REVIEW ARTICLE

Floppy Mitral Valve (FMV) — Mitral Valve Prolapse (MVP) — Mitral Valvular Regurgitation and FMV/MVP Syndrome

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Abstract Mitral valve prolapse (MVP) results from the systolic movement of a portion(s) or segment(s) of the mitral valve leaflet(s) into the left atrium during left ventricular (LV) systole. It should be emphasised that MVP alone, as defined by imaging techniques, may comprise a non-specific finding because it also depends on the LV volume, myocardial contractility and other LV hemodynamics. Thus, a floppy mitral valve (FMV) should be the basis for the diagnosis of MVP. Two types of symptoms may be defined in these patients. In one group, symptoms are directly related to progressive mitral regurgitation and its complications. In the other group, symptoms cannot be explained only by the degree of mitral regurgitation alone; neuroendocrine dysfunction has been implicated for the explanation of symptoms in this group of patients that today is referred as the FMV/MVP syndrome. When significant mitral regurgitation is present in a patient with FMV/MVP, surgical intervention is recommended. In patients with a prohibitive risk for surgery, transcatheter mitral valve repair using a mitraclip device may be considered. Furthermore, transcatheter mitral valve replacement may represent an option in the near future as clinical trials are underway. In this brief review, the current concepts related to FMV/MVP and FMV/MVP syndrome will be discussed.
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I. Introduction

Few diseases have evoked more interest and controversy during the previous century than floppy mitral valve (FMV)/ mitral valve prolapse (MVP). These controversies are related, at least in part, to the following four reasons.[1,2]

1. There is a lack of a precise definition for FMV/MVP. MVP occurs when one, both, or a portion of the mitral valve leaflets extend above the plane of the atrioventricular junction during left ventricular (LV) systole.[1-6] However, it should be noted that MVP may be a non-specific finding because it also depends on LV haemodynamics, such as myocardial contractility, LV volume, and heart rate.[3,6] Furthermore, the evolution of technology over the years has resulted in various definitions of MVP. For a long period of time, MVP was the central or only issue, and the diagnosis of MVP was completely dissociated from the FMV morphology.[3,6] However, to date, it is apparent that FMV is the central issue in the MVP - mitral valvular regurgitation story. The term FMV originates from surgical and pathological studies and refers to the expansion of the area of the mitral valve leaflets with elongated chordae tendineae, chordae tendineae rupture, and mitral annular dilatation. Thus, rather than asking the question does this individual have MVP, the question should be does this individual have FMV[2,3,6]?

2. The natural history of FMV/MVP and the occurrence of mitral regurgitation requires long-term follow-up with several evaluations to understand the life history of the disease. The follow-up of an uncomplicated course during a relative short period of time has resulted in the misconception that FMV/MVP is benign.[2,7,8]

3. A subgroup of patients with FMV/MVP may have symptoms that are not directly related to the severity of mitral regurgitation, but rather neurohumoral activation and other abnormalities (subsequently discussed); these patients today are referred to as having the FMV/MVP syndrome. The lack of an association between the severity of mitral regurgitation and symptoms was also a cause of confusion for a long period of time.[1,3,8]

4. FMV/MVP may be a part of a well-recognised syndrome of heritable connective tissue disorders, such as Marfan syndrome, Ehlers-Danlos syndrome, and adult polycystic kidney disease.[9-12] The fact that clinicians were often not able to separate isolated FMV/MVP from FMV/MVP that was a component of a systemic heritable connective tissue disorder was also a cause of confusion. Furthermore, FMV/MVP often shares several manifestations of Marfan syndrome, including long limbs, thoracic cage deformities, striae atrophicae, and, in some cases, mild dilatation of the aorta or abnormal aortic function. The acronym MASS (mitral, aorta, skeleton, skin) was introduced to emphasise the involvement of the mitral valve, aorta, skeleton and skin.[12] Thus, the clinical phenotype of FMV/MVP represents a heterogeneous group of patients with mitral valve or other abnormalities from mild to severe and constitutes a continuum from Marfan syndrome at one extreme to isolated FMV/MVP at the other extreme. To date, isolated FMV/MVP is considered a cardiovascular abnormality with a connective tissue origin, which, in most instances does not fit the presently recognised heritable connective tissue disorders.[2,9,12] By virtue of its high frequency in the general population, FMV/ MVP comprises a larger group of patients with a connective tissue abnormality of the heart. In this brief review, the current concepts related to FMV/MVP and FMV/MVP syndrome will be discussed.

2. Inheritance

From a genetic perspective, FMV/MVP is a heterogeneous group.[2,3,13-17] To date, at least two forms of inheritance exist. FMV/MVP may be transmitted by an autosomal dominant form (most common) with a variable degree of penetrance. Another less common form is transmitted through the X-chromosome (chromosome Xq28).[16] For autosomal dominant transmission, three gene loci have been reported: chromosome 16 (16p12.1-p11.2); chromosome 11 (11p15.4); and chromosome 13 (13p31.3-p32.1).[15] The elucidation of the genetic details in the near future will enable a better classification of this common valvular abnormality and will result in novel diagnostic pathways.

3. Pathology - Histopathology

1. *Pathology.* Surgically excised mitral valves from patients with FMV/MVP and significant mitral valvular regurgitation have a substantial surface area on both leaflets (18-25, Fig. 1). The typical 2:1 ratio of the anterior to posterior leaflet surface area is altered because of the enlargement of all portions of the posterior leaflet. The mitral annular size is also increased, and the chordae tendineae are frequently thin, elongated or ruptured.[18-20] Pathologic studies have suggested that prolapse is limited to the posterior leaflet in 67% of cases, the anterior leaflet in 10% of cases, and both leaflets in 23% of cases.[20] In a recent study of 98 patients with FMV/MVP who had reconstructive mitral valve surgery for severe mitral regurgitation, prolapse of the posterior leaflet was identified in 53 patients, the anterior leaflet in 4 patients, and both leaflets in 41 patients.[26] Mitral valves with diffused thickening are currently referred to as Barlow's valves, whereas regional thickening of the mitral valve leaflets are referred to as fibroelastic deficiency valves. To date, it is not clear whether these two entities are genetically different or represent a different spectrum of abnormalities of the same disease (or both). For this reason and to avoid further confusion, we believe that it is better to define patients with FMV/MVP as having diffuse or regional thickening of the mitral valve leaflets.[3]

2. *Histology.* The gross pathologic changes occur in the presence of histological evidence of myxomatous degeneration, collagen disruption and dissolution, mucopolysaccharide infiltration, and elastin fragmentation.[18-24] The most specific fundamental and characteristic changes appear to comprise collagen dissolution and disruption in the pars fibrosa of the mitral valve leaflets, which is accompanied by proteoglycan accumulation. Similar histological abnormalities have also been demonstrated in the chordae tendineae.[24] Continuous pressure and stress during LV systole on the mitral valve leaflets and chordae tendineae contribute to the gradual progression of these histological abnormalities. In some cases, similar histological
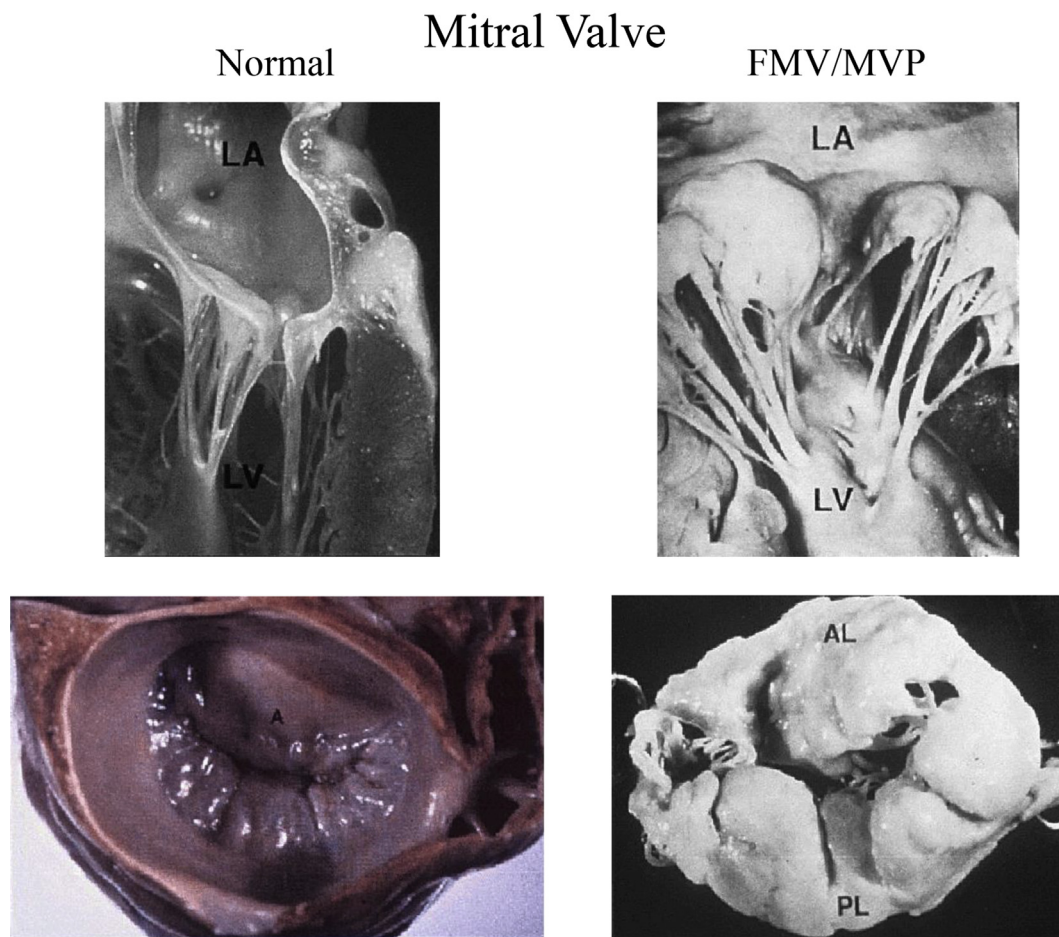
Mitral Valve

Normal
FMV/MVP

Figure 1 Left upper and lower panels: Normal mitral valve. Right upper and lower panels: Floppy mitral valve. A = anterior, AL = anterior leaflet, FMV/MVP = floppy mitral valve/mitral valve prolapse, LA = left atrium, LV = left ventricle, PL = posterior leaflet (modified from ref 27).

abnormalities have been identified in the tricuspid and/or aortic valves that are associated with tricuspid or aortic valve prolapse, respectively, and valvular regurgitation.[2,3] The precise incidence of tricuspid or aortic valve abnormalities in patients with FMV/MVP remains elusive.

3. *Scanning electron photomicrograph*. Scanning electron photomicrographs demonstrate surface folds and the focal loss of endothelial cells on mitral valve leaflets obtained from patients with severe FMV/MVP and significant mitral valvular regurgitation (18, Fig. 2). These surface abnormalities may predispose an individual to infective endocarditis and/or thromboembolic phenomena.

4. Diagnostic Considerations

It is clear that FMV should be the basis for the diagnosis of MVP.[1-3,25] Auscultatory findings and imaging characteristics are directly related to the underlying pathology (Fig. 3). The prevalence of clinically significant FMV/MVP in adults is 2 to 3%; the incidence and severity of abnormalities in FMV/MVP increases with age.[20,26-30] A family history is important because FMV/MVP may be inherited, and it also may be associated with heritable connective tissue disorders (e.g., Marfan syndrome).

Figure 2 Left panel: Mitral valve from a patient with floppy mitral valve/mitral valve prolapse (FMV/MVP) and severe mitral regurgitation; scanning electron microphotograph (original magnification 400 X) indicates an irregular surface with deep infolding. Right panel: Normal mitral valve; scanning photomicrograph (original magnification 280 X) indicates a smooth valve cusp surface covered by endothelial cells (from ref 18).

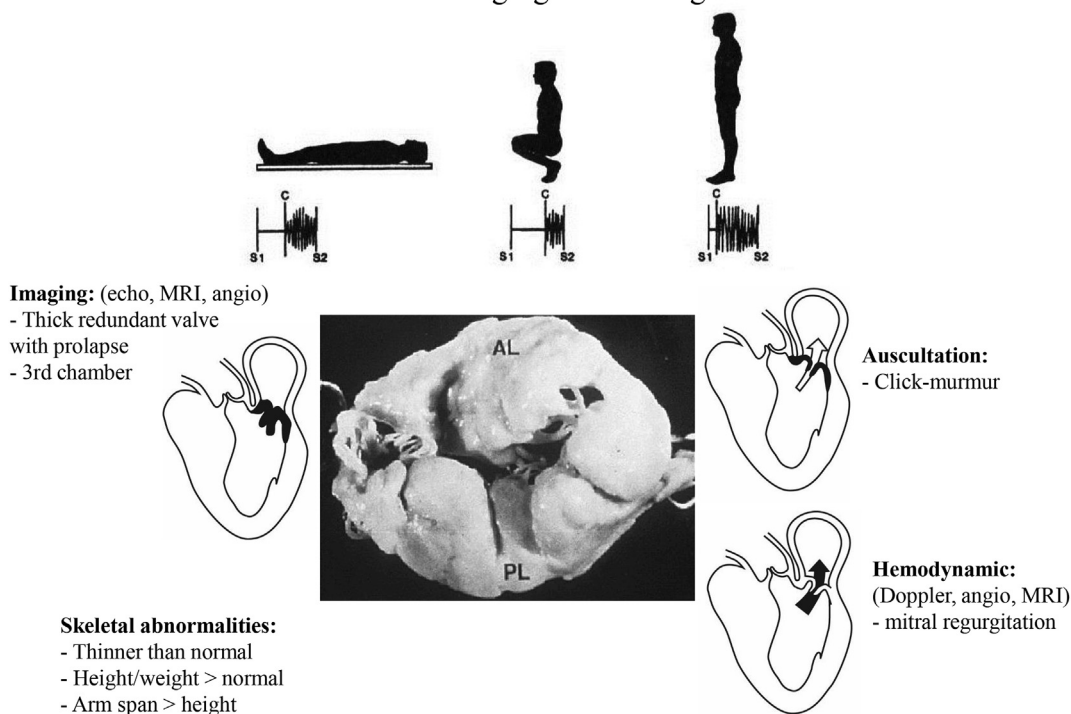FMV/MVP/Mitral Valvular Regurgitation: Diagnostic Considerations

Figure 3 Floppy mitral valve (FMV) is indicated in the center. FMV is the central issue in floppy mitral valve/mitral valve prolapse (FMV/MVP) and mitral valvular regurgitation. Imaging techniques (e.g., echo: echocardiogram, MRI: magnetic resonance imaging, and angio: ventricular angiogram) provide detailed information related to the mitral valve apparatus, leaflet thickness, and chordae tendineae. Hemodynamics (e.g., Doppler, cardiac catheterisation, and MRI) can demonstrate the mitral regurgitation severity. Auscultation or phonocardiogram provide information on the murmur or click. A late systolic murmur with postural changes is also indicated. Skeletal or other abnormalities, if present, should also be defined. AL = anterior leaflet, PL = posterior leaflet, C = systolic click, S1 = first heart sound, S2 = second heart sound (modified from ref 99).

1. *Physical examination.* Skeletal abnormalities, such as a narrow anteroposterior chest diameter, straight back, pectus excavatum, and scoliosis, may be present in FMV/MVP. Patients with FMV/MVP may have an arm span greater than the body height, are often thinner than normal, and their height to weight ratio exceeds normal controls.[3,25,31–34] The presence of a non-ejection apical systolic click with or without late apical systolic murmur comprise the auscultatory criteria for the diagnosis of FMV/MVP.[3–5,8,21] A high-pitched mid to late apical systolic murmur of mitral regurgitation frequently preceded by a click may also be present. When the posterior mitral valve leaflet prolapses, the murmur may radiate to the left sternal border; in contrast, when the anterior leaflet prolapses, the murmur may radiate to the axilla and/or spine. In the upright posture, the systolic click moves toward the first heart sound, and the murmur becomes longer and often louder. A systolic murmur may be present only in the upright position. The auscultatory changes that occur with posture in patients with FMV/MVP are predominately related to changes in the LV volume, myocardial contractility, and heart rate. With the progression of disease and when mitral regurgitation becomes significant, the click may disappear, and the murmur may become holosystolic.[3,21]

2. *Electrocardiogram and chest-x-ray.* In the majority of patients with FMV/MVP, the electrocardiogram is normal. Non-specific ST and T wave changes, especially in the

inferior leads, have been described; however, they are non-specific to FMV/MVP. These changes often improve with exercise and/or beta-blockade therapy. When LV hypertrophy/enlargement or left atrial enlargement are present as a result of chronic mitral valvular regurgitation, these abnormalities may be identified via electrocardiogram.[1,2] Chest X-ray typically indicates normal heart and lungs; the skeletal abnormalities previously described may also be identified if present. Patients with significant mitral regurgitation may have left atrial and LV enlargement and different degrees of pulmonary venous congestion following heart failure development. Calcification of the mitral annulus may be present in elderly patients. Acute rupture of the chordae tendineae, which produces severe acute mitral regurgitation, may result in pulmonary edema with a nearly normal cardiac silhouette.[2,3]

3. *Echocardiography and Doppler echocardiography.* To date, echocardiography and Doppler echocardiography are the most widely used and most useful methods for the diagnosis and follow-up of patients with FMV/MVP.[3,35–43] The structure and function of the entire mitral valve apparatus (e.g., leaflet thickness, chordae tendinae length, and annular diameter), and LV and left atrial structure and function may be precisely defined via echocardiogram. Doppler echocardiography provides important information related to the presence and severity of mitral valvular regurgitation and indirect information related to pulmonary

artery pressure not only at rest, but also during exercise. MVP is typically defined as leaflet(s) displacement at least 2 mm above the mitral annulus in the parasternal long-axis view. However, the diagnosis of FMV/MVP should be based on firm criteria regarding structural changes and not only on the presence of prolapse, which may represent a non-specific finding. Leaflet thicknesses greater than 5 mm are considered abnormal.[26,36,37] The introduction of three-dimensional echocardiography in clinical practice provides more accurate information regarding the mitral valve structure and function, and enables the precise definition and measurement of the volume in the third chamber (subsequently described; Fig. 4).[39,40] During the early stages of the disease, distinguishing a normal mitral valve from a FMV with minor abnormalities may be difficult. In some cases, repeat examination over several years may be necessary to define FMV/MVP because of the progressive nature of the disease.[2,3]

4. *Cardiac magnetic resonance imaging (MRI)*. Cardiac MRI may be used in clinical practice for the diagnosis of FMV/MVP and especially for follow-up. Cardiac MRI is currently the most accurate method used to follow changes in the LV size, function and mass, determine the left atrial size and function, and define the severity of mitral valvular regurgitation. The thickness of the mitral valve leaflets and the third chamber may also be defined using cardiac MRI[3,41,44] (Fig. 5).

5. *Cardiac catheterisation*. Today, cardiac catheterisation is predominately performed prior to surgical intervention in order to define the coronary anatomy. Performing ventriculography may determine the severity of mitral regurgitation and define LV and left atrial volumes and function. Furthermore, intra-cardiac and pulmonary artery pressure measurements provide important information in certain cases. In addition, the characteristic appearance of the mitral valve apparatus and the thickness of mitral valve leaflets may be defined[3,18,21] (Fig. 6).

6. *Surgical inspection*. The inspection of the mitral valve at the time of surgery has contributed to a better definition of the etiology of the disease and has provided a basis for *in vivo* correlates with imaging techniques.[3,26]
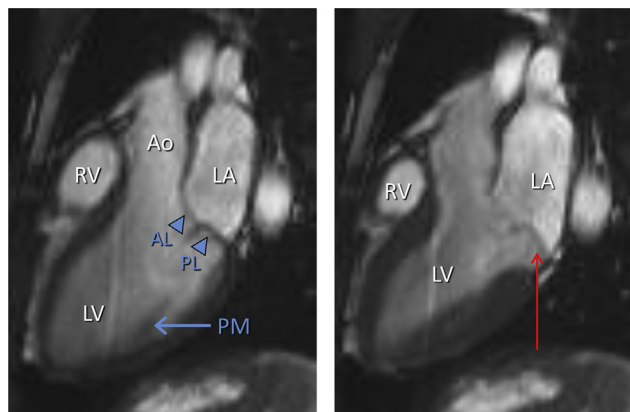

Figure 5 Cardiac magnetic resonance imaging (courtesy of Subha Raman, MD, The Ohio State University, Columbus Ohio, USA). Note the thickness of the mitral valve leaflets (short arrows on left panel) and the third chamber (arrow on right panel). Ao = aorta, AL = anterior leaflet, LA = left atrium, LV = left ventricle, RV = right ventricle, PL = posterior leaflet, PM = papillary muscle.

7. *Post-mortem examination*. The characteristic macroscopic appearance of FMV may easily be recognised. A dynamic post-mortem examination with inspection of the mitral valve from the left atrium prior to opening the LV and observation of the mitral valve dynamics following LV filling with fluid allows the identification of cusp prolapse. These studies have provided important post-mortem observations that parallel imaging techniques and surgical inspection. After LV opening, the mitral valve leaflet area and chordae tendineae length or rupture may be identified.[19,20]

5. Effects on Circulation

The pathophysiological consequences of the mitral valve apparatus in patients with FMV/MVP may affect the entire *circulation*. These effects of FMV/MVP on the *circulation* will be briefly described.[45]
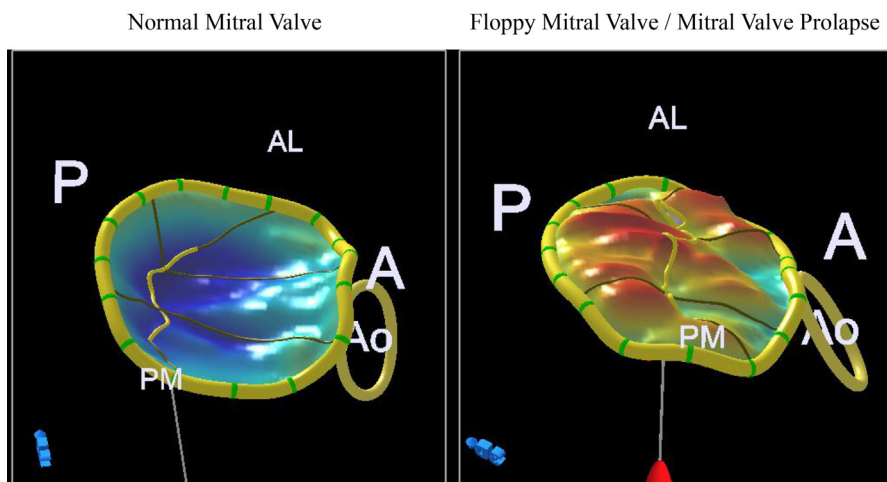

Figure 4 Three-dimensional echocardiography (courtesy of Vlasis Ninios, MD, St Lucas Hospital, Thessaloniki, Greece) indicates a normal mitral valve (left) and a floppy mitral valve (right); third chamber is also shown. A = anterior, AL = anterior leaflet, Ao = aorta, P = posterior, PM = posterior papillary muscle.
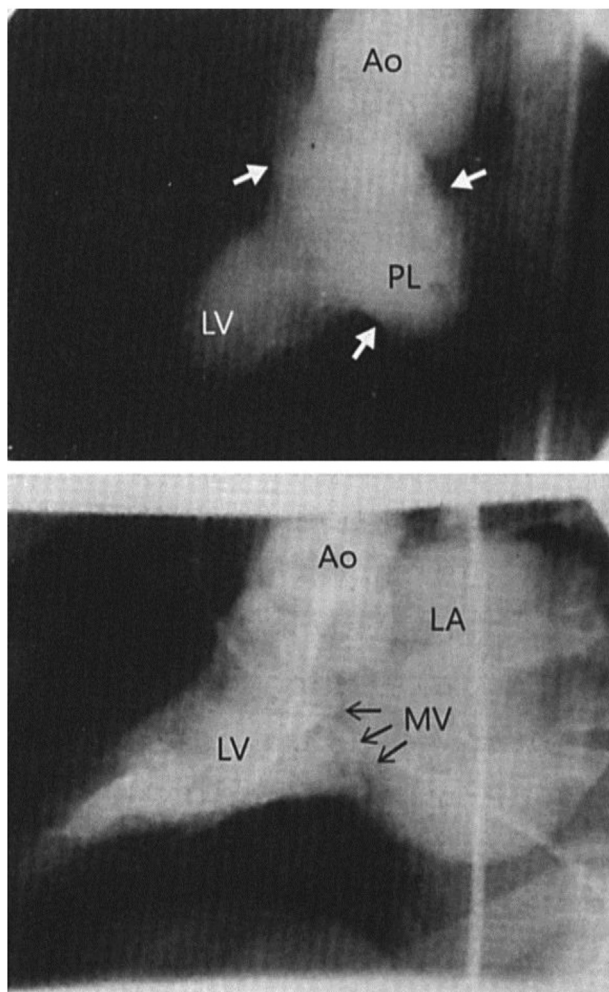
FMV/MVP: Ventriculogram

Figure 6 Upper panel: Ventriculogram in a patient with floppy mitral valve/mitral valve prolapse (FMV/MVP) without mitral regurgitation; arrows indicate posterior mitral leaflet (PL) prolapse. Lower panel: Ventriculogram in a patient with FMV/MVP and severe mitral regurgitation during systole; note the large left atrium (LA) and the thickness of the mitral valve (MV) leaflets (arrows). Ao = aorta, LV = left ventricle (from ref 2).

1. *Third chamber*. When prolapsing into the left atrium, the FMV occupies part of the left atrial cavity that develops a new chamber between the mitral annulus and the prolapsing mitral valve leaflets during LV systole (Fig. 7). Thus, during LV systole, even without mitral regurgitation, a specific amount of blood occupies the space between the mitral annulus and the mitral leaflets (i.e., the third chamber).[3,45] In severe FMV/MVP, the amount of blood within the third chamber may represent a substantial amount of the total potential LV stroke volume, which results in a significant decrease in the effective stroke volume. The degree of MVP increases in the upright posture, which will result in an increase in the third chamber size and may contribute to a further decrease in the effective stroke volume and forward cardiac output.[3,21,45] These

alterations may explain the fatigue and exercise intolerance in specific patients with FMV/MVP. Previous studies from our laboratory have demonstrated an inability of patients with FMV/MVP to maintain the LV diastolic volume and cardiac output during upright exercise (Fig. 7).[3,46]

2. *Papillary muscle traction-stretch receptor activation*. In normal subjects, the distance between the papillary muscle tips and the mitral annulus during LV systole remains relatively constant. In contrast, in patients with FMV/MVP, mitral valve leaflet displacement into the left atrium results in papillary muscle displacement and an increase in traction on the papillary muscle[3,26] (Fig. 8). Normal LV function is dependent on the integrity of papillary muscle and chordae tendineae function; thus, these changes may result in disorders of contractile patterns of the LV. Furthermore, stretch receptors are activated as a result of papillary muscle traction; stretch receptor activation may result in LV and papillary muscle membrane depolarization and ventricular arrhythmias.[47–50]

3. *Mitral valve-brain interactions*. Human cardiac valves have distinct patterns of innervation. The presence of these nerve terminals suggests a neural basis for interactions between the central nervous system and the mitral valve (Fig. 8). The sub-endocardial surface on the atrial aspect at the middle portion of the mitral valve is rich in nerve endings, including afferent nerves. Mechanical stimuli from this area caused by abnormal coaptation in patients with FMV/MVP may cause abnormalities in autonomic nerve feedback between the central nervous system and the nerve endings of the mitral valve.[3,45,47]

4. *Left atrial-LV structure/function and pulmonary circulation*. In patients with FMV/MVP, the mitral valve abnormalities progress over time and mild mitral valvular regurgitation may become severe. The progression of mitral valvular regurgitation is typically gradual, which permits adaptive compensatory mechanisms. During LV systole in patients with mitral regurgitation, part of the LV stroke volume is ejected into the low pressure left atrium. The left atrium gradually dilates and accommodates the extra load. Chronic left atrial dilatation results in an increase in left atrial compliance with relatively normal left atrial pressure despite a substantial left atrial volume. The LV volume also gradually increases because, in addition to the blood flow from the pulmonary veins, blood ejected into the left atrium during LV systole returns to the LV during diastole. Thus, in patients with mitral regurgitation, significant left atrial and LV dilatation and dysfunction may occur.[2,3] LV dilatation may cause papillary muscle displacement, which further exacerbates mitral regurgitation and results in a vicious cycle.[51] In specific cases, the left atrium may be affected more than the LV, and atrial fibrillation may often occur. Atrial fibrillation may also increase the severity of mitral regurgitation that improves following restoration of sinus rhythm.[52] Thus, the left atrial and LV structure and function, as well as the cardiac rhythm are important determinates of the natural history in patients with FMV/MVP and mitral regurgitation. Furthermore, transmission of the left atrial pressure into the pulmonary veins and pulmonary arterial capillaries may lead to pulmonary arterial hypertension, which also comprises a poor prognostic indicator. Factors that accelerate the natural course of mitral valvular regurgitation include chordae
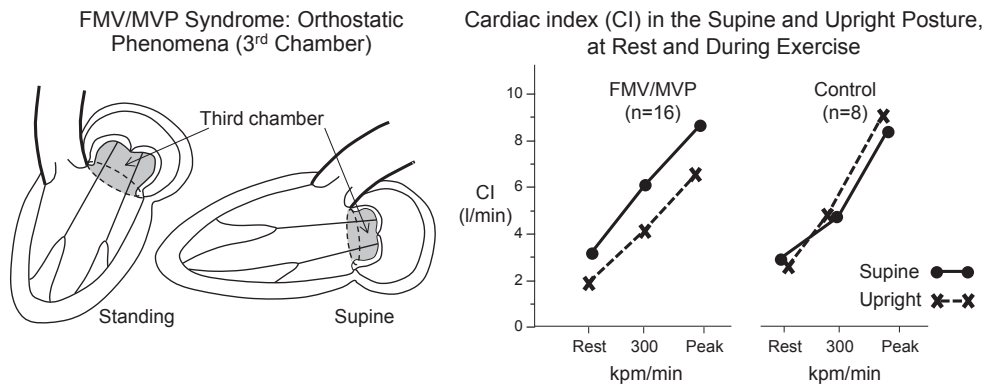
FMV/MVP Syndrome: Orthostatic Phenomena (3rd Chamber)

Cardiac index (CI) in the Supine and Upright Posture, at Rest and During Exercise

Figure 7 Left panel: Third chamber, which comprises the space between the mitral valve annulus and the prolapsing mitral valve leaflets, in floppy mitral valve/mitral valve prolapse (FMV/MVP) is schematically presented; note that the size of the third chamber increases in the upright position (modified from ref 2). Right panel: Cardiac index (CI) in patients with FMV/MVP syndrome was lower in the upright compared with supine position, whereas in normal subjects, the CI was similar in the supine and upright positions. The lower CI was related to a smaller left ventricular volume because the left ventricular ejection fraction was similar in the supine and upright positions during exercise. Kilopond-meters per minute (kpm/min) (modified from ref 46).
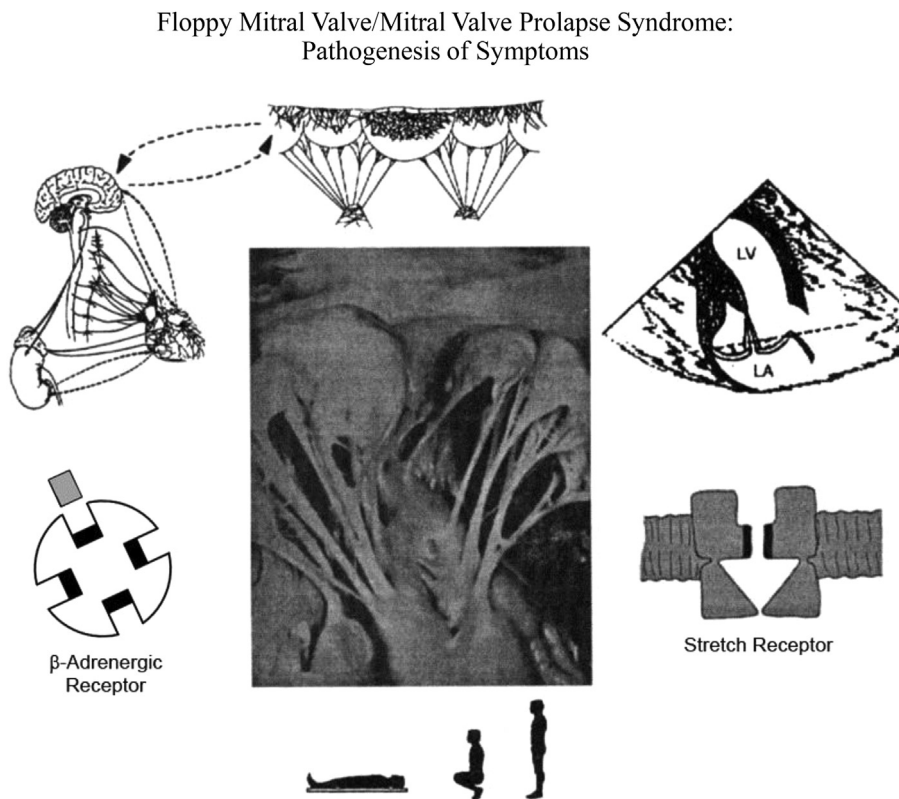

Floppy Mitral Valve/Mitral Valve Prolapse Syndrome: Pathogenesis of Symptoms

Figure 8 Floppy mitral valve/mitral valve prolapse (FMV/MVP) is indicated in the center (modified from ref 27); the prolapsing mitral valve becomes a space-occupying chamber in the left atrium (LA). FMV/MVP innervation is schematically demonstrated; upper right panel indicates papillary muscle traction during left ventricular (LV) systole; lower right panel indicates a schematic stretch activated receptor; left upper panel indicates interactions between the brain, heart, kidneys and adrenals; lower left panel indicates a schematic beta-adrenergic receptor; lower panel indicates orthostatic phenomena (modified from ref. 47).

tendineae rupture, infective endocarditis, stiffening of the aorta, and arterial hypertension.[53–60]

5. *Aortic function*. Evidence suggests that specific patients with FMV/MVP may have abnormal elastic properties of the aorta. The aorta also stiffens with age. Stiffening of the aorta that results in systolic hypertension provides resistance to LV ejection and increases the degree of mitral regurgitation. These factors may accelerate the progression of mitral regurgitation after the age of 50, when the aorta typically becomes stiff.[2,3,12]

6. FMV/MVP and Mitral Valvular Regurgitation: Symptoms, Natural History, Complications Related to Mitral Valve Abnormalities, and Management

The symptoms and serious complications related to mitral valve dysfunction in patients with FMV/MVP include progressive mitral valvular regurgitation, which may lead to congestive heart failure, rupture of the chordae tendineae, infective endocarditis, cardiac arrhythmias, and thromboembolic phenomena. As a general rule, complications increase with age (Fig. 9).

1. *Symptoms related to mitral valvular regurgitation.* Significant symptoms related to mitral regurgitation typically develop at 50 to 60 years of age or later. Progressive mitral regurgitation is related to various combinations of annular dilatation, elongation or rupture of the chordae tendineae, and ventricular dilatation. In some cases, chordae tendineae rupture may lead to acute mitral regurgitation. Patients with thick mitral valve leaflets, mitral systolic murmur, men, and an age greater than 50 years are at increased risk for the development of significant mitral regurgitation.[2,3,18,25,37,53] When FMV/MVP is part of a recognised heritable connective tissue disorder, the natural history may primarily be related to the underlying disease rather than the FMV/MVP.[9–11]

2. *Infective endocarditis is a complication of FMV/MVP.* Antibiotic prophylaxis for infective endocarditis is currently a matter of considerable debate, as well as a subject of changing attitudes and recommendations. Patients should be encouraged to maintain the best possible oral hygiene to reduce potential sources of bacterial seeding. The current guidelines do not recommend prophylaxis for endocarditis in patients with FMV/MVP; however, it should be noted that an abnormal area of valve leaflets and not the mitral regurgitation per se is responsible for endocarditis (Fig. 2). It should also be highlighted that, in general, the incidence of infective endocarditis has mildly increased following the introduction of the most recent guidelines in which antibiotic prophylaxis is not recommended.[61–63]

3. *Thromboembolic complications are another controversial issue.* Patients who exhibit clinical manifestations of cerebral, retinal, or peripheral emboli should discontinue oral contraceptives, abstain from tobacco smoking, and undergo a careful cardiovascular and haematological evaluation prior to the consideration of long-term anticoagulation or antiplatelet therapy. In the case of atrial fibrillation, the same approach should be used as in patients without FMV/MVP.[3,64,65]

4. *Cardiac arrhythmias and sudden cardiac death.* Cardiac arrhythmias appear to be more frequent in patients with FMV/MVP compared with the general population.[66–68] The same diagnostic and therapeutic approach should be used as in patients without FMV/MVP. Sudden cardiac death in patients with FMV/MVP in the absence of significant mitral regurgitation may occur; however, it is extremely rare. Autopsy studies in patients with FMV/MVP who died suddenly have demonstrated that the mitral leaflet length and posterior leaflet thickness were increased in the hearts from patients who had sudden cardiac death compared with patients with FMV/MVP who died from other causes. Patients with FMV/MVP who died suddenly without significant mitral regurgitation tend to be relatively young women.[69–71] Ventricular fibrillation was the cause of cardiac arrest in patients with FMV/MVP who had successful cardiac resuscitation. Beta-blockade therapy may be beneficial in patients with FMV/MVP who were successfully resuscitated from cardiac arrest. Prophylactic use of an implantable cardioverter defibrillator for secondary prevention is recommended in these patients.[69]

5. *Medical management of mitral regurgitation in FMV/MVP.* To date, there are limited data regarding the use of pharmacologic agents to delay the progression of mitral regurgitation. One study that comprised a small number of patients suggested that therapy with Toprol XL, a beta-1 adrenergic receptor blocker, improved LV function in patients with isolated mitral regurgitation.[72] The usefulness of this therapy in clinical practice remains to be defined. Furthermore, the attenuation of transforming growth factor beta with angiotensin II receptor blockers may prove to be effective in the modulation of FMV/MVP progression. As previously discussed, stiffening of the aorta with age may increase the degree of mitral regurgitation and precipitate the natural history of the disease.[73] Better control of systolic hypertension, which is associated with a stiff aorta, especially with drugs that improve aortic function, such as angiotensin-converting enzyme inhibitors or calcium channel blockers, may prove effective in slowing the disease progression; however, this concept remains to be defined.[45] Thus, when significant mitral regurgitation is present in a symptomatic patient with FMV/MVP or new onset of atrial fibrillation, surgical intervention is recommended.[2,3]

Interventional therapy in patients with FMV/MVP and mitral regurgitation

a. *Surgical management.* When severe mitral regurgitation is present in a symptomatic patient with FMV/MVP, especially when the LV ejection fraction (LVEF) is > 30%, surgical intervention is recommended. If mitral valve repair
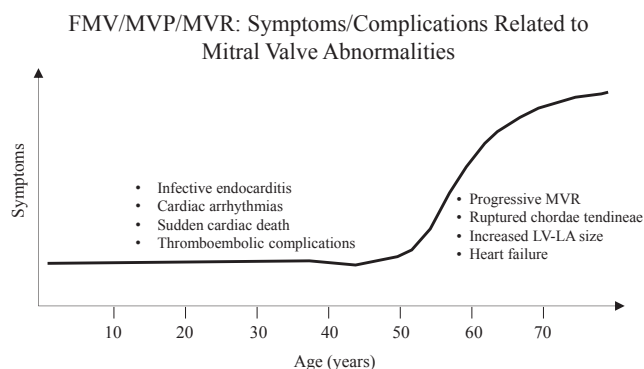

FMV/MVP/MVR: Symptoms/Complications Related to Mitral Valve Abnormalities

- Infective endocarditis
- Cardiac arrhythmias
- Sudden cardiac death
- Thromboembolic complications

- Progressive MVR
- Ruptured chordae tendineae
- Increased LV-LA size
- Heart failure

Figure 9 Floppy mitral valve/mitral valve prolapse/mitral valvular regurgitation (FMV/MVP/MVR). Symptoms and complications related to FMV/MVP with MVR are plotted against age in years. Increased symptoms related to MVR typically occur after the age of 50 years. Left ventricular (LV) and left atrial (LA) structural and functional abnormalities, atrial fibrillation and heart failure (HF) may occur. Thromboembolic complications, infective endocarditis and cardiac arrhythmias have been reported in a wide range of ages (modified from ref. 2).

is highly likely, which is the treatment of choice, then surgery is recommend in symptomatic patients with severe mitral regurgitation as a result of FMV/MVP even if the LVEF is < 30%. Mitral repair is also indicated in asymptomatic patients with FMV/MVP and severe mitral regurgitation with an LVEF > 60% and LV end systolic diameter < 40 mm or a new onset of atrial fibrillation or pulmonary hypertension, particularly if the likelihood of mitral valve repair is high. If the likelihood of mitral repair in these asymptomatic patients is not high, then frequent follow-up (e.g., every 6 months) is a reasonable approach. An exercise tolerance test may be useful to determine whether patients are truly asymptomatic or if they develop pulmonary hypertension (systolic >60 mm Hg), which is also an indication for surgery. Furthermore, mitral valve surgery is indicated in asymptomatic patients with FMV/MVP and severe mitral regurgitation when the LVEF is between 30% to ≤ 60% or the LV end systolic diameter is ≥ 40 mm. However, it should be noted that LVEF may be underestimated in patients with mitral regurgitation. The left atrial volume and function may also facilitate a better definition of the timing for surgical intervention. Mitral repair is preferable compared with replacement for the treatment of mitral regurgitation as a result of FMV/MVP because it better preserves LV function compared with mitral valve replacement. Furthermore, inherent adverse effects related to prosthetic valves (e.g., anticoagulation therapy, risk of endocarditis or thrombosis, noise of the mechanical prosthesis, or structural valve deterioration) may be avoided. In the previous several years, the use of artificial chords has further expanded the number of patients with FMV/MVP who may effectively undergo mitral valve repair. This is especially true for bileaflet and anterior leaflet prolapse.[3,74–82] In the previous few years at St. Luke's Hospital, Thessaloniki, Greece, a new, tailor-made, inexpensive annuloplasty device has been used that preserves annular valve function. Furthermore, it helps to eliminate the development of systolic anterior motion (SAM) of the mitral valve, which comprises one complication associated with mitral valve repair that it is difficult to manage (Fig. 10). This technique has been used in more than two hundred patients to date
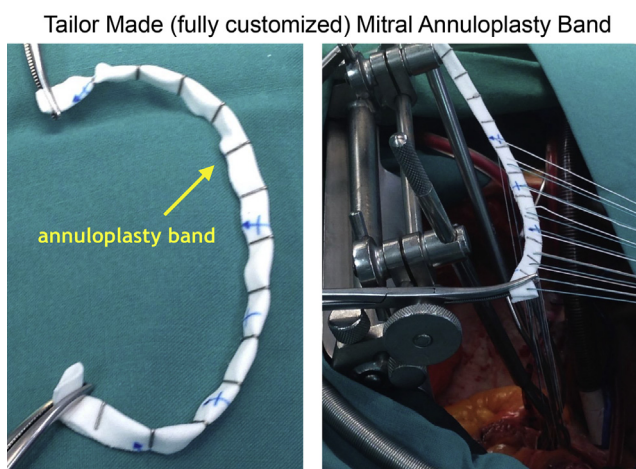
Tailor Made (fully customized) Mitral Annuloplasty Band

Figure 10   Tailor-made mitral annuloplasty band used at St Luke's Hospital is shown. Surgical implantation of the mitral annuloplasty band is also shown (left image).

(bileaflet and anterior repairs included) with excellent results and without an incidence of SAM. The custom-made annuloplasty band is composed of dacron and titanium clips.

b. *Transcatheter interventions of mitral regurgitation in FMV/MVP*. In patients who are at a prohibitive risk for surgery, transcatheter mitral valve repair using the mitraclip device can be used. Furthermore, transcatheter mitral valve replacement may be an option in the near future as clinical trials are underway.[83–86]

7. Acute Mitral Regurgitation

The most common causes of acute mitral regurgitation are chordae tendineae rupture, papillary muscle rupture and infective endocarditis. Distinguishing the three most common types of acute mitral regurgitation based on clinical evaluation is relatively easy. Rupture of the chordae tendineae is the most common cause of acute mitral regurgitation in patients with FMV/MVP. In severe acute mitral regurgitation, a substantial volume of blood is ejected into the low pressure left atrium during LV systole. There is insufficient time to enable left atrial and LV dilatation; thus, the amount of the regurgitant volume will result in a substantial increase in the left atrial pressure. Left atrial v-waves > 60 mmHg are not uncommon. The marked increase in the pulmonary venous pressure may result in pulmonary edema. Since the LV is of normal size and a large amount of blood goes into the left atrium during LV systole, the forward stroke volume is markedly diminished. In addition to pulmonary oedema, the net result is tissue hypoperfusion and shock. The systolic murmur typically peaks in mid-systole and diminishes in intensity prior to the second heart sound in contrast to chronic mitral regurgitation where the murmur is holosystolic. The sudden appearance of a new systolic murmur associated with dyspnea, tissue hypoperfusion and shock should raise the suspicion of acute mitral regurgitation. In cases of FMV/MVP with a previously identified systolic murmur, patients present with an alteration in the quality of the murmur, tissue hypoperfusion and/or dyspnoea. In severe acute mitral regurgitation, an emergent surgical intervention is indicated. Patients with less severe mitral regurgitation may gradually progress and may respond to medical management without surgery at least during the acute phase. However, most patients with chordae tendineae rupture will require mitral valve surgery in 6 to 12 months following the rupture.[2,3,19]

8. FMV/MVP Syndrome

Certain patients with FMV/MVP may have symptoms that cannot be explained based on the severity of mitral regurgitation alone. Neuroendocrine or autonomic nervous system functional abnormalities have been postulated as an explanation for the symptoms in this patient group, which is currently classified as the FMV/MVP syndrome.[2,3,25]

1. *Symptoms related to FMV/MVP syndrome*. The most common symptoms in these patients include palpitations, orthostatic phenomena (tachycardia, hypotension), cardiac arrhythmias, syncope or pre-syncope, exercise intolerance/

fatigue, chest pain, or dyspnea. The median age of symptom onset is approximately 30 years of age with a wide range of symptom onset. The symptoms of FMV/MVP syndrome have been previously reported from numerous investigators.[87–96] In most of these studies, however, symptoms were reported at one particular time during the natural course of the disease and thus, the duration of symptoms was not precisely defined. Furthermore, in the majority of these studies, the diagnosis of MVP was based on "soft" echocardiographic criteria (M-mode or two dimensional) without defining whether the mitral valve was floppy. In a recent study from our laboratory, the symptoms related to FMV/MVP syndrome were analysed in 98 patients from the time of onset until reconstructive surgery was performed.[26,97] The median age of symptom onset was 30 years (range 10 to 63 years) and the median duration of symptoms from onset to mitral valve surgery was 16 years (range 3 to 50 years). Thus, it is unlikely that these symptoms were related to the severity of mitral regurgitation. The diagnosis of FMV in our study was established with transoesophageal two- and three- dimensional echocardiography, and it was also confirmed with direct inspection of the mitral valve in the operating room in all patients. Patients had diffuse (n = 40) or regional (n = 58) thickening of the mitral valve leaflets. Leaflet thickening was often associated with an elongated chordae tendineae, chordae tendineae rupture, flail mitral leaflet, and mitral annular dilatation. The incidence of symptoms related to FMV/MVP syndrome in the entire group was 42%. The incidence of symptoms consistent with FMV/MVP syndrome was increased in the patients with diffuse thickening of the mitral valve leaflets (52.5 %) compared with the patients with regional thickening of the mitral valve leaflets (31%). Palpitations were persistent in most patients, whereas other symptoms, such as fatigue, dyspnea and chest pain, disappeared after surgery. The cause of the palpitations was not precisely defined. It was not clear whether the patients were aware of a "fast heart beat" or had premature atrial or ventricular contractions. It is also possible that the patients were more sensitive in recognising premature beats or changes in heart rate compared with the general population. Atrial fibrillation was not responsible for symptoms in patients with palpitations. It can be concluded therefore, that patients with FMV/MVP may have symptoms consistent with the FMV/MVP syndrome for many years prior to the development of significant mitral regurgitation and thus, cannot be attributed to mitral regurgitation per se. These symptoms were more prominent in women compared to men.[25]

2. *Pathogenesis of symptoms in FMV/MVP syndrome.* Symptoms in women with FMV/MVP syndrome may be related, in part, to beta-adrenergic receptor polymorphisms that increase the sensitivity to adrenergic stimulation.[25] In addition to a high adrenergic tone, there are several other mechanisms that may be related to the pathogenesis of symptoms in patients with FMV/MVP syndrome.[87–96] These mechanisms include the development of the third chamber, which may result in a low stroke volume, particularly in the upright position[45,46]; papillary muscle traction, which may produce chest pain that results in the activation of stretch receptors that lead to membrane depolarisation and cardiac arrhythmias; and mitral

valve nerve ending stimulation, which may cause an abnormal autonomic nerve feedback between the central nervous system and the mitral valve[3,47–50] (Fig. 8).

3. *Management of patients with FMV/MVP syndrome.* Careful explanation to patients of the findings and potential mechanisms of symptoms will provide a foundation for long-term management. Importantly, patients with FMV/MVP syndrome should be protected from unnecessary surgery if they do not exhibit severe mitral regurgitation. The prognosis regarding life expectancy appears to be very good. In some cases, patients with FMV/MVP syndrome may be sensitive to volume depletion and should be advised to avoid or discontinue chronic diuretic therapy if not absolutely indicated. Fluid intake before, during and after exercise may be beneficial, especially in patients with a low intravascular volume. Catecholamine and cycle AMP stimulants, such as caffeine, cigarettes, alcohol and over-the-counter medications that contain epinephrine, should be avoided. Low doses of beta-blockers during a short period of time, especially if the patient is sensitive to adrenergic stimulation during stressful periods, may be beneficial. Studies suggest that aerobic exercise may provide good results in specific patients. At present, there is insufficient information for the use of the bradycardic drug procoralan in cases of orthostatic tachycardia in patients with FMV/MVP syndrome.[2,3]

9. Individual Patient Analysis

FMV/MVP includes a heterogeneous group of patients with a broad spectrum of mitral valve abnormalities that range from mild to severe. Thus, in each case, it is important to
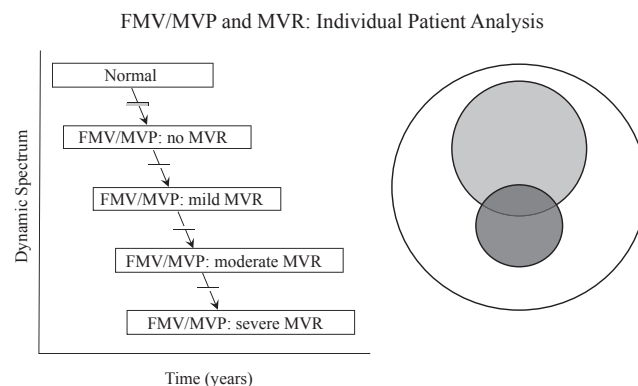

Figure 11   Left panel: Dynamic spectrum, time in years, and progression of floppy mitral valve/mitral valve prolapse (FMV/MVP) are indicated. A subtle gradation exists between the normal mitral valve and valves with mild FMV/MVP without mitral valvular regurgitation (MVR). Progression from FMV/MVP without MVR to FMV/MVP with MVR may occur. Right panel: Large circle represents the total number of patients with FMV/MVP. Patients with FMV/MVP may be symptomatic or asymptomatic. Symptoms may be directly related to mitral regurgitation (dark grey circle) or FMV/MVP syndrome (light grey circle). Patients with symptoms related to mitral regurgitation may also have symptoms related to FMV/MVP syndrome. In the individual patient analysis, anatomical and pathophysiological abnormalities for each individual patient at each stage should be defined, and therapy should be based on these findings (modified from ref. 1).

not only establish the diagnosis of FMV/MVP, but also define the abnormalities and their severities. Symptoms in patients with FMV/MVP may be directly related to the underlying mitral valve pathology, as well as progressive mitral regurgitation and its complications. However, in some cases of FMV/MVP, the symptoms cannot be explained based only on the severity of mitral regurgitation alone (Fig. 11). Activation of the autonomic nervous system or neuroendocrine dysfunction has been implicated in the explanation of symptoms in this group of patients that at present it is referred as the FMV/MVP syndrome.[3,25] Symptoms in patients with FMV/MVP syndrome may coexist with symptoms related to significant mitral regurgitation and, in certain instances, may persist following mitral valve surgery. The individual patient analysis represents a logical approach to the diagnosis and risk stratification of each patient in this heterogeneous group.[2,18,98] Anatomical and pathophysiological abnormalities for each individual patient should be defined, and therapy should be based on these findings.

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