posterior prolapse demonstrated by angiography. Eleven of these 20 patients had auscultatory evidence of MVP, 9 had pansystolic murmurs and 2 had mid-systolic clicks. Mitral regurgitation was present in 12 of the 20, including all 9 with murmurs. Five had inferior T wave inversions despite right axis deviation or a rightward axis. These adult patients (mean age 43 years) had findings typical of the mitral valve prolapse syndrome, with chest pain, dyspnea, and both atrial and ventricular arrhythmias. They appeared to have mitral valve prolapse syndrome and an ASD.

Miller (1975) reported a 23-year-old woman with dyspnea and fatigability who had Holt-Oram syndrome (ostium secundum ASD and hypoplastic thumbs). Mitral valve prolapse was seen during catheterization and a ballooning mitral valve was noted during surgery.

Keck (1976) reviewed the angiograms of 46 children with documented ostium secundum ASD's. Forty-one percent had MVP that was minimal in 12, moderate in 4 and pronounced in 3 cases. None were found to have mitral valve abnormalities during surgery. They concluded that left ventricular angiography was not warranted in children with secundum ASD's unless significant mitral regurgitation or left axis deviation was present. Leachman (1976) reported MVP in 16 of 92 patients with ASD's in whom angiography was carried out (1970-1974). He also reviewed their surgical experience (1956-1969) (Cooley) and found mitral regurgitation with intact chordae in 9 of 122 adult patients 15 to 55 years of age. Three of the 9 required reoperation 2-6 years later for mitral regurgitation resulting from chordal rupture. They concluded that "the outlook...[for MVP] may be less benign than is usually believed." As with other conditions associated with MVP, the nature of the

relationship is not clear. Jeresaty (1974) suggested a secondary relationship, i.e., that the ASD was "unloading" the left ventricle and that the resultant smaller LV volume produced prolapse of a secondary nature. However, there is no evidence that inter-atrial shunts cause "unloading" of the left ventricle. The presence of myxomatous degeneration of the mitral valve and the presence of typical ECG changes and symptoms of MVPS suggest an increased association of true mitral valve prolapse syndrome and ostium secundum ASD's.

Coronary Artery Disease

Steelman (1971) noted mid-systolic clicks in 15 patients of a clinical population of 2200. He estimated that about 1/3 of the total clinical population had coronary artery disease. This diagnosis was made on the basis of a history of previous myocardial infarction or the presence of angina pectoris. Eleven of the 15 patients were male, mean age 58 years. Eight had previously documented myocardial infarctions, 8 had typical angina pectoris, but only 1 of the 15 was catheterized. He had papillary muscle dysfunction with mild mitral regurgitation. None of the 15 had the inferior T wave changes typical of mitral valve prolapse syndrome. Both click and murmur behaved in the expected fashion after amyl nitrite inhalation. This group concluded that: 1) the MVP developed concurrently with coronary artery disease, and 2) the expected responses of MVP to alterations in LV volume were present. Thus, the role of coronary artery disease in mitral valve prolapse may be causal. Further evidence to support this theory was published by Crawford (1977). A 35-year-old man without mitral valve prolapse either by cath or by physical exam after his first myocardial infarction subsequently developed MVP after his second MI. Jeresaty (1979) criticized this paper and stated that the first ventriculogram, taken in the RAO position, really did show MVP, and that the second, taken in the LAO position (actually, it was a left lateral view), was even more diagnostic. Systolic frames from both studies are included in the original paper and allow the reader to decide. In my opinion, the RAO ventriculogram does not show MVP, but is a good example of what Cohen (1979) showed as pseudo-prolapse. What Jeresaty is calling prolapse in this case is the fulcrum of the mitral valve and not the leaflet. The leaflet does not extend beyond the annulus posteriorly. This kind of controversy over diagnostic criteria is typical, and exemplifies the difficulties one has in understanding the literature of MVP.

As noted in the section "Angiography," Verani (1976) found no correlation between the presence of MVP and the distribution of coronary artery disease. Two of his patients with coronary artery disease and clear-cut mitral valve prolapse on angio had normal mitral valves at autopsy, proving that myxomatous degeneration was not necessary to have mitral valve prolapse concurrently with coronary artery disease. This supports the works of Steelman and Crawford (described above). Aranda (1975) reviewed 95 patients with coronary artery disease and found 30 with angiographic MVP. No auscultatory or echo data were presented, so the relationship of this angiographic finding to mitral valve prolapse syndrome cannot be determined. They did note a rather

poor correlation between MVP and the extent and location of coronary artery disease. The report of Smith (1977) has already been reviewed; a 40% incidence of MVP was found in 355 cases of coronary artery disease and 6 patients with mitral valve prolapse syndrome clinically had positive echoes, mid-systolic clicks, late-systolic murmurs on auscultation and had MVP on angio. The others had negative echoes, no click or murmur, and no symptoms of MVP.

A final comment should be made about coronary anatomy and MVP. Gentzler (1975) reported the congenital absence of the left circumflex coronary artery in 19 patients with MVP. This has not been found in studies involving hundreds of patients (Smith, 1977; Glassman, 1977).

Psychiatric Manifestations

Neuropsychiatric symptoms were noted in the original series of patients by Hancock and Cohn (1966). Fifteen of 40 patients had psychosis, hyperventilation, and psychoneurosis. Fifteen percent of Jeresaty's patients (1973) had similar symptoms. Shappell (1974) administered Minnesota Multiphasic Personality Inventories (MMPI) to 14 patients with MVPS and found abnormal scores in 6 symptomatic patients, with elevations in categories of hysteria, hypochondriasis, depression, psychopathic deviation, and schizophrenia. We have examined 34 persons with MMPI and have found similar results. However, if one examines the test items used to derive these profiles, one realizes that they have an amazing similarity to the typical complaints of mitral valve prolapse syndrome: chest pain, palpitations, dyspnea, shortness of breath, poor exercise tolerance, fatigue, syncope, and disturbed sleep patterns.

Many of these complaints are typical of conditions such as DaCosta syndrome, soldiers heart, neurocirculatory asthenia, and the effort syndrome as described by Wooley (1976). Many of the symptoms in MVPS have a clear-cut physiological basis, e.g. palpitations and syncope, arrhythmias (Swartz, 1977), poor exercise tolerance (Crowe, (1979), sleep distrubance and sleep apnea (Clark, 1980), and orthostatic intolerance (Pasternac, 1979). Thus, it would appear that many of the patients with MVPS are voicing genuine complaints with sound physiological bases, and are not merely psychoneurotics with a multitude of psychosomatic disorders.

Complications

Mitral valve prolapse would be a benign curiosity like innocent flow murmurs and early repolarization on the electrocardiogram were it not for the puzzling constellation of complications associated with the syndrome. Arrhythmias, the most common and bothersome complication, will be discussed first.

Arrhythmias and Sudden Death

Virtually every type of arrhythmia, both supraventricular and ventricular, has been seen with mitral valve prolapse. Swartz (1977) reviewed the English literature to that date and found 589 reported cases. (see Figure 8).

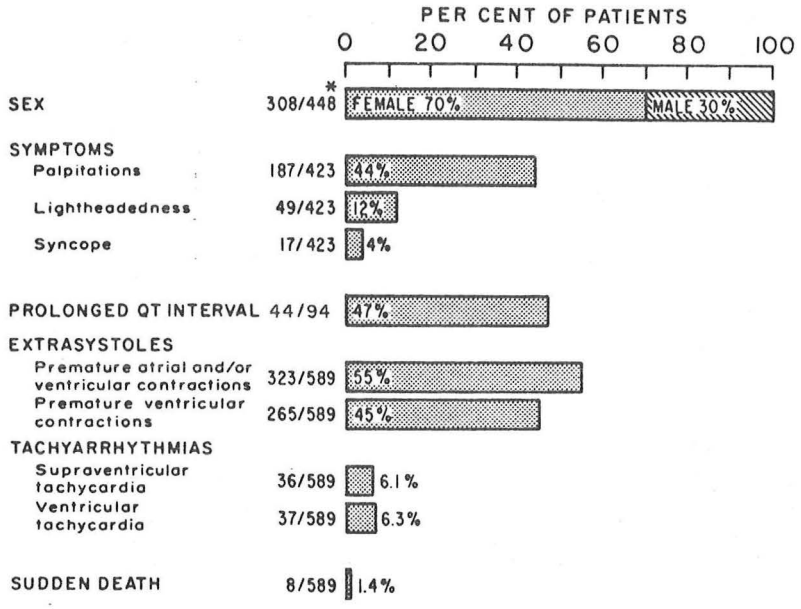


Figure 8. *A summary of the major symptoms and arrhythmias in mitral valve prolapse. Asterisk denotes denominator which represents the total number of patients in whom data were available. Numerator represents those patients with positive findings.*

Seventy percent of the patients were women. Symptoms included palpitations in 44%, lightheadedness in 12%, and syncope in 4%. Premature ventricular and/or atrial contractions were seen in 55%; of these, PVC's only were observed in 45%, supraventricular tachycardia in 6.1%, and ventricular tachycardia in 6.3%. Sudden death was noted in 1.4% of the patients reported. A prolonged QT interval was noted in 7.5%, but about half of these were receiving drugs known to prolong repolarization. Of course, published studies are generally biased toward a greater severity and incidence of arrhythmias, but these figures are probably a reasonable reflection of the findings in clinical practice, i.e., in symptomatic patients who present for medical care. The true incidence of arrhythmias in asymptomatic patients with MVP is not known, but it is common to find mitral valve prolapse in patients who are serendipitously found to have arrhythmias, (e.g. Gyn exams, employment physicals, etc.). This would suggest that their incidence in asymptomatic mitral valve prolapse is substantial. These arrhythmias, in otherwise healthy individuals, would be of no importance were it not for the reports of

sudden death associated with mitral valve prolapse syndrome -[Hancock (1966) 1 case; Barlow (1968) 2 cases; Trent (1970) 1 case; Shappell (1973) 1 case; Marshall (1974) 1 case; Jeresaty (1974) 4 cases; Gulotta (1974) 1 case; Appleblatt (1975) 1 case; Rakowski (1975) 2 cases; Guthrie (1976) 3 cases; Belardi (1976) 2 cases; Koch (1976) 4 cases; Cobbs (1977) 1 case; Mills (1977) 1 case; Davies (1978) 13 cases]. An additional 21 cases of successfully resuscitated ventricular fibrillation in mitral valve prolapse exist (Jeresaty, 1979). The majority of patients had normal coronary arteries either at cath or autopsy. Complete information is not available in each case, but 22 of 30 cases were women, 6 of 8 had normal QT intervals, 16 of 20 had PVC's or documented ventricular arrhythmias, and 9 of 10 had abnormal rest ECG's, with ST and T changes most commonly found. Jeresaty (1976) reviewed the question of sudden death in two of his cases and in ten others cited above. He and Campbell (1976) have derived a "typical" composite picture from these fatal cases: a woman 30-50 years old with syncopal episodes, resting ECG abnormalities including QT prolongation, and ventricular arrhythmias. Unfortunately, this picture fits a large fraction of all women with mitral valve prolapse syndrome. If one accepts a 1% incidence of prolapse millions of otherwise healthy and asymptomatic women are at risk, The need for a multicenter, prospective evaluation of this problem is obvious, but unfortunately, it is not yet being done. Treatment of the arrhythmias will be discussed below.

Wolff-Parkinson-White Syndrome

WPW with mitral valve prolapse has been reported by a number of authors. Gallagher (1968) noted that approximately 10% of his series of patients with WPW also had MVP. Similar reports by Krickler (1976), Bjerregaard (1977), and Grassi (1977) have appeared. Mirvis (1978) reported two sisters with pre-excitation (short PR and normal QRS), a markedly prolonged QT interval, and mitral valve prolapse. It is of note that all but Grassi's patients had evidence of left-sided bypass tracts. Josephson (1978) investigated supraventricular tachycardias electrophysiologically in 12 patients, 7 of them women. Eight had normal resting electrocardiograms, 3 had Lown Ganong Levine (LGL-short PR, normal QRS) and one had WPW, type A (left-sided bypass tract). Six of the 8 with normal rest ECG's had atrio-ventricular nodal bypass tracts. All of these were left-sided, suggesting that the bypass tract and the mitral valve abnormality were developmentally related. WPW, when associated with Epstein's anomaly of the tricuspid valve, is almost always type B or a right-sided tract. A common developmental abnormality is probably responsible, although some have given the interpretation that contraction abnormalities produced by WPW cause prolapse, as has been seen with premature ventricular contractions (Chandraratna, 1974). It is unlikely that the WPW causes prolapse. Echocardiographic studies have shown a wide variety of ventricular contraction abnormalities in WPW, not all of which are severe enough to cause prolapse.

Myocardial Infarction and Coronary Spasm

Pseudo-infarct patterns on ECG have been recognized for a long time in mitral valve prolapse (Lobstein, 1973; Tuquan, 1975; Aintablian, 1976, 1978). These are most often inferior in location, although anterior myocardial infarction patterns have also been reported. A new twist to this story was added when reports of documented myocardial infarctions with MVP in patients with normal coronaries appeared in the literature (Barlow, 1975; Chesler, 1976; Imaizuim, 1978; Jennings, 1978). A summary of the findings is shown in Table 7.

MYOCARDIAL INFARCTION AND MVP

AUTHOR	AGE	SEX	INFARCTION	PHONO	CATH*
CHESLER 1976	40	F	INF	MSC	NL
	21	M	INF	MSC	NL
	23	M	ANT	MSC	NL
	32	M	INF/ANT	MSC-LSM	NL
IMAIZUMI 1978	17	M	INF	MSC-LSM	APICAL ANEURYSM
	38	F	INF	MSC-LSM	NL
JENNINGS 1978	14	M	INF	LSM	INF HYPOKINESIS

*ALL HAD MVP AND NORMAL CORONARIES BY ANGIO

In none of the cases is the etiology clear, although spasm, and emboli have been discussed. A bothersome aspect is that only 2 of the 7 patients showed left ventricular wall motion abnormalities on ventriculography. At the time of "infarction," cases 3, 4, and 7 were engaged in heavy physical activity, a known cause of elevated serum muscle enzymes. One of the subjects (Case 2) had nocturnal pain typical of coronary artery spasm but ST changes were not documented at that time. As with sudden death, this complication must be extremely rare if only 7 cases have been found among the millions of patients potentially at risk. The inability to differentiate ECG changes of MVP from those of an MI, the lack of wall motion abnormalities, and confusing enzyme data lead me to believe that the association of MVP and infarction is coincidental, if it exists at all.

Coronary Spasm

Although Barlow (1975) and Chesler (1976) suggested that coronary spasm could be present in MVP (in patients with infarcts and normal coronaries), this was not shown until Buda (1976) reported 10 patients with MVP and spasm of the right coronary artery at catheterization. They reviewed 745 cases from 1969-1975 and found a 1.34% incidence of coronary spasm. Of the 10 patients, 8 of whom were women, 5 had a click and a murmur on auscultation, 7 had ECG abnormalities at rest, 8 had normal coronaries, and all had normal right coronary arteries (RCA). The location of spasm was the proximal RCA in 8, the mid-left anterior descending in 1 and the left main in 1. Awadeh (1977) published an additional case report with mid-RCA spasm. Prinzmetal-type ECG changes were seen in only 1 of the 11 patients. The meaning of RCA spasm during catheterization in the absence of ECG changes or symptoms is unknown.

Sabom (1978) took the investigation a step further by administering ergonovine maleate intravenously to 28 patients [the use of this agent and the subject of coronary artery spasm have been recently reviewed in Grand Rounds (Hillis, 1979)]. Sabom's patients had a mean age of 51 years, all had chest pain leading to catheterization, 7 had mid-systolic clicks, 15 systolic murmurs, but 6 had neither. Of the 28 patients, 6 developed chest pain, 2 of these with minor ST changes and diffuse coronary spasm. Whether similar results would be found in patients with chest pain and typical mitral valve prolapse syndrome is not known. LeWinter (1974) administered phenylephrine, another potent α-adrenergic vasoconstrictor to three groups, one with typical prolapse syndrome, one with prolapse but without chest pain, and a group of "normal" controls. Only the patients in the first group developed pain with phenylephrine infusion. The authors concluded that prolapse pain was caused by papillary muscle ischemia produced by an increased left ventricular after-load. Buda (1976) and Gaffney (1978) have pointed out that direct α-adrenergic effect on coronary arteries may also play a role in this syndrome.

Cerebrovascular Accidents (CVA)

Perhaps related to the discussion of emboli or coronary spasm are multiple reports of CVA's, transient ischemic attacks (TIA), and amaurosis fugax associated with MVP. [Barnett, 1976 (12 cases); Kostuk, 1977 (14 patients); Kimball, 1977 (1 case); Wilson, 1977 (10 cases); Cooke, 1978 (1 case); Julien, 1978 (2 cases); Hirsowitz, 1978 (4 cases); Watson (1979) 8 cases; Saffro, 1979 (1 case)]. Most of the patients were less than 45 years of age and had normal cerebral arteriograms. The cause of the attacks was postulated to be either emboli or cerebral artery spasm. Several workers quoted a study by Pomerance (1969) that noted the presence of small fibrin clots and "jet" lesions associated with mitral valve prolapse; but Pomerance herself (1977) replied that the thrombotic lesions seen at autopsy were tiny, and therefore unlikely to produce major strokes such as those reported. A similar opinion was expressed earlier in the same journal by Cohn (1977)

whose patient with TIA's had recurrent atrial fibrillation and probably had embolic disease related to the arrhythmias and not to prolapse per se. None of the studies has ruled out arrhythmias as a cause of emboli or of cerebral ischemia due to spasm. MVP should be sought among younger patients with transient ischemic attacks, CVA's or amaurosis fugax. Additionally, one should look for arrhythmias and endocarditis in these patients.

In an attempt to understand the process by which MVP might cause CVA's, etc., Steel (1979) examined platelet survival in patients with prolapse, including 5 with recent CVA's despite normal cerebral arteriograms. He found platelet survival to be decreased in MVP patients, including those with a history of CVA. The authors suggested that anti-platelet-aggregation agents such as aspirin or sulfinpyrazone might be of use in MVP associated CVA's. An accompanying editorial (Cheitlin, 1979) urges caution in interpretation of these findings. First, the shortened platelet survival exists in a number of other cardiac disorders such as arteriosclerotic heart disease and rheumatic heart disease, regardless of whether there has been a history of embolic disease or not. Several long term follow-up studies did not mention strokes at all in MVP, suggesting that there is a "vanishingly small" incidence of CVA's in MVP. The author of the editorial recommends that CVA's not be mentioned to patients with MVP in that 1) the association is unproven and, 2) no effective therapy currently exists, as opposed to bacterial endocarditis for which antibiotic prophylaxis is probably effective.

Bacterial Endocarditis

There is no question that patients with prolapse syndrome characterized by the murmur or mid-systolic click and murmur are at a very slight, but increased, risk of bacterial endocarditis. Kincaid, 1974 (1 case); Leachman, 1975 (10 cases); Corrigall, 1977 (25 cases). The latter group reviewed records at Stanford University Hospital over a five year-period and found that of 87 patients with infective endocarditis, 28 had isolated mitral regurgitation, 10 with mitral valve prolapse. Thus, about 1/8 of the patients with endocarditis in that period at that institution had prolapse. Jeresaty (1979) has assembled 115 cases from the literature, including those cited above. A majority were male despite the female predominance of MVPS in clinical practice. None of these cases had "silent" MVP (echo or angio only) and only 6 had isolated systolic clicks. Follow-up studies (see Table 8) would support the notion that the patients at risk are those with mitral regurgitation murmurs and not those with isolated systolic clicks. Diagnosis is made in the usual fashion: fever, weight loss, petechiae, and other embolic manifestations, and positive blood cultures. Echocardiographic detection of valvular vegetations can be obtained during routine diagnostic studies. False-positive patterns of endocarditis have been seen in patients with large, redundant or flail leaflets (Chandraratna, 1977). Two-dimensional echocardiography is considerably more sensitive in detecting these vegetations, and in some cases may provide the diagnosis unexpectedly. Bacteriological findings and treatment of endocarditis in MVP are the same as in any other

Follow-up Studies in Mitral Valve Prolapse

	Allen et al.	Bensman et al.	Appelblatt et al.	Belardi et al.	Koch et al.	Mills et al.
Number of patients in whom information was available	62	14	69	137	38	53
Percentage of women	45%	NA	49%	NA	65%	64%
Mean age (years) when first seen	38	NA	NA	47.1	40.5	41.1
Follow-up time in years	13.8 Mean	4.2 Mean	10–40	4.2 Mean	> 10	13.7 Mean
Prospective (P) Retrospective (R)	R	P	R	P	P	R
Development of late systolic murmur in patients with isolated click	NA	NA	12/16 (1)	NA	4/7	NA
Basis for diagnosis of MVP	Auscultation	Auscultation and echocardiography	Auscultation	Angiography	Auscultation	Auscultation
Development of pansystolic murmur or severe mitral regurgitation in patients with click and/or late systolic murmur	9/16 (2)	3/14	11/69	NA (3)	6/38	7/53 (4)
Ruptured chordae tendineae	2	1	None	7	NA	2
Infective endocarditis	5	None	None	3	None	3
Sudden death	None	None	1	2	5	1 (Quinidine) 1 Ventricular fibrillation successfully resuscitated

Table 8

endocarditis. Large vegetations are often seen and embolic disease is common, but there is no evidence that surgical intervention is warranted unless chordal rupture and/or failure occur. Careful studies correlating embolic events and the presence of vegetations on echo might produce different recommendations, but, to date, such studies have not been carried out.

Mitral Regurgitation with and without Chordal Rupture

Progressive mitral regurgitation eventually requiring surgery has been noted in both medical series (Allen, 1974; Appleblat, 1975; Belardi, 1976; Koch, 1976; Mills, 1977) and surgical series (Read, 1966; Cooley, 1972; McKay, 1973; Hill, 1974; Goodman, 1974; Luxton, 1975; Baehrel, 1978; Carpentier, 1978). Several generalizations can be made from these studies: 1) the incidence of serious MR and/or chordal rupture is low even among highly symptomatic patients with mitral valve prolapse syndrome, 2) patients with pan-systolic murmurs are at greatest risk [virtually all the patients in the surgical series had either pan-systolic murmurs or had had chordal rupture and/or endocarditis], 3) men have a higher incidence of surgical complications of mitral valve prolapse syndrome [about 2/3 of the patients in the surgical series are male] 4) significant aortic involvement in the absence of the Marfan syndrome is very rare, 5) mitral valve prolapse accounts for 25-40% of patients requiring surgery for mitral regurgitation, 6) About 2/3 of

the patients present with chronic mitral regurgitation; the rest have an acute onset, virtually always due to chordal rupture with or without endocarditis, 7) the posterior leaflet is most often involved, 8) the type of surgery performed varies greatly from center to center and seems most dependent on the surgeon rather than the type of pathological processes present 9) valve prosthesis dehiscence, like that seen with other connective tissue disorders, has not been a major problem in prolapse, and 10) significant tricuspid valve disease occurs in less than 10% of the cases operated.

Etiology and Unifying Concepts

With over 600 articles published on mitral valve prolapse during the last decade, it is not surprising that a great deal of confusion exists. One should think of prolapse as an event that occurs in the presence of a variety of abnormalities of the mitral apparatus and left ventricle. Included in this category would be mitral valve prolapse associated with cardiomyopathies, whether ischemic, hypertropic or idiopathic.

Myopathic Theory

Several studies examining myocardial metabolism and function have been carried out in mitral valve prolapse patients with abnormal cardiac function. Findings that support an etiological role for cardiomyopathy in mitral valve prolapse include:

1) Left ventricular contraction abnormalities
2) Myocardial lactate production
3) Myocardial fibrosis on biopsy and autopsy

Natarajan (1975) studied 23 prolapse patients with exertional or resting chest pain. Echocardiography was not done. Thirteen patients had murmurs of mitral regurgitation but only 3 were documented by catheterization; 5 had clicks. Abnormal lactate production was noted in 7 patients, 6 of whom had a history of exertional chest pain. Abnormal lactate production occurred in the absence of chest pain during atrial pacing. These patients' histories were not typical of mitral prolapse syndrome in that the pain was anginal or exertional in nature - something very unusual in mitral valve prolapse syndrome. Diagnostic criteria were more compatible with "angiographic" prolapse in the absence of typical physical or echocardiographical findings of MVP. The author of this paper even stated that prolapse reflects two underlying mechanisms: 1) a contraction abnormality produced by a cardiomyopathy (secondary MVP), and 2) pathology "primarily" of the mitral chordae and leaflets. It would appear that this study and that of Gulotta (1974) belong in the category of "secondary" mitral valve prolapse. The presence of MVPS symptoms, auscultatory findings and pathological or echocardiographical identification of a voluminous myxomatous mitral valve would be required before a diagnosis of MVPS could be assigned in these patients.

Even if one is able to eliminate the secondary forms of MVP, the pathophysiology of MVP syndrome is not clear. How does an enlarged valve "produce" symptoms in so many different systems, (fatigue, sleep disturbance, increased catecholamines, etc.)? The theory favored by Jeresaty (1979) is that of mechanically-induced ischemia of the mitral papillary muscles. Two alternate theories are discussed below.

Valvular Theory

According to the so-called "Valvular Theory," the large leaflets have a greater "shadow area," which means a greater tension on the chordae and papillary muscles at any given left ventricular pressure. This increased tension in the papillary muscles produces a relative ischemia which can then lead to changes in resting electrocardiograms (especially inferiorly), ventricular irritability (PVC's), and chest pain (ischemic - angina). There is, however, little proof for this theory. Arrhythmias in MVP are both ventricular and supraventricular and are associated with bypass tracts, so they are not likely to be due to ischemia. Myocardial perfusion studies fail to demonstate areas of ischemia at times when prolapse, ECG abnormalities, and arrhythmias are present. Small areas of ischemia could be missed by the thallium technique, but large amounts of ischemic tissue are almost certainly not present. Pathological studies have likewise failed to document infarction or chronic ischemic changes in the papillary muscles. Syncope and orthostatic intolerance in the presence of minimal mitral regurgitation is also not explained by the "valvular theory". A more ecletic theory is that the MVP syndrome represents a generalized developmental abnormality.

Generalized Developmental Defect

A number of lines of evidence lead to the conclusion that MVPS is really a complex syndrome including the presence of 1) skeletal abnormalities; characteristic dermatoglyphics, and an anthropometrically distinctive habitus, 2) multiple cardiac defects; myxomatous chordal and leaflet degeneration, ostium secundum ASDs, and left-sided bypass tracts, 3) neuropsychiatric symptoms, 4) electrocardiographic changes often associated with autonomic nervous system instability, 5) syncope, orthostatic intolerance, and cold extremities all general symptoms of poor vasomotor control.

While skeletal and cardiac defects have been well described, the etiological role of the autonomic nervous system in MVPS has not received such wide-spread attention. In fact, Jeresaty's (1979) monograph on MVP fails to mention it at all. The first study on this subject was by Abinader (1976). He examined the response of 35 patients with MVP and abnormal resting electrocardiograms to intravenous propranolol. Twenty-eight showed ECG improvements, although abolition of resting tachycardia played an important role in his results. Leichtman (1976) reported a family with profound bradycardia, syncope, and mitral valve prolapse. These patients had excessive vagal tone demonstrated by high-normal heart rates following atropine administration.

Coghlan (1979) reported a similar vagal abnormality in patients subjected to head-up tilting. These patients had prolonged bradycardia upon resumption of the supine position. Marked increases in sinus arrhythmia were also noted in these patients with a history of bradyarrhythmias.

Studies in our laboratory (Gaffney, 1979) suggested that a variety of autonomic abnormalities were present in patients with MVPS. Rather than tilting, we used lower body negative pressure, (LBNP), a stress that shifts blood from the thorax into the lower extremities. MVPS patients had diminished pooling of blood in the legs during LBNP compared with normal controls, suggesting diminished calf venous compliance. They also had an increase in blood pressure despite a 25% drop in cardiac output during this procedure. These findings suggest an increased α-adrenergic tone and responsiveness. β-adrenergic activity, assessed by measurements of resting heart rate, blood pressure, cardiac output, plasma catecholamine levels and echocardiographic indices of contractility, was normal.

Vagal activity, assessed by measurement of baroreflex-mediated changes in heart rate during phenylephrine infusion, was markedly diminished. The response to the potently vagatonic "diving maneuver," (facial immersion in ice water), was likewise blunted in prolapse patients. Sinus arrhythmia was also greatly reduced.

A recent abstract by Pasternac (1979) reported increased catecholamines in 5 women with mitral valve prolapse syndrome and bradyarrhythmias. Heart rate and blood pressure responses to standing were also exaggerated. Studies underway in our laboratory appear to confirm these findings, but with a different interpretation. Pasternac assumed that increased catecholamines were proof of a "hyper β-adrenergic state," but no measurement of cardiac output was made in this study. We find that patients with increased heart rates on standing have a normal cardiac output with dramatic decreases in stroke volume with little or no mitral regurgitation. Thus, the "excessive" rise in catecholamines on standing is an entirely appropriate response, necessary to maintain cardiac output. Measurements of leg volume changes during LBNP showed that MVPS patients actually pool less blood than normal controls. This would suggest that intravascular hypovolemia is present, and may play an important role in producing symptoms of MVPS. Plasma volume determinations are currently being obtained in patients with MVP syndrome.

Treatment

Little data is available on treatment of mitral valve prolapse. The prolapse itself requires no treatment, so only treatment of its complications will be discussed.

Arrhythmias

Controversy surrounds both when and what treatment should be given for arrhythmias in MVPS. Jeresaty (1979) states that "Despite their frequency,

arrhythmias in MVP are usually benign and asymptomatic. However, in a few patients, complex, repetitive, and life-threatening arrhythmias may occur, requiring aggressive management". Unfortunately, he fails to state which arrhythmias are benign, and which are malignant. Barlow (1979) suggests treatment when multifocal PVC's, R on T phenomena, or ventricular tachycardia are present. This seems to be reasonable, particularly if there are associated symptoms. Holter monitoring, with a diary of symptoms, should be obtained in all cases prior to beginning therapy. There are several reasons for this.

1) There is often no correlation between symptoms and arrhythmias. Some patients have complex arrhythmias without symptoms while others complain anytime their heart rate increases. Treatment goals should be clearly defined, i.e. abolition of arrhythmias, symptomatic improvement, etc.
2) Response to therapy should be determined by repeat Holter monitoring unless relief of symptoms is the goal.
3) When complete abolition of arrhythmias is not possible, as is often the case, quantification of arrhythmias can be done to gauge therapeutic efficacy.

Propranolol has been recommended in virtually all reviews of prolapse, but evidence for any specific efficacy in the condition is lacking. The underlying assumption is that inappropriately increased β-adrenergic activity is present, but this is probably not the case. Winkle (1975, 1976) studied the response of 16 symptomatic prolapse patients to propranolol, doses of up to 320 mg per day. The expected decrease in heart rate was observed, but the effect on arrhythmias was variable. One patient had a 160% increase in the number of PVC's per 15 minutes. Five averaged a 90% reduction, and 3 had no change.

It is worth trying propranolol in that it does seem to abolish the frequent episodes of sinus tachycardia with palpitations, and it will suppress PVC's in a certain number of patients (regardless of etiology). It should not be given on a PRN basis, as is often done, in order to prevent the occurrence of withdrawal or rebound increases in tachyarrhythmias. We have observed several patients who, following abrupt cessation of propranolol, had dramatic increases in both frequency and malignancy of arrhythmias. If propranolol therapy fails, other agents can be used. Quinidine should be avoided in patients with a prolonged QT interval. Diphenylhydantoin (Dilantin) may be of use in that situation in conjunction with other agents. Wei (1978) and Troup (1979) demonstrated excellent responses to aprindine therapy, but this agent is not yet available clinically in the United States. Significant side effects were also a problem in the aprindine studies.

Bacterial Endocarditis

Prophylaxis is recommended for patients with MVPS and mitral regurgitation murmur. Most authors would probably not give prophylaxis to patients

with "silent" MVP, or those with only a mid-systolic click, although endocarditis has been reported in the latter group. Although data are not available, it would seem reasonable to give prophylaxis to patients with an echocardiographically abnormal valve, that is, one prolapsing in the presence of a click on phono. Endocarditis, when it occurs, is treated in the usual fashion.

Mitral Regurgitation and Chordal Rupture

As noted previously, all men with MVP and male and female patients with holosystolic mitral regurgitation murmurs are more likely to develop serious mitral regurgitation. These patients should be followed more closely with periodic physical and echocardiographic examinations to assess cardiac chamber size and function. Decisions regarding surgery are made on the same basis as in other causes of valvular mitral regurgitation.

Psychoneurotic Complaints

Probably the most bothersome complaints, to both patient and physician, are the various "psychoneurotic" complaints associated with the syndrome. There is no proven therapy for any of these symptoms, but some things do seem to work.

1) An understanding, supportive attitude toward the patient is essential. Patients often have been told they are neurotics, crocks, etc. Simply knowing that a "physical" diagnosis is present relieves the patient of a great deal of guilt and anxiety and allows him/her to deal with the symptoms better.
2) Investigate the patients complaints. Arrhythmias, orthostatic hypotension, and diminished exercise capacity are often present, and can provide a physiological basis for the symptoms, and suggest directions of treatment.
3) Stress to the patient that he or she has substantial control over the symptoms despite the diagnosis of MVPS. One should avoid converting a general neurosis into a cardiac neurosis.

Medication for MVPS symptoms is generally not helpful. Propranolol may diminish palpitations, but it often worsens or doesn't improve other symptoms such as fatigue, shortness of breath, poor exercise tolerance, and chest pain. If poor physical fitness is present, dramatic results can sometimes be achieved by an effective exercise program. Pick one suitable for the patient's life style, then follow and encourage progress.

Digitalis, salt restriction, and diuretics are of no use in the absence of documented congestive heart failure in MVP, and may actually worsen certain aspects of the syndrome, such as orthostatic hypotension, syncope, arrhythmias, etc. More than one episode of sudden death following diuretic-induced hypokalemia has been reported.

Summary

Mitral valve prolapse is a common, non-specific, cardiac finding manifest by a mid-systolic click and/or a late-systolic murmur. Factors which alter the mitral apparatus, including enlarged leaflets, elongated chordae, abnormal papillary muscles, diminished left ventricular volume or abnormal left ventricular contraction may cause the mitral leaflets to prolapse into the left atrium during systole. The click is probably produced by tensing of the chordae tendineae and the murmur is a result of mitral regurgitation. Specific myopathic causes of MVP include the ischemic cardiomyopathy of coronary artery disease, asymetric septal hypertrophy, myotonic dystrophy and X-linked muscular dystrophy. Multiple connective tissue disorders including the Marfan syndrome, Ehlers-Danlos, and osteogenesis imperfecta produce myxomatous valvular degeneration leading to MVP.

In distinction to these secondary forms of MVP, a specific condition, Mitral Valve Prolapse Syndrome, also exists. Its incidence is unknown but it is much less common than mitral valve prolapse itself. It is inherited as an autosomal dominant trait although women tend to be more affected than men or children. Symptoms are "psychoneurotic" in nature, and include atypical chest pain, shortness of breath, orthostatic intolerance, syncope, fatigue, diminished exercise capacity, poor sleep habits, and palpitations. Patients are often tall and thin, with long arms and a narrow AP chest diameter, and have skeletal defects including straight back, pectus excavatum, and scoliosis. Electrocardiograms are frequently abnormal with ST and T wave abnormalities and occasionally pseudo-infarction patterns inferiorly and anteriorly. Both ventricular and supraventricular arrhythmias are common. There is an increased association of cardiac defects including ostium secundum ASD's, and left-sided bypass tracts. Complications include arrhythmias causing syncope and sudden death, bacterial endocarditis, chordal rupture, progressive mitral regurgitation, and cerebrovascular accidents. Fortunately, their incidence is extremely low. Many of the findings in this syndrome are unexplained, but in addition to the cardiac abnormalities, autonomic nervous system dysfunction appears to play an important pathophysiological role. Treatment is directed toward specific symptoms and complications. An understanding and compassionate approach to the MVP syndrome patient is important. Although many of the patients' complaints seem psychoneurotic, they often have a definite organic basis that should be sought in the work-up of the patient.

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