LEFT VENTRICULAR CARDIOMYOPATHY IN MITRAL VALVE PROLAPSE: FACT OR FICTION?

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ABSTRACT

In most patients with mitral valve prolapse (MVP) without severe mitral regurgitation (MR), left ventricular (LV) function is preserved. There are, however, patients with MVP who have unexplained LV dilatation and/or decreased LV function. An association between MVP and sudden cardiac death has also been reported. LV size and function may be affected by the type of MVP, severity of regurgitation, and cause of MVP (myxomatous degeneration versus fibroelastic deficiency). There is increasing evidence suggesting an intrinsic cardiomyopathy associated with MVP. The cardiomyopathy associated with MVP can also affect the right ventricle (RV). Although the impact on ventricular dimensions and function are usually subtle, these abnormalities can affect clinical and echocardiographic estimation of the severity of MR and may thus have an impact on therapeutic decisions. Particularly in patients with the most extreme forms of MVP (Barlow disease), and in patients with Marfan syndrome or other connective tissue disorders, a cardiomyopathy affecting the LV and RV may thus occur occasionally. A better understanding of LV impairment associated with MVP is important for risk assessment and clinical decision-making.

Keywords: Mitral valve prolapse, cardiomyopathy, heart failure, ventricular function, asymmetric hypertrophy.

INTRODUCTION

Mitral valve prolapse (MVP) is defined as displacement of one or both mitral leaflets during systole of >2 mm above the mitral annular plane into the left atrium with or without mitral regurgitation (MR).[1,2] The prevalence of MVP in the general population is 0.6-2.4%. It is the most common cause of referral for mitral valve (MV) surgery in developed countries.[2-6] Typically, MVP is caused by a myxomatous degeneration of the MV leaflets, which in its extreme form is called 'Barlow disease' (BD). This is characterised by myxomatous infiltration of the entire MV with excess thickening of the leaflets, detectable at a young age.[7] Myxomatous MV disease can occur as an isolated finding, in Marfan syndrome (MFS) or other connective tissue disorders. Less often, MVP is caused by fibroelastic deficiency with thinning and elongation of the leaflet tissue and chordal tissue often associated with chordal rupture;[2,7] this usually affects older patients. The natural history of MVP is very heterogeneous, ranging from an incidental finding in an asymptomatic patient to a severe disease with considerable morbidity and mortality.[8-11] MVP can lead to MR, endocarditis, cerebral embolism, arrhythmias, sudden cardiac death (SCD), and heart failure (HF).[9] The most common complication is, however, progressive MR, which can be associated with left ventricular

(LV) dysfunction and clinical features of HF. An association between MVP and SCD has been reported, even in the absence of severe MR.[12-20]

GLOBAL AND REGIONAL VENTRICULAR FUNCTION IN MVP

In a small proportion of patients with MVP unexplained LV dilatation and/or decreased LV function is observed that cannot be explained by the degree of valvular dysfunction. This suggests an intrinsic cardiomyopathy may be associated with MVP. Abnormal LV structure has been reported in patients with MVP.[21] This abnormal structure could potentially explain the increased incidence of life-threatening arrhythmias reported in patients with MVP.[22-25] Several groups have reported myocardial abnormalities in patients with MFS, suggesting that the underlying connective tissue disorder causing aortic dilatation and valvular abnormalities may also lead to a specific cardiomyopathy affecting both ventricles.[26-29] In patients with MVP, LV wall motion abnormalities can be observed[14,24,25] in the absence of significant coronary artery disease or MR. Typical wall motion abnormalities include the early diastolic posterior dip which can be best shown by M-Mode echocardiography and other abnormal contraction patterns such as the 'ballerina foot' pattern (Figure 1).[14] These asynchronies do not usually cause a decrease in LV function. However, an otherwise unexplained decrease in left and/or right ventricular ejection fraction[30,31] can still occur. An example of LV changes of a 17-year-old male adolescent with bileaflet MVP, mild MR, and a mild decrease of LV function of an enlarged LV is shown in Figure 2. Enlargement of the LV in MVP in the absence of significant regurgitation was also described in the literature in a small study.[32] HF symptoms in patients with MVP are usually related to severe MR, but intrinsic myocardial dysfunction (MD) may be another cause.

The natural history of asymptomatic MVP in the community shows that apart from progressive MR, an ejection fraction of <50% is one of the most important independent predictors for cardiovascular mortality.[9] In multiple studies it has been shown that reduced LV ejection fraction in MR worsens the prognosis considerably.[33] Since LV ejection fraction is an imperfect measure of LV systolic performance, and grossly dependent on loading conditions, additional parameters of LV function in patients with MVP may be required.[34]

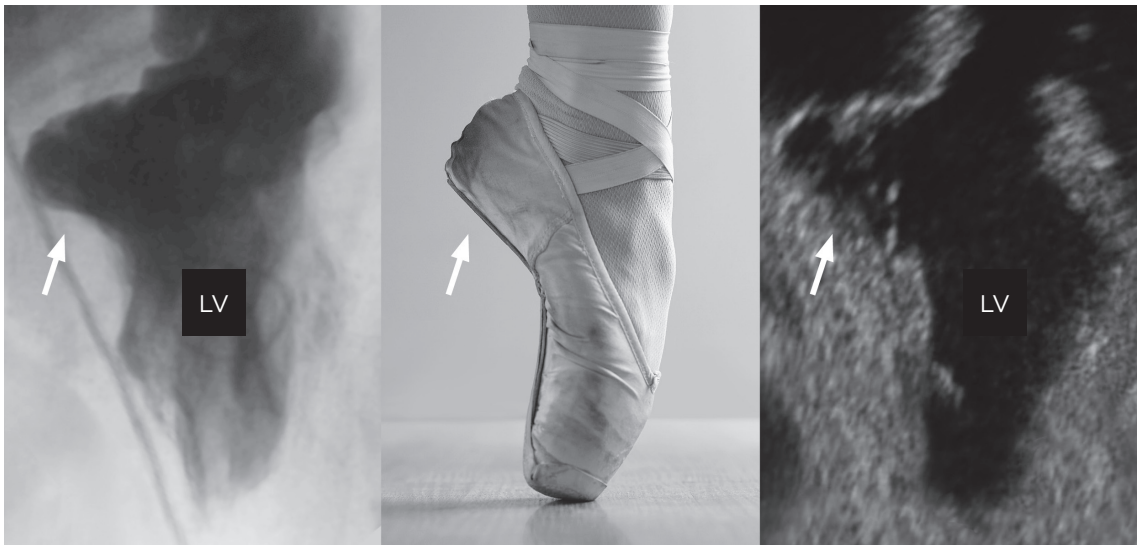

Figure 1: 'Ballerina foot' pattern in mitral valve prolapse (MVP).
The 'ballerina foot' pattern (middle) as an example of typical wall motion abnormality in pronounced MVP is observed during left ventriculography in the right anterior oblique projection (left) and in a transthoracic echocardiogram (right). A vigorous early contraction of the midventricular portion of the left ventricle at end-systole, coupled with anterior wall bulge causes this pattern and is the most frequent wall motion abnormality observed in patients with MVP. Arrow points to the dyskinetic region which mimics the ballerina foot heel.
LV: left ventricle.

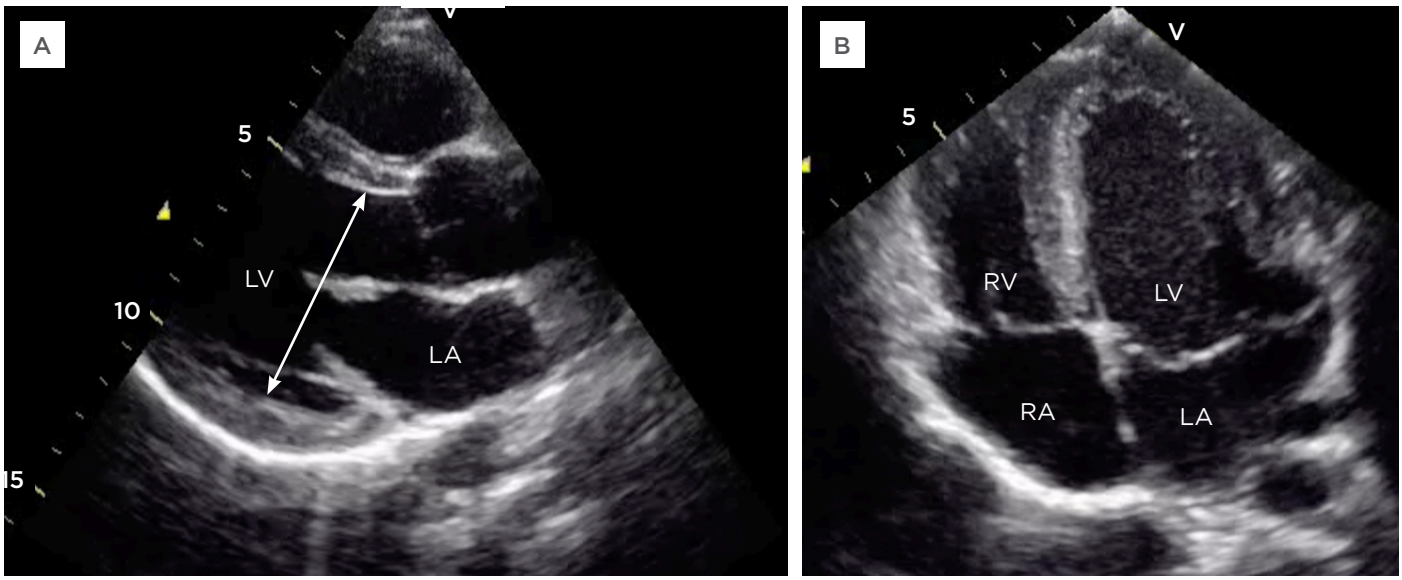

Figure 2: Left ventricular enlargement in the absence of significant mitral regurgitation (MR).
A: Parasternal long axis view of a 17-year-old male with mild MR due to bileaflet prolapse; his left ventricle (LV) is enlarged (arrow: 5.8 cm; 3.2 cm/m^2 body surface area) despite a normal sized left atrium (LA).
B: Apical four-chamber view of this 17-year-old with bileaflet mitral valve prolapse shows the enlarged LV at end-systole; his biplane left ventricular ejection fraction is 42%.
L/RA: left/right atrium; L/RV: left/right ventricle.

A recent study examined myocardial strain in 78 asymptomatic young patients with MVP (none to maximally mild MR) and 80 control patients:[35] they included 29 patients with 'classic' MVP (defined as MVP with leaflet thickness of >5 mm) and 49 patients with 'non-classic' MVP. Patients with MFS and Ehlers-Danlos syndrome (EDS) were excluded. In classic MVP, there was a significant reduction in global strain (-15.5±2.9%) compared with non-classic MVP (-18.7±3.8; p=0.0002) and control patients (-19.6±3.4%; p<0.0001). Transforming growth factor-β_1 (TGF-β_1) and β_2 serum levels were elevated in the classic MVP group compared with the control group and the non-classic MVP group. In non-classic MVP, only regional septal myocardial deformation indexes were decreased so this might be due to mechanical stress to the myocardium owing to the prolapsing leaflets. However, in patients with classic MVP, this reduction in global strain could be due to an underlying cardiomyopathy, due to increased TGF-β signalling.[35] In this study, in patients with classic MVP, LV end-systolic and end-diastolic diameters were significantly larger than in non-classic MVP despite similar left atrial size and LV ejection fraction.

OTHER LV ABNORMALITIES IN MVP

In our experience, as well as multiple descriptions in the literature, LV abnormalities are relatively common in patients with MVP. These abnormalities include LV diverticula[36,37] (Figure 3), posterobasal LV free wall hypertrophy,[38] asymmetric septal hypertrophy,[39] and LV non-compaction.[40] Thus, LV abnormalities should be carefully sought by echocardiography in all patients with MVP. The combination of LV diverticulum and MVP has been described in occasional cases.[36,41] LV diverticula can be associated with ventricular arrhythmias.[36] Additionally, MVP by itself has been suspected not to be an innocent bystander, but to have a direct impact on ventricular structure by the prolapsing valve.[42,43] The traction of the prolapsing MV on the LV walls may not only cause LV wall motion abnormalities and fibrosis of papillary muscles,[43] but possibly also causes asymmetric muscular hypertrophy of the basal walls. These changes may exacerbate the MVP and lead to a vicious cycle.[43]

Myxomatous MV disease is common in dogs. A recent interesting study was performed in 50 euthanised dogs with myxomatous MV disease. Autopsies and plasma collection were performed 70 days after the last examination.[44] In this study,

circulating troponin I concentration correlated well with the degree of cardiac fibrosis and arteriosclerosis. *In vivo* troponin I concentrations in these dogs with myxomatous mitral valves reflected myocardial fibrosis, fibrosis in the papillary muscles, and the degree of arteriosclerosis ($p<0.001$). Papillary muscle fibrosis has also been observed in a small study with cardiac magnetic imaging in humans (46%).[45] Thus it may be interesting to test, if troponin I levels in patients with MVP could identify a subset of patients prone to myocardial fibrosis and whether this translates into adverse outcomes. So far, this has never been examined in humans. In patients with MVP, asymmetric hypertrophy of the basal septum and posterior LV wall motion abnormalities can occur independent of MR. These findings are, however, more common in patients with at least moderate MR. Hypertrophy of the basal posterior wall has recently been described as a distinct form of hypertrophic cardiomyopathy.[38] An interesting combination of MVP and LV non-compaction together with MVP has been recently described and associated with sinus node dysfunction and *HCN4* mutation in two papers.[46,47] This intriguing occurrence of MVP in patients with *HCN4* mutation might be another explanation for an increased incidence of arrhythmias in MVP.[40]

CARDIOMYOPATHY IN MFS AND OTHER CONNECTIVE TISSUE DISORDERS

In the setting of connective tissue disorders,[48] such as MFS,[49-52] MVP is found in approximately 35% of patients and primary cardiomyopathy with reduced LV ejection fraction can be detected in at least 25% of cases (Table 1).[49] The intrinsic MD can affect both ventricles.[53]

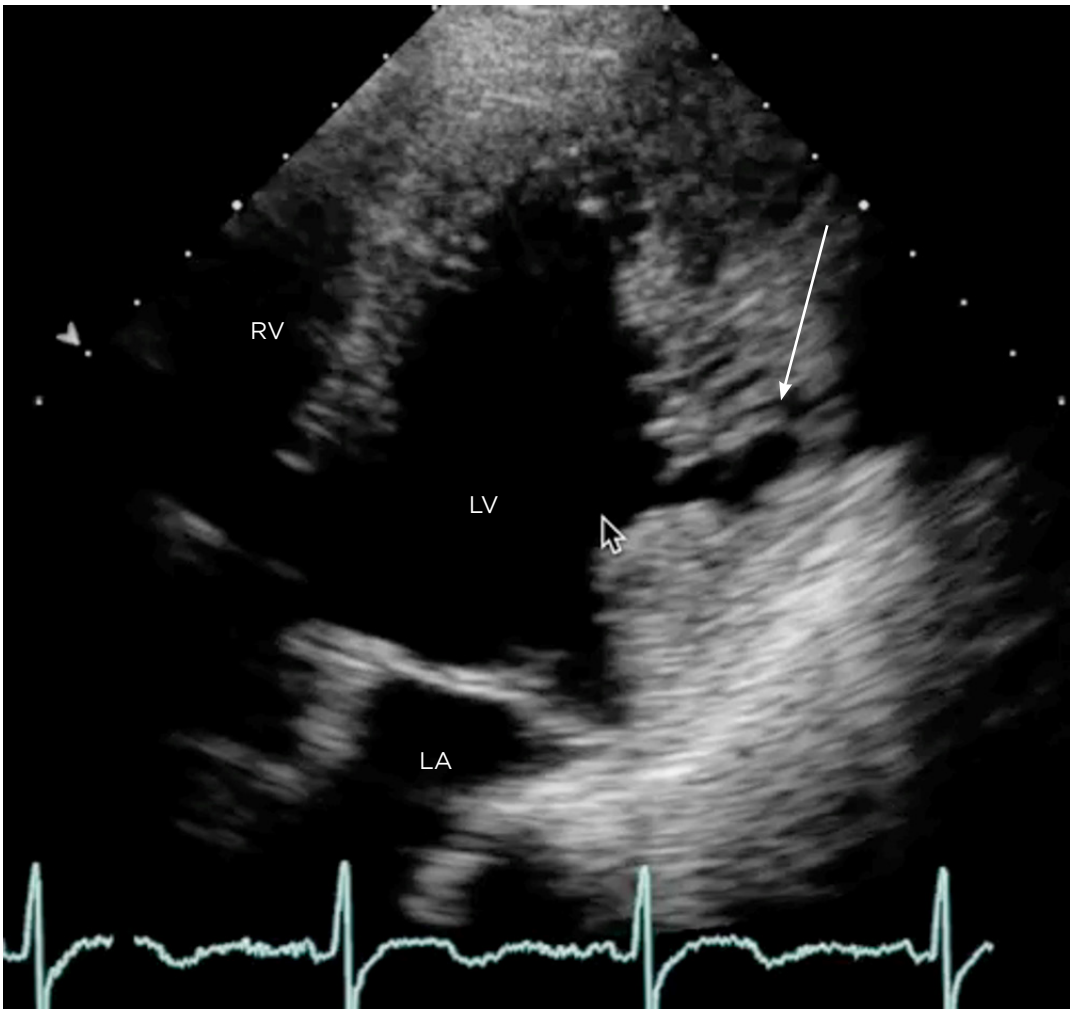

Figure 3: Diverticulum of the posterior wall of the left ventricle (LV).
Apical two-chamber view of the LV with the posterior wall on the right side in a patient with mitral valve prolapse showing a diverticulum of the inferior wall. Arrow points to the diverticulum.
RV: right ventricle; LA: left atrium.

Table 1: Summary of left and right ventricular abnormalities described in mitral valve prolapse (MVP) with or without Marfan syndrome (MFS).

Author/ imaging method	Number pt	Mean age, y	%MFS	Significant MR	Reduced LV EF	Increased LVEDD	Reduced RV EF	Comment
Alpendurada et al.[50] CMR	68	34±12	100% of pt	0%	25%	25%	10%	-
Malev et al.[35]/ echo/speckle tracking	79	18±2	0%	0%	NA (no difference to normal)	NA	NA	TGF-β_1 and β_2 elevated in classic MVP; speckle tracking of LV decreased
Kiotsekoglou et al.[66]/ echo/strain imaging	44	30±12	100% of pt	45% MVP	Significantly lower than normal	20%	NA	Uniform reduction in biventricular deformation in MFS
Roman et al.[67]	59 MFS, 59 MVP, 59 controls	29±13	50% of pt	?	No	No	No	-
Savolainen et al.[27]/echo	22 MFS, 22 controls	3-17	100% of pt	?	No	No	No	Diastolic dysfunction in MFS
Yetman et al.[68]/echo	70 MFS	17 Median (birth-52)	100% of pt	2/70	11%	49%	NA	4% Death of arrhythmias
Chatrath et al.[28]/echo	36 MFS	26	100%	0% (Exclusion criteria 50% MVP)	0%	19%	NA	No change LV size first to last echo
Meijboom et al.[29]/ echo	234	29 First, 6y FU	100%	0% (?MVP)	0%	7%	NA	-
De Backer et al.[69]/echo/ strain/CMR	26 MFS, 26 controls	32±11	100%	0% (?MVP, at least 2 pt)	Yes	Yes	NA	Diastolic dysfunction in MFS
Das et al.[70]/ echo	40 MFS, 40 controls	17±12	100%	0% (Exclusion criterion)	0% (Exclusion criteria)	Yes	Unknown	Diastolic dysfunction in MFS
Rybczynski et al.[71]/ echo/strain	66 MFS, 61 controls	31±13	100%	?	?	17%?	Unknown	Abnormal systolic and diastolic function
Kiotsekoglou et al.[72]/echo	72 MFS, 73 controls	32±12	100%	0% (Exclusion criterion) 47% MVP	0%	?	?	Significant biventricular diastolic and biatrial systolic and diastolic dysfunction

Pt: patient; y: years; MR: mitral regurgitation; LVEDD: left ventricular end-diastolic diameter; R/LV: right/ left ventricle; EF: ejection fraction; NA: not available; CMR: cardiac magnetic resonance imaging; echo: echocardiography; TGF-β: transforming growth factor β; FU: follow-up.
Modified from Kiotsekoglou et al.[55]

Myocardial impairment including abnormal LV relaxation is increasingly noticed in MFS.[54] In a mouse model of MFS, it was shown that fibrillin 1 plays an important role in cardiac muscle function: partial fibrillin 1 gene inactivation precipitated dilated cardiomyopathy due to abnormal mechanosignalling.[55] Normal cardiac size and function could be restored in these mice with an angiotensin II Type 1 receptor antagonist but not by angiotensin-converting enzyme inhibition. Fibrillin 1 assemblies are distributed in the myocardium coupling individual myocytes to the pericellular matrix. So analogous to the media of the aortic wall, the interconnected meshwork of fibrillin 1 assembled in the myocardium may represent a key component of the structure believed to support proper muscle function and fibrillin 1 also modulates TGF bioavailability.[55-57] These data suggest that patients with MVP, due to a connective tissue disorder, have an increased incidence of impaired LV function independent of the degree of MR. Additionally, right ventricular dysfunction can occur in MVP. This has been described to occur in 10% of 68 patients with MVP without significant valvular regurgitation.[50] In EDS, characterised by joint hypermobility, skin hyperextensibility, tissue fragility, and occasional MVP in a few patients with diastolic dysfunction and low normal systolic function, have been described.[58] HF in EDS has not been described so far.

CORRELATION OF LV FUNCTION WITH VENTRICULAR ARRHYTHMIAS IN MVP

The increased risk of ventricular arrhythmia and SCD in a small subset of patients with MVP is of great concern but not well understood.[1,59,60] In autopsy series after SCD, the incidence of MVP has been reported to be about 4-5%, which exceeds the prevalence of the disease in the general population (0.6-2.4%).[61] It is thought that SCD in the setting of MVP is mainly arrhythmic, and autopsy reports of previously asymptomatic patients who experience SCD have demonstrated MVP with or without MR.[15,62-64] A recent paper by Sriram et al.[20] investigated a small group of patients with MVP who had survived a SCD event and received an internal cardioverter defibrillator (ICD) for secondary prevention (24 patients). Ten of these patients had MVP. Only bileaflet MVP was found to be an independent predictor of subsequent appropriate ICD shocks for ventricular fibrillation. This subset of patients was characterised by female preponderance and frequent complex ventricular arrhythmias including ventricular premature contractions of the outflow tract alternating with papillary muscle/fascicular origin.

CONCLUSION

In patients with MVP, especially in conjunction with a connective tissue disorder or in the presence of BD, LV, and possibly RV myocardial abnormalities can be found, independent of the degree of MR. Additional LV abnormalities such as asymmetric hypertrophy or diverticula can be found, some of which may be explained by abnormal mechanosignalling caused by the prolapsing valve. We suggest that cardiologists should actively screen patients with MVP, for abnormal LV morphology by echocardiography or cardiac magnetic resonance imaging. In the absence of definitive data on the impact of these findings, it may be wise to closely follow such patients for progressive LV dysfunction, HF, and arrhythmias. To date, unfortunately, the identification of patients with MVP at risk for SCD death is imperfect and evaluation must be individualised, based on symptoms, findings on imaging, exercise testing, and electrocardiogram-monitoring. The detection of myocardial abnormalities may add to the individual risk assessment and risk stratification.

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