

## Malignant Mitral Valve Prolapse Substrates to Ventricular Remodeling and Arrhythmias

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*No good ending can be expected in the absence of the right beginning.*

—I Ching

Mitral valve prolapse (MVP) is the most frequent cause of primary mitral regurgitation in western countries.<sup>1</sup> The diagnosis can be suspected from cardiac auscultation in some cases but is mostly confirmed by echocardiography. MVP has been for long suspected of being more than a benign disease.<sup>2,3</sup> Nonspecific symptoms and major consequences, such as symptomatic severe mitral regurgitation, infective endocarditis, and cerebrovascular accidents, have been reported as non-arrhythmic complications of MVP.<sup>4</sup> In some patients, atrial or ventricular arrhythmias can occur as serious clinical manifestations even in the absence of significant mitral regurgitation or hemodynamic compromise.<sup>3</sup> Though still controversial, arrhythmic MVP patients are likely at increased risk of sudden cardiac death as compared with either nonarrhythmic MVP patients or the general population. Prior cardiac arrest and sustained ventricular tachycardia are strong predictors of sudden cardiac death in patients with MVP.<sup>5</sup> Other features, such as electrocardiographic abnormalities (QT interval prolongation, repolarization abnormalities), flail mitral leaflet, significant mitral regurgitation, left ventricular (LV) dysfunction, or the presence of ventricular fibrosis, have also been highlighted as potential predictors of sudden cardiac death.<sup>6–8</sup> Although the propensity of MVP to cause sudden cardiac death has been extensively discussed because of the high prevalence of MVP in the general population, no specific recommendations for risk stratification of patients with MVP have been defined in the current European and American guidelines.<sup>9,10</sup> Refining risk factors and identifying mechanisms causing/associated with malignant arrhythmias are of paramount clinical significance.

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**See Article by Perazzolo Marra et al**

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Ventricular arrhythmic MVP seems to be characterized by LV fibrosis and myxomatous disease.<sup>3</sup> With the aim to identify features related with stretch-induced scar/fibrosis and arrhythmic MVP, Perazzolo Marra et al,<sup>11</sup> in this issue of *Circulation: Cardiovascular Imaging*, performed a morphological assessment of the mitral valve with a particular focus on mitral annular disjunction (MAD). They studied 2 distinct populations: patients with arrhythmia and cases of sudden death. Direct observation and measurements on a magnified image were used for assessment of the pathology specimens, whereas cardiac magnetic resonance (CMR) was used in the clinical study, both for detection of myocardial fibrosis and for morphological assessment. They also examined the correlation of auscultative and clinical findings to develop a comprehensive predictive scenario for identifying high-risk MVP patients with serious arrhythmias.

A total of 36 (median age 44 years) arrhythmic MVP patients with LV late gadolinium enhancement (LGE) on CMR and no or trivial mitral regurgitation and 16 (median age 40 years) MVP patients without LGE (control group) were evaluated. Complex ventricular arrhythmias consisted of ventricular fibrillation and sustained or nonsustained ventricular tachycardia. The pathology arm of the study included sudden cardiac death victims with MVP and LV fibrosis and hearts from sex- and age-matched patients who died suddenly as a result of extracardiac causes as controls.<sup>1</sup> MAD, mitral annulus diameter, posterior systolic curling, and the lengths of the mitral valve leaflets were the morpho-functional parameters assessed. The real amplitude of mitral valve leaflet excursion into the left atrium, the presence of leaflet eversion into the left atrium, and the area of the leaflets were not described.

MAD was described in 1986 by Hutchins et al based on pathology assessment of 900 hearts, only 25 of which had MVP.<sup>12</sup> MAD was defined as separation between the junction of the left atrial wall with the mitral valve leaflet and the junction of the left atrial wall with the myocardium of the LV. In other words, MAD comprises a spatial displacement of the point of insertion of the mitral valve leaflet in the left atrial wall away from the myocardium. Being found in ≈6% of the hearts, MAD was considered to be an anatomic variation of mitral annulus morphology. However, the incidence of MAD was found to be higher in MVP (23 out of the 25 cases), leading to the conclusion that MAD is specifically associated with MVP. Furthermore, the relatively younger age (60±2 years old versus 68±3 years old) of the 42 cases with MAD but without MVP led to the hypothesis that MAD could be incriminated for the later development of myxomatous degeneration and prolapse of the mitral valve leaflets. The significance given to MAD by Hutchins et al and their interpretation of the results were questioned at the time by a series of pathology experts

who argued that MAD is only an anatomic variation of mitral annulus morphology present in the general population in a certain proportion of the annular circumference, rather than a feature specifically associated with MVP and the development of it.<sup>13</sup>

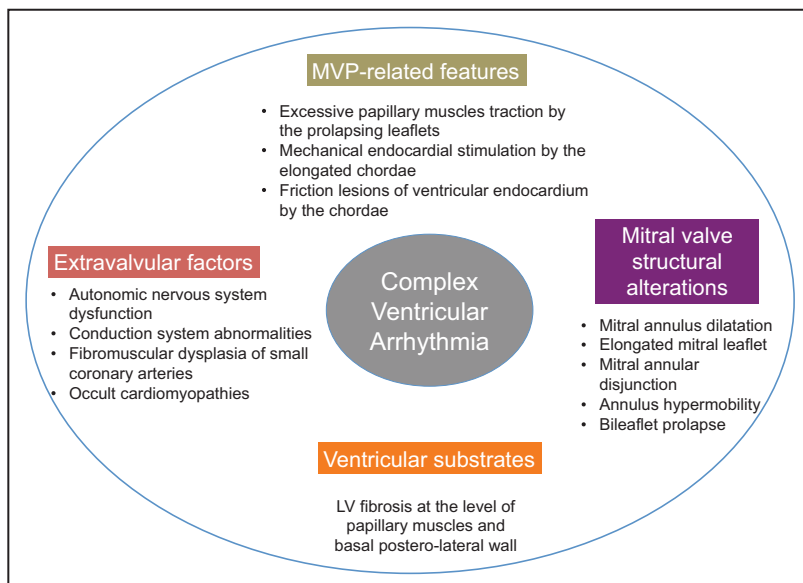
The prevalence of MAD in patients with MVP and its implications remained, thus, unknown. Carmo et al,<sup>14</sup> using 2D echocardiography, reported a prevalence of 55% of MAD ( $7.4 \pm 8.7$  mm) in the setting of myxomatous mitral valve disease. In their study, Perazzolo Marra et al had lower CMR MAD values, which also differed from those obtained on pathology specimens.<sup>11</sup> Median CMR-measured MAD length was 4.8 mm in MVP patients with myocardial fibrosis and 1.8 mm in MVP patients without myocardial fibrosis. Median pathology-measured MAD length was 3 mm in sudden death cases with MVP and 1.5 mm in sudden death cases without MVP. These median pathology-measured MAD length values also differ remarkably from the transoesophageal echocardiography-measured values in the surgical study of Eriksson et al.<sup>15</sup> In this study, the mean MAD value was  $10 \pm 3$  mm in patients with severe degenerative mitral valve disease and  $8.2 \pm 4.7$  mm in patients with mild to moderate degenerative mitral valve disease. This wide range of obtained MAD length values might be explained by inherent variations related to the measurement method used, technical imaging considerations (limited spatial and temporal resolution), difficulty in defining the margins of MAD (separation between the left atrial wall-mitral valve junction and the top of the LV wall), and different patient population analyzed. For instance, during pathology assessment (direct observation of specimens) or surgical inspection, the heart dimensions appear maximized, corresponding more to diastolic rather than systolic dimensions in the beating heart as obtained on echocardiographic or CMR imaging. All this means that MAD values obtained by different methodologies and techniques are not interchangeable and should be compared and interpreted with caution.

Carmo et al<sup>14</sup> were the first to show an association between MAD and the presence of chest pain, mitral annulus

dysfunction (paradoxical systolic increase of the mitral annulus diameter), an increased frequency of premature ventricular beats, and nonsustained ventricular arrhythmias in patients with MVP and different degrees of mitral regurgitation. The wider the magnitude of the MAD, the higher was the incidence of nonsustained ventricular arrhythmias. A disjunction  $>8.5$  mm predicted nonsustained ventricular arrhythmias with a sensitivity of 67% and a specificity of 83%. In their study, Perazzolo Marra et al<sup>11</sup> confirmed and extended these observations. In fact, MAD was a common feature in arrhythmic MVP patients with LV LGE CMR (36/52, 69%) and in sudden cardiac death cases with LV fibrosis. No specific MAD threshold was provided to discriminate arrhythmic MVP patients.

Malignant MVP likely represents a specific entity, most often observed in young adult women with a midsystolic click on auscultation, bileaflet mitral valve involvement, repolarization abnormalities in the inferior ECG leads, RBBB-type or polymorphic ventricular arrhythmias, and no or trivial mitral regurgitation on echocardiography.<sup>3-7</sup> The mechanisms of ventricular arrhythmias in these MVP patients remain speculative. Extravalvular factors (autonomic nervous system dysfunction, conduction system abnormalities, fibromuscular dysplasia of small coronary arteries, and occult cardiomyopathies), MVP-related features (excessive papillary muscles traction by the prolapsing leaflets, mechanical stimulation of the endocardium by the elongated chordae, diastolic depolarization of muscle fibers in redundant leaflets with triggered repetitive automaticity), ventricular substrates (LV fibrosis at the level of papillary muscles and basal postero-lateral wall), and mitral valve structural abnormalities (mitral annulus dilatation, elongated mitral leaflet) have been advocated (Figure).<sup>3,16-20</sup> Unexpectedly, no study assessed the morpho-functional abnormalities of the mitral valve complex as potential promoters of regional ventricular remodeling/alterations.

As previously reported in their first study,<sup>3</sup> Perazzolo Marra et al<sup>11</sup> showed that LV fibrosis was mostly located close to the annulus in the basal LV wall (papillary muscles and infero-basal free wall). In the arrhythmic MVP patients,



**Figure.** Mechanisms of ventricular arrhythmias in mitral valve prolapse (MVP) patients with preserved left ventricular (LV) ejection fraction and no or trivial mitral regurgitation.

a relative hypertrophy of inferobasal wall compared with the adjacent mid portion was also found. Additionally, the authors identified that posterior systolic curling of the mitral annulus was associated linearly with MAD and accounts for annular hypermobility. Mid-mural LGE in the LV inferobasal wall was demonstrated in 72% of cases, all having MAD and curling. A positive linear correlation was observed between the length of MAD and the extent of fibrosis (LGE CMR). Interestingly, MAD was longer in bileaflet than in single leaflet MVP patients. The prevalence of curling and LGE was also higher in bileaflet MVP. On auscultation, 32 MVP patients had a midsystolic click. Patients with midsystolic click had longer MAD, curling, LGE on CMR, and complex ventricular arrhythmias as compared with those without a click. This auscultatory click was likely because of the tension produced on the mitral valve apparatus by the abnormal posterior leaflet systolic curling. So, the altered mechanical stresses that this unique annular morphology/hypermobility results in may cause stress-induced LV infero-basal lesions (hypertrophy/scar) that could be clinically suggested by auscultatory midsystolic click. Therefore, MAD, curling, and mitral annular abnormal contractility are associated with arrhythmic MVP, whereas the absence of these features seems to imply a low risk. However, although the abovementioned morpho-functional abnormalities could be potential substrates for ventricular remodeling and consequent electric instability, their association with malignant arrhythmias and sudden cardiac death require further confirmation. Also, whether the presence of these mitral valve anomalies in MVP patients without arrhythmia might predict future mitral valve disease progression and development of complex ventricular arrhythmia is unknown. Efforts to describe morphological features associated with arrhythmia with the aim to identify candidates for preventive management should be continued.

### Disclosures

None.

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