The Knot That Binds Mitral Valve Prolapse and Sudden Cardiac Death

Running title: Noseworthy et al.; MVP and SCD

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Journal Subject Code: Etiology:[5] Arrhythmias, clinical electrophysiology, drugs

Key words: Editorial, sudden cardiac death, arrhythmia, ventricular tachycardia, mitral valve, mitral valve prolapse
Solving the puzzle that ties mitral valve prolapse (MVP) to sudden cardiac death (SCD) necessarily means overcoming two central challenges: establishing a mechanistic association between a very common disorder (MVP) and a rare outcome (SCD) and discerning the cause and effect of an increasing array of associated structural, electrocardiographic, and now pathological findings.

In this issue of Circulation, Basso et al demonstrate an important and possibly critical piece of this association—pathologic and MRI evidence of a possible underlying arrhythmogenic substrate. Studying two distinct and complementary populations (young patients who died suddenly with MVP as the sole structural cardiac abnormality and a group of patients with mitral valve prolapse and complex ventricular arrhythmia) and suitable control groups, they report pathological and MRI findings that strongly suggest arrhythmogenic substrate in the region of the mitral valve apparatus that may explain a hitherto missing link between MVP and SCD.

The Second Hit

A tenable assumption, given the widespread prevalence of MVP, is that when sudden death occurs, the typically innocent valvular abnormality is a bystander with no pathogenic significance. However, researchers in this field have cyclically readdressed a possible link with a series of anecdotes and retrospective analyses. This would appear as futile an endeavor as trying to link gray hair to the risk of developing atypical atrial flutter, except for the fact that the population of interest, as is the one studied by Basso, is young, otherwise healthy and should not be dying suddenly. Given that MVP is so common, it seems likely that patients who develop malignant arrhythmia have a second, unrelated proarrhythmic factor that (although by itself may be relatively benign) creates a potentially fatal admixture of trigger and substrate. In a recent report, benign outflow tract ectopy was associated with malignant MVP syndrome. Both entities
(outflow tract ectopy and MVP) are common and independently benign, but with the potential for relative entrance block and non-suppressibility as a result of heterogenous tissue at the semi-lunar valve and papillary muscle region may have been the mutual second hit needed for malignant arrhythmogenesis.

**Chickens and Egg**

Several other potential pathogenic risk factors with MVP have been explored in trying to explain why only a minority of patients have major arrhythmia. Bileaflet MVP was found in 70% of affected patients in the present study and was nearly universal in a prior report. Complex ectopy, including nonsustained arrhythmia and now the fibrosis/scar reported by Basso et al may well be the differentiating factors for malignant outcomes. However, defining these associations as causative is problematic. For example, in fetal development, dysplastic and progressive changes in the perimital apparatus may be the forerunner for myxomatous prolapsing leaflets and not vice versa. Similarly, complex ectopy may exaggerate the amount of regurgitation or prolapse detected with echocardiography done during arrhythmia.

**Pushes and Pull**

The structural changes noted around the mitral valve apparatus could be, as pointed out by Basso et al, a result of increased tension on the chordae and transmission of this force to the mitral support apparatus. However, perhaps equally important are the contact lesions that result from the redundant valve prolapsing into the atrium in systole and snapping back against the ventricular myocardium during diastole. The difference between these mechanisms is more than semantic, since while stretch may produce fibrotic changes and abnormal substrate, excessive contact may do the same but also represent a mechanical triggering source for PVCs that may set off ventricular arrhythmias.
Regionality

A unique finding in the present study is that the “second hit” discussed above (scarring and possibly mechanical triggers) may well arise from the first hit (mitral valve prolapse) itself. Striking is the regionality of the structural changes at MRI and autopsy. On pathology, 88% of sudden death victims have fibrosis in the papillary muscle or inferobasal portions of the LV, and on MRI, 93% of patients with complex arrhythmia had scarring in this region. We do not know the clinical follow up of these potentially abnormal controls, but presumably, the structural abnormalities may precede clinically manifest severe arrhythmias.

Electrocardiographic Abnormalities

Abnormal T waves were clearly evident, and were present in 10 of 12 of their patients who had an EKG available for analysis. Endocardial and superficial mid-myocardial changes on the papillary muscles and neighboring LV could potentially create an abnormal repolarization gradient and cause inverted T waves. If true, such a finding is relevant for the type arrhythmias that cause sudden death, i.e. polymorphic ventricular tachycardia rather than monomorphic and inducible reentrant VT.

The patients studied by Basso et al \(^1\) had what appears to be exclusively right bundle branch block morphology PVCs and VT. However, in the figures they supply, it is clear that the arrhythmia morphology changes, suggesting either multiple sources or multiple exits from a single source. The morphology of the PVCs in their figures is also conspicuous for a rapid initial portion of the QRS, implying fascicular origin. Fascicular PVCs have now been well-established to be particularly important in triggering ventricular fibrillation.\(^4\)\(^-\)\(^6\) Also noteworthy in their examples are varying coupling intervals of the PVCs, a finding which in some circumstances suggests reentrant PVCs, which would also explain why when they induced VT in the EP
laboratory, the VT morphology resembled the discrete and single PVCs. Often in ischemic VT, automatic PVCs that trigger sustained monomorphic VT will have a completely different morphology, and this finding is used by clinicians to distinguish an automatic mechanism of the tachycardia itself when there is no difference between single PVCs and the VT itself. This discrepancy may be explained in Basso et al’s study by the PVCs themselves being single echo beats of reentry. This distinction may be important for ablationists, who would need to induce the VT to map and ablate with standard techniques, including entrainment, since simply finding the earliest site of activation of the PVCs themselves would not work when the mechanism is reentrant.

The Crux of Maneuver

An increasing number of ventricular arrhythmia substrates have been recognized in proximity to the central fibrous skeleton of the heart. The aortic mitral continuity and aortic sinuses of Valsalva are important examples. Similarly, suprapulmonary valve ectopics triggering polymorphic ventricular tachycardia and the atrioventricular valve annuli being common sites for both ventricular and atrial tachycardias have been established. Perhaps the heterogeneity of tissue in these regions, as well as its unique innervation is a primary abnormality and excessive motion and stretch with resulting fibrosis from MVP is the second hit.

The Perfect Storm

Just as MVP itself is common, the multiple potential second, third, or fourth hits that may be a part of malignant MVP syndrome are frequently encountered. Perhaps for the unfortunate individuals who die suddenly from this seemingly benign structural problem, a perfect storm of stretch and contact-induced fibrotic changes, mechanical triggering PVCs, a just-right autonomic milieu, bileaflet and excessively redundant mitral valve tissue, along with being young and
female, creates a lurking danger, greater than the sum of its parts.

Basso et al\(^1\) have clearly demonstrated that MVP is common among those who die suddenly (13\% of young females in their autopsy series), and that findings of fibrosis are common. This study is a veritable catechization for cardiac epidemiologists and electrophysiologists to find best ways to effectively identify patients at risk and prevent their untimely death from malignant arrhythmia. To answer these summons, we need to acknowledge that with retrospective studies, we cannot unravel this Gordian knot but rather we need to cut it (surgically treat less severe forms of MVP) or ablate it (the abnormal fibrotic and heterogenous substrate) and determine in large prospective studies whether we can have positive impact on the natural history of malignant MVP. Until such time it may be prudent in patients with MVP and perimital annular and papillary muscle related complex arrhythmias to consider MRI and possibly EP study for risk stratification. Indeed Basso et al’s findings\(^1\) now make it difficult to universally reassure patients with MVP and previously considered benign non-sustained ventricular arrhythmia.

**Conflict of Interest Disclosures:** None.

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Electrophysiologist. 2015;26:116-117.


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Circulation, published online July 9, 2015;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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