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Mitral Valve Prolapse:

A Disease of Valve and Ventricle*

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Mitral valve prolapse (MVP) affects 1 in 40 people in the general population (1), and it is the primary indication for mitral valve (MV) surgery. Myxomatous degeneration, chordal rupture, and mitral regurgitation (MR) indicate the primary role of valvular disease. Traditionally, ventricular remodeling has been considered secondary to volume overload, by acting through b-adrenergic, cellular, and metabolic reductions in contractility leading to heart failure (2,3).

However, not all clinical observations are consistent with the concept that left ventricular (LV) involvement in MVP is purely secondary to volume load. Evidence of electrical instability (mainly ventricular ectopy and nonsustained ventricular tachycardia) supports the presence of an arrhythmogenic state with MVP (4). This fits with published reports that have recently expanded from case series and that link MVP and arrhythmic death (5). In cases of sudden death, MVP may be the only abnormality in an otherwise structurally normal heart (6). These observations may easily be coincidental in such a common condition as MVP, and a pathophysiological basis to explain the association has been lacking. However, over the last few years, cardiac magnetic resonance (CMR) has shown fibrotic changes in MV supporting structures, including papillary muscles (PMs) and basal myocardium (5,7,8), along with more diffuse fibrosis in patients with heart failure and arrhythmia (9,10). Such nonischemic fibrosis, studied in select patients, has been associated with sudden cardiac arrest (5,7,11,12) and ventricular remodeling (13–15).

In this issue of the Journal, Kitkungvan et al. (16) report their use of CMR in a larger-scale study of myocardial fibrosis in 365 referral patients with primary MR. Myocardial replacement fibrosis, detected by late gadolinium enhancement (LGE), was far more

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prevalent in patients with MVP, predominantly but not entirely in the inferobasal myocardium. Differences persisted over the range of LV volume and MR; fibrosis paralleled MR in MVP. In MVP, arrhythmic events and sudden cardiac arrest were more common in patients with fibrosis. These findings reinforce LGE as a powerful (17), technically robust arrhythmic prognosticator in nonischemic heart disease.

In this study, replacement fibrosis was also associated with LV dilation and reduced ejection fraction. These findings have potential impacts on the unresolved controversies about timing of interventions in MVP. Through prospective studies, nonischemic fibrosis may emerge as an important factor for risk stratification to improve decision making, preserve myocardial function, and prevent sudden cardiac death.

This study raises intriguing questions regarding the mechanism and possible prevention of MVP-associated fibrosis. Recently discovered causal mutations in DCHS1 (18) may induce fibrosis by altering fibroblast mechanosignaling through the Hippo pathway (19). Kitkungvan et al. (16) postulate mechanical induction of fibrosis localized to myocardium that is under increased stress and PM traction by the prolapsing leaflets (Figure 1) (20,21). Systolic annular expansion in MVP will increase PM and myocardial stress (8,22), as evidenced by reduced basal contraction that improves with repair (23). This postulate is supported by evidence for fibroblast mechanosignaling that induces myofibro-blast transformation and extracellular matrix production (24).

Future directions include exploring how these changes evolve: Does fibrosis precede LV remodeling, and is it associated with apoptosis? Does the “coarse” replacement fibrosis detected by LGE represent the “tip of the iceberg,” and can assessing diffuse interstitial fibrosis by CMR T1-mapping and quantification of extracellular volume expansion (25) detect fibrosis earlier with high sensitivity and better risk stratification (26)? Are CMR-assessed myocardial strain and fibrosis related (10)? Can MVP repair limit progressive fibrosis and electrical instability, or is there a point of no return? A prospective study is under way to ascertain how fibrosis affects post-repair outcomes (27). Basic studies have shown that within the myocardium, fibroblast differentiation to myofibroblasts triggers fibrogenesis, and fibrosis can be reversed by inhibiting this transition or by myofibroblast conversion into quiescent fibroblasts (28,29). These findings indicate the possibility of testing whether specifically reversing fibrosis can directly affect cardiac tissue in MVP and whether MV repair can be combined with antifibrotic therapy for better myocardial and electrical benefits. With the new molecular tools we have to modulate fibrosis, these important clinical questions can now be addressed.

In summary, this study reinforces a comprehensive view of MVP and its ventricular impact. This can provide additional therapeutic targets to prevent heart failure in this common condition.

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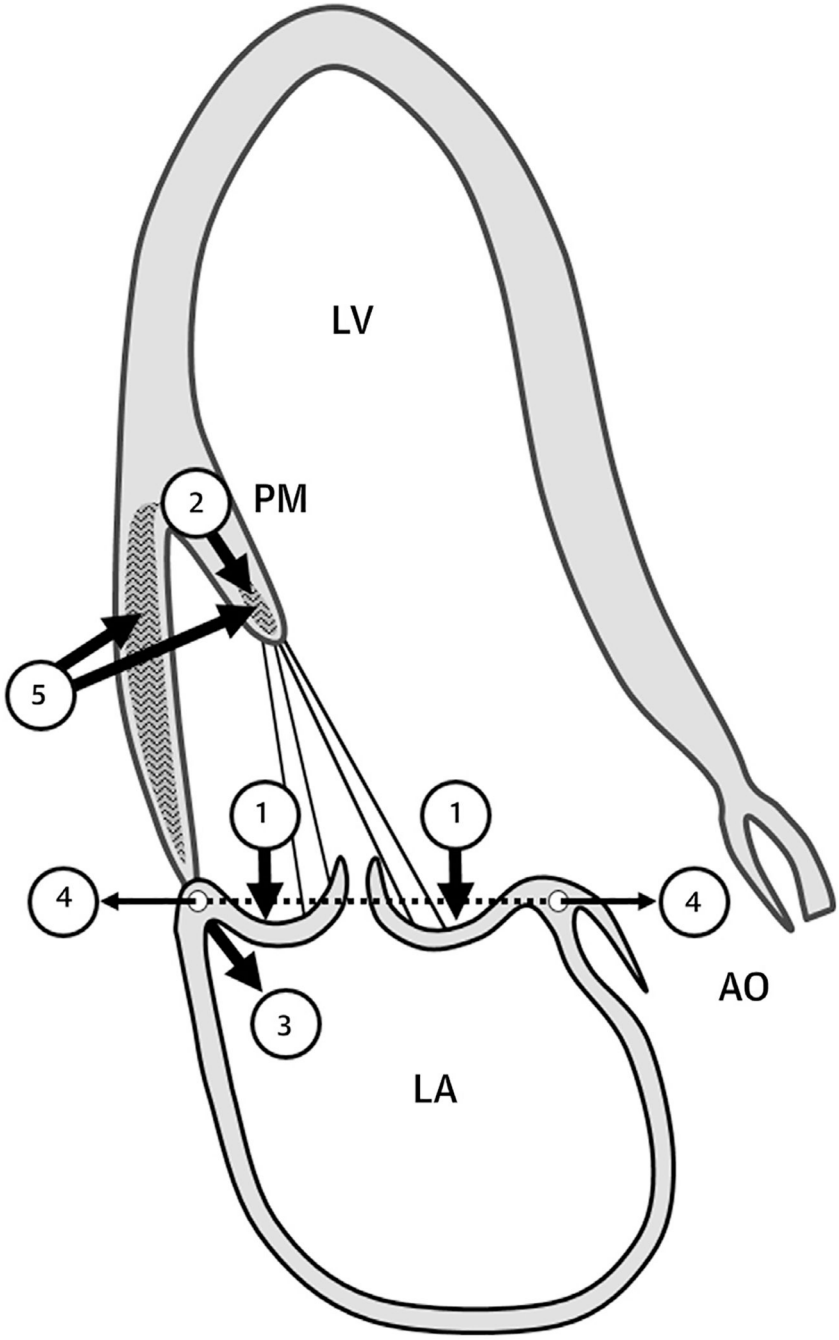

FIGURE 1.

Potential Stress-Induced Fibrotic Stimuli

Prolapse (1) induces papillary muscle (PM) traction (2) and basal LV wall tension (3), augmented by systolic annular expansion, (4) as potential fibrotic stimuli (5). (Courtesy of Mark Handschumacher.) AO = aorta; LA = left atrium; LV = left ventricle; PM = papillary muscle.