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EDITORIAL COMMENT

A New Malignant MVP Phenotype?*

Ritu Thamman, MD

The association of a common disease, mitral valve prolapse (MVP), and a rare event, sudden cardiac death (SCD), is supported by structural and electrocardiographic findings without definite proof of causality. Although SCD from MVP was reported by Barlow and Popcock (1) more than a half-century ago, identifying the small subset of patients with MVP who may be at increased risk for SCD remains difficult.

The estimated risk of SCD in MVP is at least double the general population. It varies by cohort from 0.14% in a community-based meta-analysis (2) to 1.8% in those with a flail leaflet (3). There is a high prevalence of MVP in young adult women with unexplained SCD, supporting that MVP is an underestimated cause of arrhythmic SCD (4).

"MALIGNANT" OR "ARRHYTHMIC" MVP SYNDROME

Bileaflet MVP (BiMVP) with myxomatous leaflets thicker than 5 mm, has been associated with SCD since 1985 (5). "Malignant" MVP was coined after a 2013 study showed 10 of 22 patients with unexplained SCD had BiMVP (6). Basso et al. (7) named it arrhythmic mitral valve prolapse after showing that papillary muscle fibrosis was seen 100% of BiMVP with SCD, and linked it to mitral annular disjunction (MAD) (8), which decades earlier had been associated with MVP. Because MAD without MVP was seen in younger patients, they hypothesized that MAD was an anatomic variant that led to MVP by repeated mechanical injury and myxomatous degeneration over time (9); however, the MAD length on histology was 1.5 to 3.0 mm, which is difficult to distinguish from the prolapsing height of the MV leaflet in systole on imaging. The full longitudinal and circumferential extent of MAD is not detected by standard imaging views because the mitral annulus is disjuncted along the annular circumference interspersed with normal tissue (10).

LV FIBROSIS WITHOUT MAD

In this issue of *JACC: Case Reports*, Mahajan et al. (11) have a 37-year-old African American female patient with out-of-hospital arrest who survives and is found to have severe BiMVP, severe mitral regurgitation, reduced left ventricular ejection fraction of 40%, and prolonged QTc, with genetic testing revealing lamin (LMNA) and sodium voltage-gated channel alpha subunit 5 (SCN5A) mutations. This patient had inferobasal and inferior left ventricular (LV) fibrosis but no visible MAD by cardiac magnetic resonance (CMR) (11).

This suggests that the MVP occurred without MAD, perhaps related to the LMNA mutation, which causes arrhythmias and dilated cardiomyopathy and perhaps causes mechanical stretch similar to that caused by prolapsing mitral valve leaflets (12).

Because the prevalence of concomitant MAD in patients with MVP is 42% by CMR (13), and MAD has a varying amount of normal interspersed tissue, perhaps MAD was "concealed" (10). MAD is strongly associated with myxomatous mitral valve disease (14). MVP is also associated with diffuse LV myocardial fibrosis, as suggested by reduced postcontrast T_1 times and leads to subclinical systolic dysfunction (15).

PROPOSED MECHANISMS

See **Figure 1** for potential mechanisms of SCD in this patient.

Malignant arrhythmias and SCD need a substrate (fibrosis), a trigger (mechanical stretch) eliciting premature ventricular beats, and a transient initiating

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From the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

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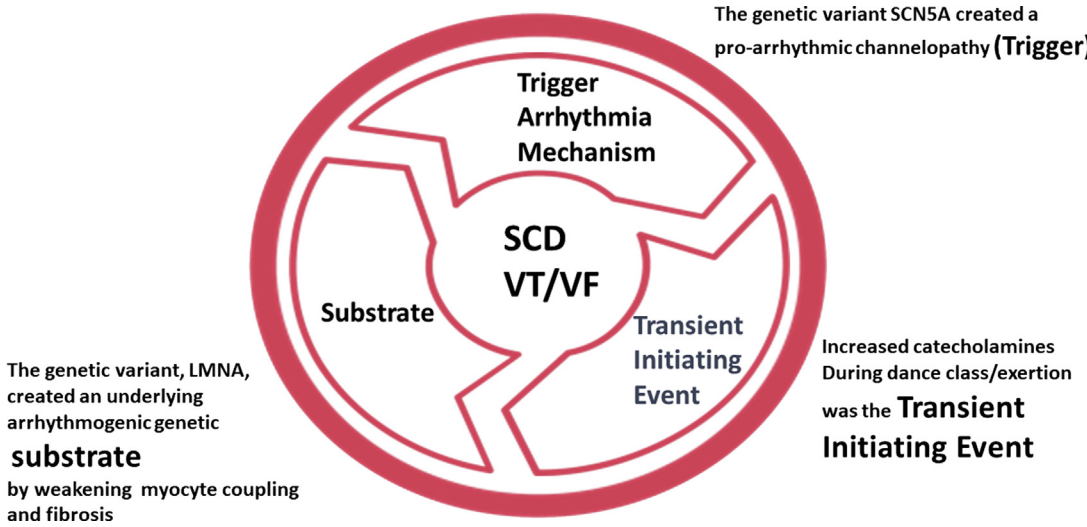
FIGURE 1 Potential Mechanism of SCD in This Patient



The major challenge is the early identification within a large population of patients with mitral valve prolapse (MVP) on echo, of the asymptomatic individual with MVP who may be at high risk for developing severe ventricular arrhythmia. LMNA = lamin; SCD = sudden cardiac death; SCN5A = sodium voltage-gated channel alpha subunit 5; VF = ventricular fibrillation; VT = ventricular tachycardia.

event like a catecholamine surge (16). In a recent meta-analysis, 47% of 123 patients with isolated MVP had SCD during physiological or psychological stress (17). Similarly, the patient, in this case, had the SCD during a dance class.

Patients with MVP have an exaggerated catecholamine response to exercise (18). The most recent European Society of Cardiology sports guidelines recommend no competitive sports for those patients with MVP and high-risk factors for SCD, of which the patient had several: LV dysfunction, female sex, and BiMVP (19).

Mechanical traction and myocardial stretch are arrhythmogenic, with early electrical dysfunction seen during electrophysiological studies in patients with MVP even in the absence of fibrosis by CMR (20).

GENETICS

It is unknown which comes first: whether malignant MVP is a focal arrhythmogenic cardiomyopathy that arises secondary to the genetically mediated weakening of cell-cell adhesion structures and unrelated to MVP, or if MVP develops first, then the genetic variant creates the proarrhythmic milieu (21).

Genetic variants may be the second proarrhythmic factor because a single gene can give rise to variable phenotypes. An example is an LMNA gene, found in this patient, which can cause dilated cardiomyopathy and arrythmias (22).

There is variability in the type and location of the genetic variants. The Filamin C (FLNC) variant, FLNC p.Trp34Ter, which truncates the actin-binding domain and reduces FLNC levels, was the first evidence that a heritable proarrhythmic genetic substrate weakens cell-cell adhesion and may underlie malignant MVP (23).

However, the interpretation of genetic variants remains an enormous challenge. CADD trains a support vector machine, a complex mathematical transformation, to separate the data into causative or noncausative mutations by using natural selection. Genetic variants occurring at high frequencies (conserved) in a population are likely benign. Harmful variants have adverse impacts and are therefore selected against and removed from the population (24). The higher the C scores, the lower the variant's frequency, and the more likely the variant is to be harmful.

A genetic variant of LMNA was implicated as pathogenic because it was above the cutoff threshold. However, another genetic variant, SCN5A, which prolongs the QTc, was below the cutoff threshold although clinically significant. However, long QT syndrome (LQTS) and BiMVP may cause a malignant MVP phenotype despite maximal LQTS therapy (25). This highlights the need for further studies to define

the genetic determinants and the environmental factors in the predisposition to arrhythmogenic MVP and SCD.

CONCLUSIONS

The hemodynamic and arrhythmogenic consequences of mitral regurgitation may cause MVP-related SCD rather than MVP itself (26). Given the patient's severe MR and LV dysfunction, the 2 genetic variants SCN5A and LMNA cannot be proved as causing her SCD.

However, as commercial kits for genetic testing proliferate, this case attests to the need to prioritize variants that substantially affect human phenotypes like MVP.

Ideally, one could identify patients with MVP at high risk of SCD at an earlier stage, appropriately selecting patients for primary prevention once prospective studies are done. Because the SCD event rate is low in MVP, this will take a large cohort to detect a significant difference.

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ADDRESS FOR CORRESPONDENCE: Dr. Ritu Thamman, University of Pittsburgh School of Medicine, 490 E. North Avenue, Suite G104, Pittsburgh, Pennsylvania 15212, USA. E-mail: rit9@pitt.edu.

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