

The Floppy Mitral Valve, Mitral Valve Prolapse, Mitral Valvular Regurgitation and the Floppy Mitral Valve/Mitral Valve Prolapse Syndrome. Current Concepts

HARISIOS BOUDOULAS

The Ohio State University, Foundation for Biomedical Research, Academy of Athens, Greece

Key words:

Floppy mitral valve, mitral prolapse, mitral regurgitation, mitral valve prolapse syndrome.

Manuscript received:
August 12, 2004;
Accepted:
September 20, 2004.

Address:

Harisios Boudoulas

*4 Soranou Ephessiou St.
115 27 Athens
e-mail:
boudoulas@bioacademy.gr*

It is well appreciated today that the floppy mitral valve (FMV) is the central issue of mitral valve prolapse (MVP), mitral valvular regurgitation (MVR) and the FMV/MVP syndrome.¹⁻⁹ Thus, for the diagnosis of FMV/MVP, the key issue is the precise definition of the FMV. New technology with three-dimensional reconstruction of the mitral valve apparatus allows better definition of the mitral valve complex and the FMV morphology and dimensions. The term “floppy” mitral valve comes from surgical and pathological studies and refers to the intrinsic morphological changes resulting in the expansion of the area of the mitral valve leaflets, with elongated chordae tendineae, frequently including a dilated mitral annulus.^{1,2,9}

The FMV is a common mitral abnormality with a broad spectrum of structural and functional changes, extending from mild to severe. Physical examination and laboratory findings are directly related to the nature and extent of the valvular abnormality. As a general rule, patients with more severe disease will have more clinical and laboratory findings and vice versa. Similarly, the management and natural history obviously differ in each subgroup of patients with FMV/MVP, as in any other situation in clinical medicine.^{1,2}

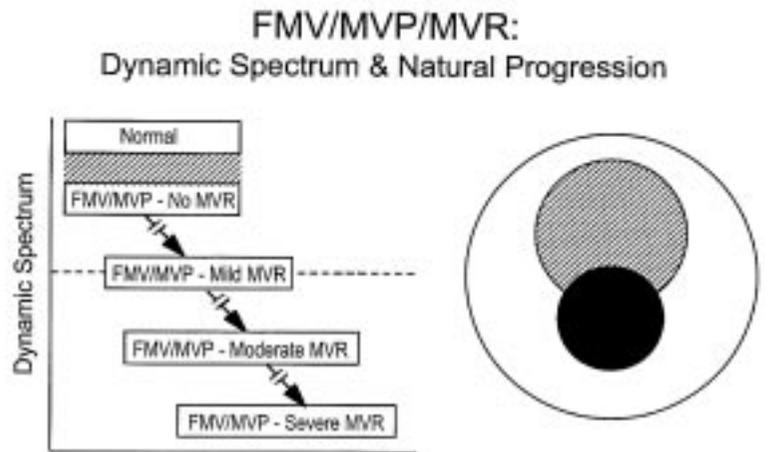
At present, the diagnosis of FMV/MVP/MVR is based on the auscultatory postural complex with confirmatory echocardiographic and Doppler findings. The likelihood of finding FMV/MVP using echocardiography in patients with normal, carefully performed dynamic auscultation is extremely low. At times, distinguishing between the normal mitral valve with its minor variants and a mitral valve with an intrinsic structural derangement may be difficult. A confounding issue arises when patients with symptoms, negative auscultatory findings and non-specific echocardiographic FMV/MVP findings are labelled as having FMV/MVP and their symptoms are ascribed to FMV/MVP. It is my opinion that labelling these patients with a diagnosis of FMV/MVP should be avoided. In certain cases, repeat physical examination and echocardiograms over several years may be necessary before the matter is resolved. Family history is important in such situations, since FMV/MVP may be inherited.^{1,11,12}

Floppy mitral valve/mitral valve prolapse: Clinical classification

Based on personal clinical experience and that of other world-wide colleagues, pa-

Figure 1. Left panel: The dynamic spectrum, time in years, and the progression of floppy mitral valve (FMV) and mitral valve prolapse (MVP) are shown. A subtle gradation (cross-hatched area) exists between the normal mitral valve and valves that produce mild FMV/MVP without mitral valvular regurgitation (MVR). Progression from the level FMV/MVP-no MVR to another level may or may not occur. Most of the patients with FMV/MVP syndrome occupy the area above the dotted line, while patients with progressive mitral valve dysfunction occupy the area below the dotted line.

Right panel: The 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 valve dysfunction (black circle), or to autonomic dysfunction (cross-hatched circle). Certain patients with symptoms directly related to mitral valve dysfunction may present and continue to have symptoms secondary to autonomic dysfunction.



From Boudoulas H, Wooley CF¹, with permission.

tients with FMV/MVP are classified into two different categories. The first includes patients whose symptoms, physical findings, laboratory abnormalities and clinical course are directly related to mitral valve dysfunction and complications (Figure 1, Table 1).^{1,12} The second category includes patients with FMV/MVP whose symptoms cannot be explained on the basis of valvular abnormality alone, but the occurrence of symptoms is a result of neuroendocrine or autonomic dysfunction in patients with FMV/MVP. At present we

refer to this group of patients as having FMV/MVP syndrome.

This clinically useful classification separates symptomatic patients with FMV/MVP and symptoms related primarily to neuroendocrine or autonomic nervous system dysfunction from patients whose symptoms are related primarily to mitral valve dysfunction. It specifies a group of patients with FMV/MVP and autonomic dysfunction, who require consideration for antibiotic prophylaxis for infective

Table 1. Classification of floppy mitral valve-mitral valve prolapse.

Floppy Mitral Valve (FMV), Mitral Valve Prolapse (MVP), Mitral Valvular Regurgitation (MVR)	Floppy Mitral Valve/Mitral Valve Prolapse Syndrome
<ul style="list-style-type: none"> • Common mitral valve abnormality with a spectrum of structural and functional changes, mild to severe. <p>The basis for:</p> <ul style="list-style-type: none"> • Systolic click, mid-late systolic murmur • Mild or progressive mitral valve dysfunction • Progressive mitral valvular regurgitation, atrial fibrillation, congestive heart failure • Infective endocarditis • Embolic phenomena • Characterized by long natural history • May be heritable or associated with heritable disorder of connective tissue • Conduction system involvement possibly leading to arrhythmias and conduction defects • FMV/MVP/MVR post-surgical intervention 	<ul style="list-style-type: none"> • Patients with FMV/MVP • Symptom complex: palpitations, fatigue, exercise intolerance, dyspnoea, chest pain, postural phenomena, syncope-presyncope, neuropsychiatric symptoms • Neuroendocrine or autonomic dysfunction (high catecholamines, catecholamine regulation abnormality, β-adrenergic receptor abnormality, hyper-responsive to adrenergic stimulation, parasympathetic abnormality, baroreflex modulation abnormality, renin-aldosterone regulation abnormality, decreased intravascular volume, decreased left ventricular volume with upright posture, atrial natriuretic factor secretion abnormality) may provide explanation for symptoms. • Floppy mitral valve/mitral valve prolapse: a possible marker for autonomic dysfunction

From Boudoulas H, Wooley CF¹, with permission

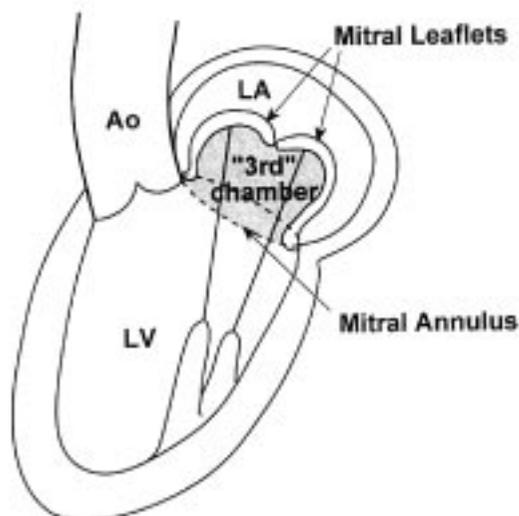


Figure 2. The third space between the mitral valve annulus and the prolapsing mitral valve leaflets is shown schematically. LV - left ventricle, LA - left atrium, Ao - aorta.

From Boudoulas H, Wooley CF¹, with permission.

endocarditis, in addition to other forms of treatment. It also defines a group of symptomatic patients who need attention from physicians who are aware of newer developments in neuroendocrine and autonomic nervous system function and dysfunction.^{1,12}

Floppy mitral valve/mitral valve prolapse/mitral valvular regurgitation: Effects on the circulation

The pathophysiological consequences of mitral valve apparatus function and dysfunction in FMV/MVP are incompletely understood at present. Certainly, prolapsing mitral valve leaflet(s) result in left atrial space-occupying lesions, with development of a third chamber or "neutral" space between the mitral annulus and prolapsing mitral valve leaflet(s)¹ (Figure 2). Stretch receptors contribute significantly to the clinical picture of FMV/MVP/MVR and the FMV/MVP syndrome.

Left atrial function is an important determinant of the natural history in patients with chronic MVR. Left atrial dilatation and dysfunction resulting in left atrial myopathy may occur prior to left ventricular structural and functional changes. Monitoring indices of left atrial performance therefore provides important information for the understanding of the natural history of the disease and is as important as assessment of left ventricular function.

Aortic function is well recognized as an important determinant of left ventricular performance and myocardial perfusion. Elastic properties of the aorta, including aortic distensibility, decrease with age. Since patients with FMV/MVP/MVR have decreased aortic distensibility compared to normal subjects, it is postulated that stiffening of the aorta may increase the degree of MVR and precipitate complications in the natural history in patients with FMV/MVP. Determination of the elastic properties of the aorta, which is gradually entering clinical practice, may also help us to better understand and define the natural history of the FMV/MVP/MVR disease process with the potential for new forms of therapeutic interventions.¹³

The prolapse of the FMV into the left atrium results in the development of a third left heart chamber with decreased cardiac output, and alterations in papillary muscle traction with stretch receptor stimulation that may result in myocardial ischaemia and cardiac arrhythmias. Stimulation of nerve endings within the mitral valve apparatus as part of these interactions of the mitral valve may result in central nervous system phenomena yet to be defined. Further, alterations of papillary muscle traction as part of the MVP process may lead to left ventricular contraction and relaxation abnormalities.¹⁴

Future research will help to better define these incompletely understood and complex phenomena related to function or dysfunction of the FMV apparatus within the cardiovascular system.

Floppy mitral valve/mitral valve prolapse/mitral valve regurgitation: Natural progression

Complications directly attributable to the FMV/MVP include progressive MVR, left atrial and left ventricular enlargement and dysfunction, congestive heart failure, thromboembolic phenomena, infective endocarditis, progressive elongation or disruption of the valve apparatus associated with the rupture of abnormal chordae tendineae, the consequences of flail mitral leaflets and cardiac arrhythmias.^{1,2,5,15-18}

While the conventional wisdom presented in the medical literature states that the prognosis of patients with FMV/MVP is benign in the majority of patients, serious complications may and do occur. The long natural history of patients with FMV/MVP/MVR has served to obscure the true incidence of complications. While the prognosis is good over the short term, the same may be said for a variety of seri-

ous diseases, such as, for example, lipid abnormalities or arterial hypertension. While the extremely long clinical course of FMV/MVP makes the natural history difficult to define, important strides have been made in this area.

For better definition of the natural progression of the FMV/MVP/MVR, accurate definition of the degree of MVR at rest and during physical activities, as well as its effect on left atrial and left ventricular structure and function, are necessary. Advances in colour flow Doppler, transoesophageal and three-dimensional echocardiography allow clinicians to better define and follow the progress of the disease. In addition to endocardiographic techniques, magnetic resonance imaging offers quantitative assessment of regurgitant volume and the regurgitant fraction in patients with MVR. This is a reproducible technique and allows follow-up of patients with FMV/MVP/MVR with quantitative analysis of all three facets over time. In addition, magnetic resonance imaging gives accurate measurements of left ventricular and left atrial structure and function. Thus, progression of the FMV morphological changes, the severity of MVR and the effects on left atrium and left ventricle can be assessed and followed by magnetic resonance imaging.

Exercise testing in patients with FMV/MVP without MVR at rest may result in significant MVR in certain patients with FMV/MVP. The dynamics of postural changes and the effect of exercise testing on the degree of MVR, left atrial and left ventricular size and function in patients with FMV/MVP, as well as the effect of exercise on these parameters during the natural history of the disease, require better definition.

The long-term effect of therapeutic interventions on the natural history of patients with FMV/MVP/MVR remains to be defined. It has been suggested that therapy with angiotensin-converting enzyme inhibitors may prevent the progression of MVR, resulting in regression of left ventricular dilatation and hypertrophy. Further assessment of the effects of medical therapy will be of increasing importance to clinicians.^{1,15,16}

Subgroups of FMV/MVP patients with a higher incidence of complications – progression to severe MVR, chordae tendineae rupture, thromboembolic phenomena, infective endocarditis and sudden death – must be defined more effectively. Comparing the natural history of one group of patients with FMV/MVP to that of another without further stratification

results in fallacies similar to that of comparing the natural history of two groups of patients with coronary artery disease without further stratification.

During the long natural history of the disease, certain patients with FMV/MVP/MVR will require valve surgery, either reconstructive FMV surgery or mitral valve replacement. After valve surgery, especially after reconstructive surgery, these patients may live a long productive life. The natural history of patients with FMV/MVP/MVR after valve surgery is gradually becoming clearer and for the most part, the results are very encouraging. In fact, surgical reconstruction of the FMV has become part of the natural history of many patients with FMV/MVP/MVR.

Floppy mitral valve and the floppy mitral valve/mitral valve prolapse syndrome

Whether an FMV/MVP syndrome exists has been a source of concern and debate for some time. It is our present opinion that certain symptomatic patients with FMV/MVP manifest a neuroendocrine-cardiovascular process resulting from a close relationship between FMV/MVP and central or peripherally mediated states of neuroendocrine or autonomic nervous system dysfunction or imbalance.¹⁷⁻²⁷

It has been documented that the incidence of palpitations, orthostatic hypotension, low body weight and symptoms related to positive G stress are more common in patients with FMV/MVP than in the general population.²¹ Parasympathetic abnormality, baroreflex modulation abnormality, decreased intravascular volume, decreased left ventricular volume in the upright posture, renin-aldosterone regulation abnormality, catecholamine regulation abnormality, hyper-response to adrenergic stimulation or abnormal β -receptor function have been demonstrated in certain patients with FMV/MVP syndrome^{1,12} (Table 1). Just how these clinical phenomena, symptom complexes, neuroendocrine abnormalities and autonomic nervous system alterations are interrelated in patients with FMV/MVP syndrome, and how they are genetically transmitted will be better defined in the years to come.

The coexistence of FMV/MVP with anxiety states and panic disorder has stimulated a dialogue between psychiatrists, primary care physicians and cardiologists. While FMV/MVP and anxiety states may be transmitted independently, further clinical and genetic studies will be necessary to clarify possible associations.

The management of patients with FMV/MVP syndrome requires an understanding of neuroendocrine mechanisms, autonomic nervous system function and dysfunction and a better definition of hyper-responsiveness or abnormalities in these systems.

While the long term history of patients with FMV/MVP syndrome has not been well defined, their symptoms may persist for years and certain FMV/MVP syndrome patients may develop symptoms related to MVR. Patients with FMV/MVP syndrome and significant MVR may present with, and continue to have, symptoms secondary to autonomic nervous system dysfunction following satisfactory FMV surgical reconstruction.

Genetics – molecular mechanisms

As yet, genetic diagnostic testing for FMV/MVP has not entered into clinical practice. It seems likely that the patients with FMV/MVP represent a heterogeneous group in which heritable defects in protein chemistry may result in myxomatous degeneration of the mitral valve.^{11,21} Definition of genetic defects in patients with FMV will allow rational classification schemes for this complex valvular abnormality. Better understanding of the molecular mechanisms that determine the progression of a mild mitral valve abnormality to floppy mitral valve and the progress to myxomatous degeneration, collagen and elastin dissolution, changes in the extracellular matrix, and FMV surface phenomena may lead to methods preventing the progress to significant mitral valve dysfunction.

The genetic association between FMV/MVP and the FMV/MVP syndrome remains to be defined.

Floppy mitral valve/mitral valve prolapse: Frequency in relation to other cardiovascular abnormalities

In the future, as the aetiological causes and pathogenetic mechanisms of certain cardiovascular diseases become better understood, it is probable that true prevention will become a reality. The prevalence of FMV/MVP in the general population will either remain the same for the next several decades or increase in an ageing population, while the prevalence of coronary artery disease, the complications of arterial hypertension and other cardiovascular diseases will decline. Thus, in the near future, patients with FMV/MVP may constitute a greater proportion of cardiovascular abnormalities than today. Further-

more, since MVR usually becomes significant after the age of 60, complications related to MVR will increase as life expectancy increases.¹

In conclusion, for the diagnosis of FMV/MVP, the key issue is the precise definition of the FMV. New technology and three-dimensional reconstruction of the mitral valve apparatus allow this definition. The diagnosis of FMV/MVP should be based on the auscultatory postural complex with confirmation by echocardiography or other imaging techniques and Doppler findings. Symptoms in patients with FMV/MVP could be directly related to mitral valve dysfunction and/or to neuroendocrine abnormalities and/or autonomic nervous system dysfunction.

References

1. Boudoulas H, Wooley CF (eds.): Mitral Valve: Floppy Mitral Valve, Mitral Valve Prolapse, Mitral Valvular Regurgitation. 2000 Second revised Edition, Futura Publishing Company, Inc, Armonk, NY
2. Wooley CF, Baker PB, Kolibash AJ, Kilman JW, Sparks EA, Boudoulas H: The floppy, myxomatous mitral valve, mitral valve prolapse and mitral regurgitation. *Prog Cardiovasc Dis* 1991; 33: 397-433.
3. Boudoulas H, Wooley CF: Mitral valve prolapse. In Moss and Adams (eds.), *Heart Diseases in Infants, Children and Adolescents*, Sixth Edition 2001, pp 995-1014.
4. Boudoulas H: Etiology of valvular heart disease. *Expert Rev Cardiovasc Ther* 2003; 1: 523-532.
5. Nishimura RA, McGoon MD, Shub C, Miller FA Jr, Ilstrup DM, Tajik AJ: Echocardiographically documented mitral valve prolapse: Long-term follow-up of 237 patients. *N Engl J Med* 1985; 313: 1305-1309.
6. Boudoulas H: Valvular disease. American College of Cardiology Self-Assessment Program (ACCSAP VI) 2005 (in press).
7. Baker PB, Bansal G, Boudoulas H, Kolibash AJ, Kilman J, Wooley CF: Floppy mitral valve chordae tendineae: Histopathologic alterations. *Human Pathol* 1988; 19: 507-512.
8. Malkowski MT, Boudoulas H, Wooley CF, Guo R, Pearson AC: The spectrum of structural abnormalities in the floppy mitral valve: Echocardiographic evaluation. *Am Heart J* 1996; 132: 145-151.
9. Davies MJ, Moore BP, Brainridge MV: The floppy mitral valve: Study of incidence, pathology and complications in surgical, necropsy and forensic material. *Br Heart J* 1978; 40: 468-481.
10. Barlow JB, Pocock WA, Marchand P, Denny M: The significance of late systolic murmurs. *Am Heart J* 1963; 66: 443-452.
11. Disse S, Abergel E, Berrebi A, et al: Mapping of a first locus for autosomal dominant myxomatous mitral valve prolapse to chromosome 16p11.2-p12.1. *Am J Hum Genet* 1999; 65: 1242-1251.
12. Boudoulas H, Kolibash AJ, Baker P, King BD, Wooley CF: Mitral valve prolapse and the mitral valve prolapse syn-

- drome: A diagnostic classification and pathogenesis of symptoms. *Am Heart J* 1989; 118: 746-818.
13. Boudoulas H, Toutouzas PK, Wooley CF (eds.): *Functional abnormalities of the aorta*. Futura Publishing Company Inc, Armonk, NY, 1996.
 14. Boudoulas H, Schaal SF, Wooley CF: Floppy mitral valve/mitral valve prolapse: Cardiac arrhythmias. In Vardas PE (ed.), *Cardiac Arrhythmias, Pacing and Electrophysiology*. Great Britain, Kluwer Academic Publisher, 1998, pp 89-95.
 15. Wilcken DEL, Hickey AJ: Lifetime risk for patients with mitral valve prolapse of developing severe valve regurgitation requiring surgery. *Circulation* 1988; 78: 10-14.
 16. Cohn LH, Couper GS, Aranki SF, Rizzo RJ, Kinchla NM, Collins JJ Jr: Long-term results of mitral valve reconstruction for regurgitation of the myxomatous mitral valve. *J Thorac Cardiovasc Surg* 1994; 107: 143-150.
 17. Tei C, Shah PM, Cherian G, Wong M, Ormiston JA: The correlates of an abnormal first heart sound in mitral valve prolapse syndromes. *N Engl J Med* 1982; 307: 334-339.
 18. Boudoulas H, Reynolds JC, Mazzaferri E, Wooley CF: Metabolic studies in mitral valve prolapse syndrome. A neuroendocrine-cardiovascular process. *Circulation* 1980; 61: 1200-1205.
 19. Glesby MJ, Pyeritz RE: Association of mitral valve prolapse and systemic abnormalities of connective tissue: A phenotypic continuum. *JAMA* 1989; 262: 523-528.
 20. Gaffney FA, Bastian BC, Lane LB, et al: Abnormal cardiovascular regulation in the mitral valve prolapse syndrome. *Am J Cardiol* 1988; 52: 316-320.
 21. Devereux RB, Brown WT, Kramer-Fox R, Sachs I: Inheritance of mitral valve prolapse: Effect of age and sex on gene expression. *Ann Int Med* 1982; 97: 826-832.
 22. Coghlan HC, Phares P, Cowley M, Copley D, James TN: Dysautonomia in mitral valve prolapse. *Am J Med*. 1979; 67: 236-244.
 23. Davies AO, Su CJ, Balasubramanyam A, Codina J, Birnbaumer L: Abnormal guanine nucleotide regulatory protein in FMV/MVP dysautonomia: Evidence from reconstitution of Gs. *J Clin Endocrinol Metab* 1991; 72: 867-875.
 24. Whinnery FE: Acceleration tolerance of asymptomatic aircrew with mitral valve prolapse. *Aviat Space Environ Med*, October 1986: 986-992.
 25. Davies AO, Mares A, Pool JL, Taylor AA: Mitral valve prolapse with symptoms of β -adrenergic hypersensitivity: β -adrenergic receptor supercoupling with desensitization of isoproterenol exposure. *Am J Med* 1987; 82: 193-201.
 26. Anwar A, Kohn SR, Dunn JF, et al: Altered β -adrenergic receptor function in subjects with symptomatic mitral valve prolapse. *Am J Med Sci* 1991; 302: 89-97.
 27. Bashore TM, Grines C, Utlak D, Boudoulas H, Wooley CF: Postural exercise abnormalities in symptomatic patients with mitral valve prolapse. *J Am Coll Cardiol* 1988; 11: 499-507.