

Association Between Malignant Mitral Valve Prolapse and Sudden Cardiac Death

A Review

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IMPORTANCE Malignant arrhythmic mitral valve prolapse (MVP) phenotype poses a substantial risk of sudden cardiac death (SCD), and an estimated 26 000 individuals in the United States are at risk of SCD per year. Thus, identifying risk-stratification strategies for SCD is imperative.

OBSERVATIONS Patients with MVP have a heterogenous clinical spectrum, ranging from a benign course to a devastating complication such as SCD. Some of the high-risk markers of MVP, which are identified electrocardiographically, include inverted or biphasic T waves, QT dispersion, QT prolongation, and premature ventricular contractions originating from the left ventricular outflow tract and papillary muscles. Morphofunctional characteristics of SCD are leaflet thickness of 5 mm or greater, mitral annulus disjunction, paradoxical systolic increase of the mitral annulus diameter, increased tissue Doppler velocity of the mitral annulus, and higher mechanical dispersion on echocardiography and fibrosis identified by late gadolinium enhancement on cardiac magnetic resonance imaging.

CONCLUSIONS AND RELEVANCE Findings from this review suggest that SCD can occur earlier in the course of MVP from complex arrhythmias that are triggered by the repeated tugging and traction of the chordopapillary muscle unit and basal mid-myocardium, even before macrofibrosis can be identified in these regions by late gadolinium enhancement on cardiac magnetic resonance imaging. Some of the newer markers identified by speckle-tracking Doppler, such as mechanical dispersion, myocardial work index, and postsystolic shortening, need further validation in a larger population.

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Introduction

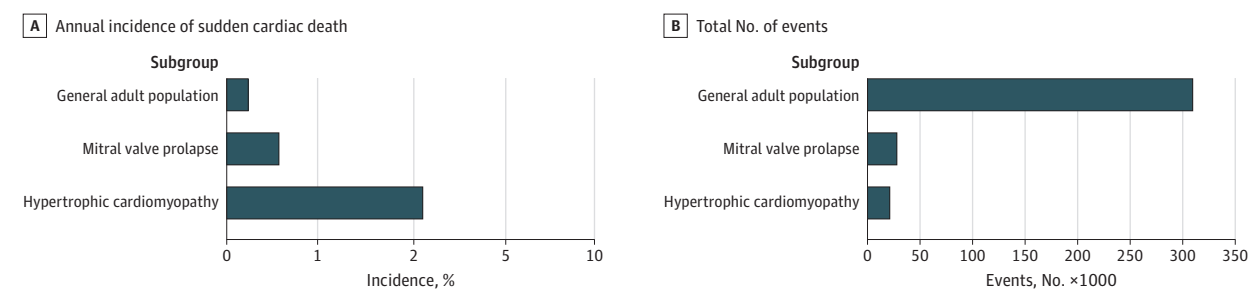
In this review, we summarized the clinical, electrocardiographic (ECG), imaging, and circulating biomarkers as well as genetic features that can serve as risk assessment tools for sudden cardiac death (SCD) in patients with mitral valve prolapse (MVP). We conducted a PubMed search for mitral valve prolapse articles published from January 1, 1953, to January 1, 2020. The search identified 7033 articles, which we narrowed to studies with SCD, yielding 379 articles. Abstracts of all 379 articles were reviewed, and 100 articles were analyzed in detail.

Historical Developments

In the early 19th century, midsystolic clicks were recognized by cardiac auscultation and were considered extracardiac in origin. Even as late as 1962, Humphries and McKusick¹ described an auscultatory-electrocardiographic syndrome but attributed these features to an extracardiac origin. Reid² in 1961 and Barlow and Pocock³ in 1963

attributed late systolic murmurs and midsystolic clicks to mitral valve-chordal origin. However, it was Criley et al⁴ in 1966 who used left ventricular cineangiography to show that late systolic murmurs were associated with voluminous and abnormal prolapse or billowing of the posterior mitral valve leaflet and that clicks were associated with pathological changes in the chordae tendineae. Criley et al⁴ coined the term *ballerina foot deformity* to describe the appearance of the prolapsing leaflets and posteromedial papillary muscle tugging on cineangiographic images.⁴ Barlow et al⁵ in 1968 confirmed these findings with morphological evidence, using surgical and autopsy specimens, and described the prolapse as a specific syndrome. Shah and Gramiak⁶ in 1970 as well as Kerber et al⁷ and Dillon et al⁸ in 1971 used M-mode echocardiography to diagnose MVP, sparking an epidemic of MVP (prevalence of 6%-20%^{9,10}) by widespread use of this modality. In 1987, Levine et al¹¹ demonstrated that the mitral valve annulus was saddle-shaped: the anterior and posterior points were high, and in the zone of coaptation, the leaflets were concave toward the left ventricle. Understanding of this anatomic concept along with the use of 2-dimensional echocardiography eliminated false-positive findings and resolved the epidemic of MVP.

Figure 1. Estimated Contribution of Mitral Valve Prolapse and Hypertrophic Cardiomyopathy to the Clinical Epidemiology of Sudden Cardiac Death in the United States vs Worldwide



The general adult population has an estimated incidence of sudden cardiac death of 0.1% per year, which accounts for a total of at least 357 000 events per year, with relative contributions from the mitral valve prolapse and hypertrophic populations.

Two-dimensional echocardiography is now considered the criterion standard for diagnosing MVP. Mitral valve prolapse is defined by the American Society of Echocardiography as the displacement of the anterior and/or posterior mitral leaflet at least 2 mm in systole above a line connecting the annular hinge points in the parasternal or apical long-axis view; it is defined by the European Society of Cardiology as the superiorly displaced mitral valve coaptation point relative to the mitral ring.^{12,13} The estimated prevalence of MVP today is 2% to 3% in the United States.^{12,14,15} Sudden cardiac death from MVP was reported by Hancock and Cohn¹⁶ and Barlow et al⁵ in the 1960s. The existence of a malignant arrhythmic MVP phenotypic entity was then recognized,¹⁷ but its prevalence has not been fully defined.

Epidemiological Findings

Among the various nonischemic arrhythmogenic syndromes, characteristics of patients at risk of SCD from hypertrophic cardiomyopathy (HCM) and MVP are similar, and both diseases have a heterogeneous clinical spectrum. The estimated risk of SCD is 0.2% to 0.4% per year.^{18,19} However, the risk has been reported to be as high as 1.8% per year in individuals with a flail leaflet²⁰ and as low as 0.14% in a community population.²¹ The risk of SCD in patients with MVP is at least 3-fold higher than the risk of SCD in the general population (0.1% per year), but it is lower than the risk of SCD in patients with HCM (2% per year), which has a prevalence of 0.3%, 10-fold lower than for MVP.²² Major progress has been made in both identification of patients with HCM at risk of SCD and primary prevention interventions, resulting in a marked reduction of SCD in the population with HCM.²³ In the United States, which has a population of 328 million (in 2019), the prevalence of MVP is estimated at 6.5 million with an estimated 13 000 to 26 000 patients at risk of SCD per year, a number of individuals similar to the number at risk in the population with HCM (Figure 1).²⁴ Such numbers are concerning, and thus the cardiology community must swiftly adopt a useful and easily applicable risk stratification strategy for SCD in patients with MVP.

SCD Redux in MVP

Although the association between MVP and SCD had already been reported, MVP was still considered to be a benign condition until a 1985 study by Nishimura et al¹⁸ described an incidence of

0.4% per year across a 6-year follow-up of 237 mostly asymptomatic patients with MVP. Furthermore, Nishimura et al¹⁸ identified high-risk markers of SCD and defined myxomatous leaflets by a thickness of greater than 5 mm as a risk marker. A redux of SCD in MVP syndrome occurred with the 2013 publication of the prevalence of out-of-hospital cardiac arrest in patients with MVP syndrome¹⁷; soon afterward, several studies and meta-analyses on the topic were published.^{21,25,26} The search for clinical, ECG, imaging, and biological markers of high-risk for SCD had begun.²⁷

Although the implantable cardioverter-defibrillator (ICD) began to be used in the 1980s for primary and secondary prevention of SCD in patients with ischemic cardiomyopathy, it was only in the 2000s that ICD use was extended to patients with genetic cardiac disorders, including HCM, long QT syndrome, Brugada syndrome, and arrhythmogenic right ventricular cardiomyopathy.²⁸ Because patients with these disorders tend to be younger individuals without major comorbidities, the expected longevity and survival after ICD placement represent a huge success. Likewise, SCD in patients with MVP occurs in a younger cohort without major comorbidities. Thus, identifying patients with MVP at risk for malignant ventricular tachycardia (VT) and SCD is crucial for preventing premature death in otherwise healthy individuals (eTables 1 and 2 in the Supplement). Although HCM and MVP were first described at about the same time, discrete guidelines and risk stratification algorithms for primary prevention of SCD in patients with HCM evolved rapidly,²³ but similar interest in MVP did not gain traction.

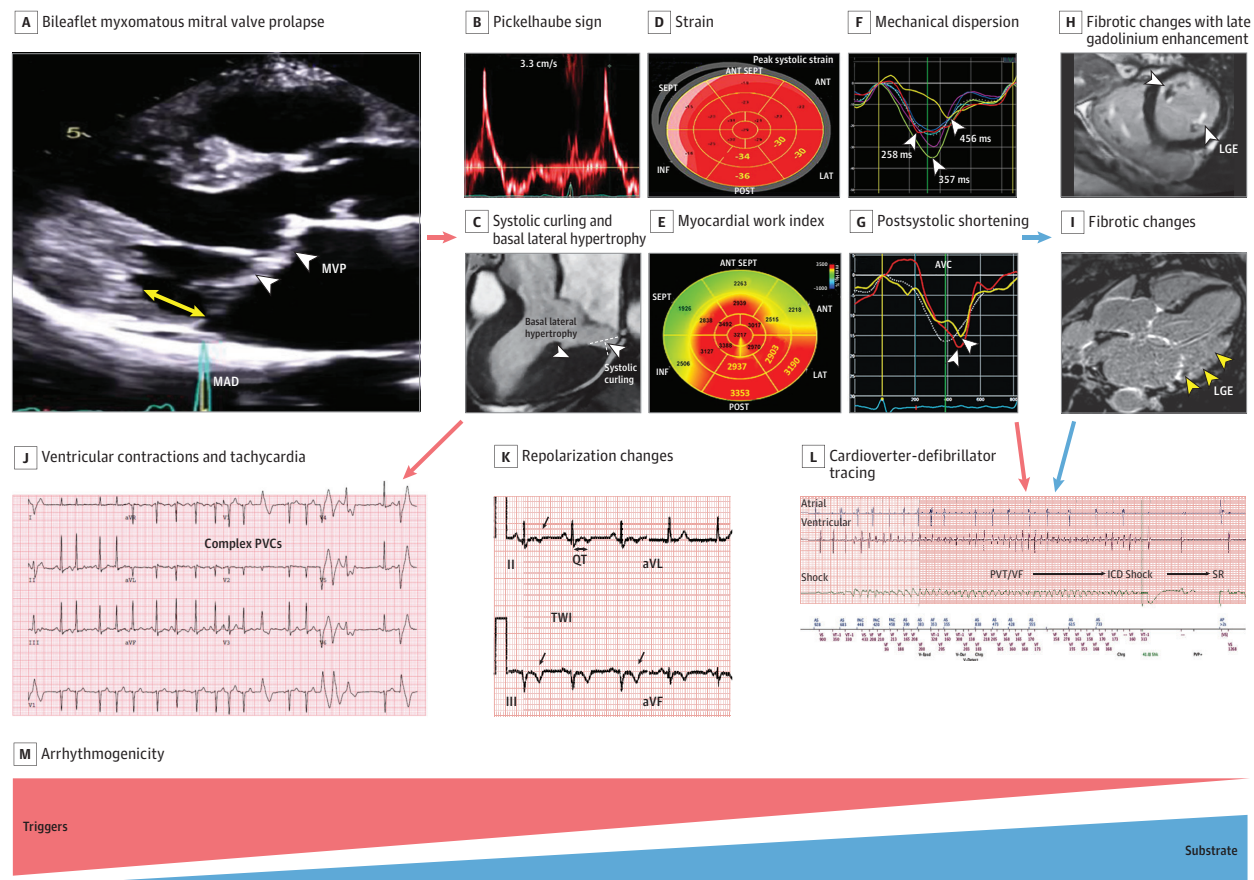
Natural History

Mitral valve prolapse has a heterogeneous presentation that ranges from a benign course that needs no intervention to a devastating complication that includes cerebral embolic event, infective endocarditis, congestive heart failure, and severe valvular regurgitation that requires surgery.^{18,29} Furthermore, a small subset of patients who are at increased risk of SCD are classified as having malignant MVP syndrome.

ECG Findings

Most patients with MVP do not have abnormal results on a 12-lead electrocardiogram. Some patients may have variable changes that

Figure 2. Mitral Valve Prolapse Schematic Progression of Arrhythmogenicity and the Role of Triggers and Substrate



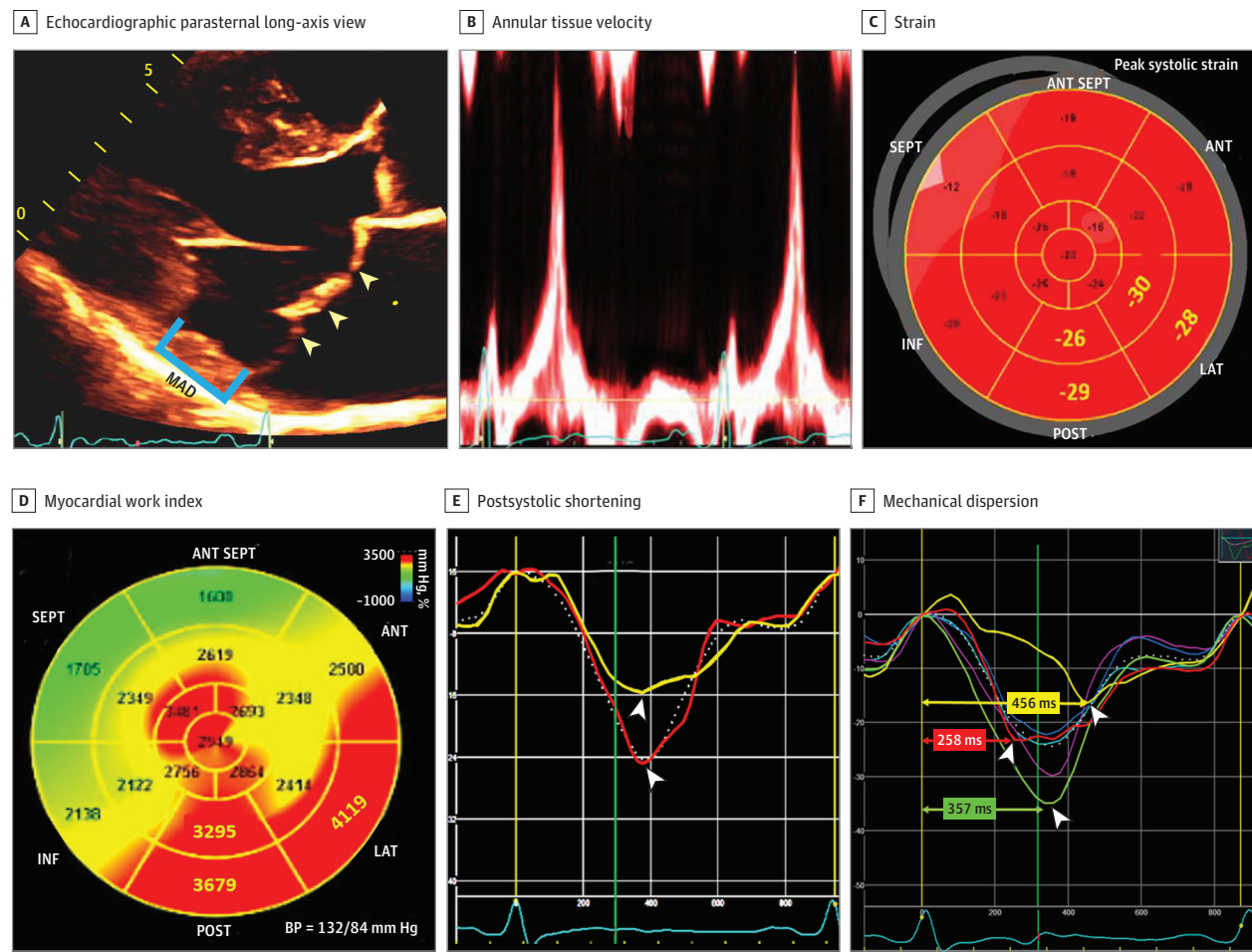
A, Mitral valve prolapse (MVP) (arrowheads) with mitral annular disjunction (MAD) (yellow arrow) associated with hypermobility and tugging on the papillary muscle and left ventricular myocardium. Mitral valve apparatus hypermobility (trigger) results in changes, including high lateral annular tissue velocities (B), systolic curling and hypertrophy (C), supranormal strain in the posterolateral trident and subnormal strain in the basal septal wall (D), an increased value of myocardial work index in the posterolateral trident (E), mechanical dispersion (SD of time to peak) (F), and shortening in the basal to midlateral regions (arrowheads show peak strain of each segment) (G). Fibrotic changes (substrate) occur from repeated traction determined by late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (H and I). Complex premature ventricular contractions (PVCs) (J), repolarization changes with T-wave inversions (K), and implantable cardioverter-defibrillator (ICD) tracing showing the onset of polymorphic ventricular tachycardia (PVT) and ventricular fibrillation (VF) rescued by an ICD shock (L). M, The schematic shows the contribution of triggered activity (red triangle) to arrhythmogenicity in earlier phases and substrate development (blue triangle) in later phases of the disease. ANT indicates anterior; AVC, aortic valve closure; INF, inferior; LAT, lateral; POST, posterior; SEPT, septum; SR, sinus rhythm.

include inverted or biphasic T waves, QT dispersion, and QT prolongation. The incidence of inverted or biphasic T-wave inversions in the inferolateral leads on a resting electrocardiogram in patients with MVP who have malignant arrhythmias has been reported to be between 33%³⁰ and 78%¹⁷ in those with MVP who have had a cardiac arrest. Because the inferolateral ECG leads overlie the area of abnormal contractility of the myocardium and papillary muscle in patients with MVP, these ECG findings are believed to be a marker of abnormal stretch and, thus, a mechanistic provocation of multi-form premature ventricular contractions (PVCs) (Figure 2). Purkinje or fascicular and papillary muscle origin of PVCs that trigger ventricular fibrillation in patients with cardiac arrest has been demonstrated,³¹ with fractionated or delayed potentials suggestive of Purkinje tissue disease even in the absence of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR). Ablation of PVCs at these foci reduced ICD shocks despite having little implication for the overall frequency of PVCs.³¹ The observa-

tion that SCD in patients with MVP results from pleomorphic or polymorphic rather than monomorphic VT is also suggestive of a lack of fixed scar-related substrate. Thus, ECG abnormalities should forewarn the possibility of an arrhythmogenic substrate.

Abnormalities in ventricular repolarization with QT prolongation³² and QT dispersion in malignant MVP syndrome³³ have been described in some, but not all, studies.³⁴ Papillary muscle traction in experimental and animal models has been shown to alter regional repolarization in the left ventricle,³⁵ and stretch-mediated triggered activity has been shown to contribute to VT and fibrosis.^{30,36} Premature ventricular contractions are frequent in the MVP population (reported in up to 49% to 85% of patients^{21,26}) regardless of malignant outcomes, thus reducing MVP's specificity as a marker for SCD. However, in patients with MVP who present with out-of-hospital cardiac arrest, ambulatory ECG monitoring identifies a higher prevalence of nonsustained VT and frequent PVCs. Patients with MVP who have a PVC morphological characteristic suggestive of

Figure 3. Echocardiographic Findings of Arrhythmic Mitral Valve Prolapse



A, Prolapsing bileaflet myxomatous mitral valve (arrowheads) with mitral annulus disjunction (MAD). B, High annular tissue velocity of 42 cm/s. C, Supranormal strain (mean value, 28%) in the posterolateral trident, and subnormal strain in the basal septal wall (mean value, <18%). D, Markedly increased value of myocardial work index in the posterolateral trident (mean value, 3376 mm Hg % for blood pressure [BP] of 132/84 mm Hg; scale, red >3000 mm Hg %; normal [SD] value, 1896 [308] mm Hg %). E, Postsystolic shortening demonstrated in the basal and midlateral regions. Arrowheads indicate peak strain. F, Mechanical dispersion (SD of time to peak, 80 milliseconds). Arrowheads indicate peak strain. ANT indicates anterior; INF, inferior; LAT, lateral; POST, posterior; SEPT, septum.

origination from the left ventricular outflow tract and papillary muscle or fascicular region are at risk of SCD.^{17,30,31} These findings are suspicious for abnormal mitral valve structure and function that are identified electrophysiologically^{31,37} or by imaging modality in patients with malignant MVP.¹⁷ For example, high posterolateral annular tissue velocity is a marker of stress on the papillary muscle and adjacent myocardium and can serve as an imaging marker for stretch-mediated triggered activity.^{25,38} The prognostic importance of an electrophysiological study is currently not fully defined and not routinely recommended for risk stratification of patients with MVP.

Morphofunctional Characteristics of the Mitral Valve

Several echocardiographic features of the mitral valve apparatus and myocardium, such as leaflet thickness ≥ 5 mm in diastole,¹⁸ mitral annulus disjunction (MAD), paradoxical systolic increase of the

mitral annulus diameter, systolic curling, and basal lateral hypertrophy²⁷ (Figure 3 and eFigure in the Supplement), have been associated with ventricular arrhythmias (Table). In addition, functional abnormalities, including greater tissue Doppler velocity of the mitral annulus (Pickelhaube sign),³⁸ increased regional postsystolic index, time-to-peak strain, and mechanical dispersion⁴¹ were previously shown to be associated with ventricular arrhythmias and risk for SCD in patients with MVP.

MAD

MAD is an altered spatial relationship defined as the systolic separation of the mitral leaflet and left atrial junction from the summit of the left ventricular posterior wall. This distance is measured echocardiographically in millimeters at end-systole in the parasternal or apical long-axis view (Figure 3 and eFigure in the Supplement), and circumferential MAD can be measured by CMR.⁴² It has been hy-

Table. Risk Factors for Sudden Cardiac Death in Mitral Valve Prolapse

Source	Risk factors	MVP, No.	Age, mean (SD), y	Female sex	VT	T-wave inversion	Bileaflet MVP
Nishimura et al, ¹⁸ 1985	Leaflet thickness ≥ 5 mm	237	10-69	60%	NA	NA	NA
Avierinos et al, ²⁹ 2002	Moderate to severe MR; LVEF <50% for increased mortality	833	50 (21)	64%	NA	NA	39%
Carmo et al, ³⁹ 2010	MAD >8.5 mm for NSVT	38	57 (15)	47%	NA	NA	NA
Sriram et al, ¹⁷ 2013	Female; VT and bigeminy; higher burden of PVCs (2%) on Holter monitor	10	33 (16)	90%	7 Patients	78%	100%
Basso et al, ³⁰ 2015	LGE fibrosis: SCD—papillary fibrosis in 100% and inferobasal wall in 88%; nonfatal complex VA—93% with LGE on CMR	SCD, 43; living, 44	19-40	SCD, 13%; Living MVP with VA, 70%	30 Patients	78%	70%
Muthukumar et al, ³⁸ 2017	Pickelhaube sign	21	52 (12)	71%	8 Events	50%	100%
Dejgaard, et al, ⁴⁰ 2018	MAD	MAD, 116; MVP, 90	49 (15)	60%	14 Patients	NA	55 (47%); VT, 5 (36%)
Ermakov et al, ⁴¹ 2018	Mechanical dispersion: 59 ms in VA vs 43 ms in no arrhythmia	59	55 (15)	51%	32 Patients	VA, 34%; No VA, 15%	VA, 69%; No VA, 44%

Abbreviations: LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MAD, mitral annulus disjunction; MR, mitral regurgitation; MVP, mitral valve prolapse; NA, not available; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contraction; SCD, sudden cardiac death; VA, ventricular arrhythmia; VT, ventricular tachycardia.

pothesized that MVP develops from the hypermobility of the valve secondary to annulus disjunction and is associated with increased mechanical stress on the myocardium, which can generate PVCs.^{43,44} Mitral annulus disjunction was shown on intraoperative transesophageal echocardiography to be present (mean [SD] value, 10 [3] mm) in all patients undergoing repair for advanced myxomatous mitral valve degeneration.⁴⁵ The magnitude of MAD later was found to be associated with the occurrence of frequent PVCs and nonsustained VT.⁴⁶ MAD has been associated with arrhythmogenicity independent of the presence of MVP.⁴⁰ In addition, MAD has been found to occur more frequently in patients with bileaflet MVP (prevalence of 47%⁴⁰ to 55%³⁹).

In a previous study, MAD was present in all patients with VT; greater dimensions were noted in the VT group (mean [SD], 12.2 [3.2] mm) than in the nonarrhythmic group (mean [SD], 7.8 [4.3] mm) (L.M., A.J., M.F.J., A.C.P.-M., B.K.K., A.J.T., unpublished data, 2020) and were greater than dimensions reported in other studies (mean [SD], 7.4 [8.7] mm³⁹ and median [IQR], 4.6 [2.8-6.4] mm).²⁷ The combination of hypermobility and MAD is associated with systolic curling in the posterior mitral annulus, which is a factor in the paradoxical increase in systolic annulus diameter, a marker present in those with arrhythmic MVP.⁴⁶ This curling has been proposed to be associated with progressive myxomatous degeneration of the mitral valve leaflets and stretch in the inferolateral myocardium and papillary muscle.²⁷ This finding suggests that MAD and MVP might be associated or coexistent with developmental syndromes; however, in the absence of longitudinal studies starting from childhood, it is difficult to conclude whether MAD is associated with floppy mitral valves, whether bileaflet MVP is a factor in MAD, or whether MAD and MVP coexist.⁴⁷

Pickelhaube Sign: Marker of Abrupt Forceful Myocardial Stretch

The hypercontractile state of the basal to midlateral myocardium manifests as a spiked configuration on basolateral annular tissue Dop-

pler imaging studies and has been termed the Pickelhaube sign.³⁸ The magnitude of tissue Doppler imaging systolic velocities is much higher in patients with arrhythmogenic MVP than in those with nonarrhythmogenic MVP or the control population (without cardiovascular disease or risk factors).⁴⁸ Higher tissue velocities represent myocardial stretch from prolapsing leaflets abruptly and sharply tugging the papillary muscles and adjacent left ventricular myocardium in systole,³⁸ and this forceful tugging may serve as a trigger to generate PVCs, nonsustained VT, or polymorphic VT associated with SCD (Figure 2). This mechanical traction and myocardial stretch have been suggested to be arrhythmogenic, with early electrical dysfunction recognized during electrophysiological studies in patients with MVP even in the absence of fibrosis by CMR imaging.³¹ We believe that the development of fibrosis and LGE represents a later phase in the evolution of the pathology of malignant or arrhythmic MVP syndrome (Figure 2).

Speckle-Tracking Doppler

Bull's-eye Plot: Heterogeneity of Strain and Myocardial Work Index

A bull's-eye plot of longitudinal strain provides a view of abnormal longitudinal strain patterns in different segments of the left ventricular myocardium in relation to the prolapsing mitral valve leaflets. Heterogeneity in strain compared with a normal homogenous distribution pattern was initially reported in patients with MVP⁴⁹ and can help to identify an underlying pathophysiological substrate. In most patients with MVP, supranormal strain (>24%) is witnessed in the posterolateral left ventricular trident (basal and mid-posterior and lateral wall segments) subtending to the tug of the voluminous myxomatous prolapsing leaflets and abrupt traction of the adjacent papillary muscles, whereas subnormal strain (<18%) is seen in the corresponding opposite basal septal wall segments.⁵⁰ This hypercontractility of the posterolateral segments noted on echocardiography in a previous study⁵⁰ also was demonstrated by Nutter et al⁵¹ in 1975 on left ventricular angiography. Nutter et al⁵¹ hypoth-

esized that chronic overload in this region would lead to ischemia, pain, and T-wave abnormalities, a hypothesis that is supported by a myocardial work index. Myocardial work index is a new parameter that considers both afterload and myocardial deformation and offers global and regional myocardial functional assessment under different loading conditions.⁵² Myocardial work is depicted in color codes within bull's-eye areas, with normal values shown in green (2400 mm Hg % for blood pressure of 120/80 mm Hg) and areas of high work shown in red (Figures 2 and 3).^{42,52} A cohort of patients with MVP who demonstrated supranormal strain in the posterolateral trident had a high regional myocardial work index (>2500 mm Hg %; normal value [SD], 1896 [308] mm Hg %) in the same region (Figures 2 and 3), according to L. Muthukumar, MD (unpublished data, March 2020). These observations support the hypothesis that higher myocardial work state associated with repeated traction increases the energy demand and oxidative stress in this region, which eventually may provoke a localized hypertrophic and fibrotic response.³⁰

Mechanical Dispersion and Postsystolic Shortening

Left ventricular mechanical dispersion, defined as the SD of the time-to-peak strain in all segments, and postsystolic shortening, defined as late systolic shortening appearing after aortic valve closure, are 2 emerging observations in arrhythmogenic MVP obtained from the longitudinal strain curves by speckle-tracking echocardiography. Mechanical dispersion was found to be higher in patients with arrhythmogenic MVP than in patients with nonarrhythmic MVP (59 milliseconds vs 43 milliseconds), which is a marker of heterogenous ventricular contraction.⁵³ Postsystolic shortening is calculated as follows: [(maximum strain % in cardiac cycle – peak systolic strain %)/(maximum strain % in cardiac cycle)] × 100. Postsystolic shortening in 2 or more segments was reported as a factor associated with mortality and morbidity.⁵⁴ In a recent study, a higher regional postsystolic shortening in the basal to midlateral segments was found in patients with malignant MVP compared with those with nonmalignant MVP (L.M., A.J., M.F.J., A.C.P.-M., B.K.K., A.J.T., unpublished data, 2020). Left ventricular mechanical dispersion and postsystolic shortening can be partially explained by a longer time-to-peak contraction of the basal to mid-posterolateral segments that are subject to forceful tugging of the papillary muscle and adjacent myocardium by the prolapsing leaflets in mid- to late systole, which alters normal myocardial deformation. These parameters require further validation.

CMR Imaging

LGE on CMR Imaging

A high incidence of fibrosis of the papillary muscles and inferobasal left ventricular wall was noted either by histological study of patients who had MVP with SCD or by LGE on CMR in those with arrhythmic MVP³⁰ (eFigure in the Supplement). Of the 43 patients who had MVP with SCD in a cardiac pathological registry, 29 (67%) had papillary muscle fibrosis by a histological study along with inferobasal left ventricular wall fibrosis interspersed between hypertrophic cardiomyocytes.³⁰ Fibrosis was identified by LGE on CMR in 93% of patients with MVP and complex ventricular arrhythmias in a similar distribution.³⁰ However, other studies

failed to show a higher prevalence of fibrosis detected by LGE on CMR in patients with MVP and ventricular arrhythmias, reporting prevalence rates between 33% and 63%.^{40,55} In a retrospective analysis by Garbi et al⁵⁶ of SCD cases with MVP, 81% had either microscopic fibrosis or none. Although an extensive pattern of LGE is a marker of SCD in pathological conditions, SCD can occur even in the absence of LGE on CMR imaging. These observations support the hypothesis that fibrosis represents a later stage of the malignant disease process and that mechanisms other than fibrosis serve as a substrate for malignant arrhythmias in patients with MVP and SCD at an earlier stage (Figure 2). The extent of myocardial fibrosis above which the risk of SCD increases in patients with MVP has not been established, and variable patterns of LGE (mid-wall, patchy, or subendocardial) have been documented⁵⁷ in papillary muscle and inferobasal myocardium.³⁰ Emerging techniques such as T1 mapping detect microscopic or diffuse fibrosis, whereas LGE detects macroscopic fibrosis.^{56,58} In addition to LGE, patients with MVP with complex ventricular arrhythmias were found to have diffuse fibrosis in the left ventricular septum, as evidenced by lower postcontrast T1 values than in patients without complex arrhythmias.^{59,60}

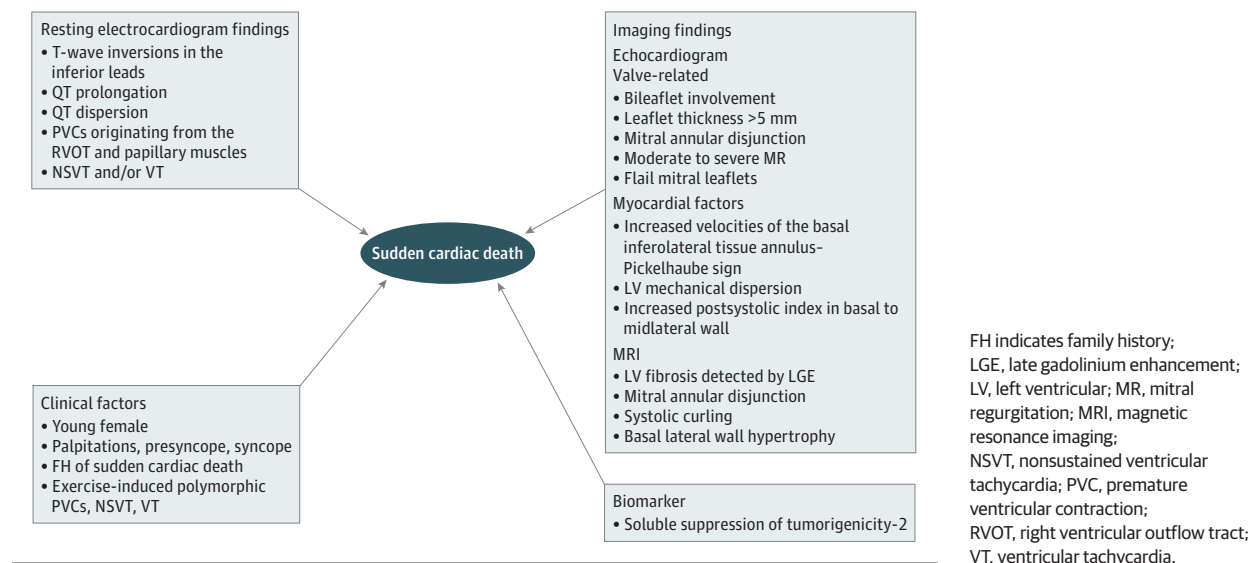
Family Screening and Genetics

Familial clustering of myxomatous MVP, particularly the association of parental MVP with a higher prevalence of MVP in their offspring, has been described in both the syndromic and nonsyndromic form of the disease.⁶¹⁻⁶³ Although no systematic study of familial sudden death syndrome in MVP has been published, family history of SCD in MVP was reported in case reports⁶⁴ and pathological^{65,66} and surgical series.⁶⁷ Three loci for autosomal-dominant, nonsyndromic MVP have been described on chromosomes 11, 16, and 13¹⁵ with mutations in *DCHS1* (OMIM 603057.0004) and *PLP1* (OMIM 300401) genes. *FLNC*-encoded filamin C is an actin-binding protein that is critical for the structural integrity of the sarcomere in cardiac and skeletal muscles for the X-linked form of MVP. A truncating variant of muscle-specific *FLNC*-encoded filamin C (p.Trp34*-*FLNC*) has been associated with arrhythmogenic MVP phenotype.⁶⁸ Arrhythmogenicity is believed to originate from the excess force generated by the prolapsing leaflet on the weakened myocardium because of variation in the *FLNC* (OMIM 102565) gene. However, the genetic risk factors for SCD in patients with MVP have yet to be identified, highlighting the need for further studies to define the genetic determinants and the environmental factors in the predisposition to arrhythmogenic MVP and SCD.

Circulating Biomarkers

Soluble suppression of tumorigenicity-2 serum level was higher in patients with MAD and ventricular arrhythmias than in those without arrhythmias (Figure 4). Soluble suppression of tumorigenicity-2 has been proposed as a marker of myocardial stretch. In patients with MVP, the prolapsing leaflets created a stretch on the papillary muscles and adjacent myocardium, and myocardial stretch has been associated with ventricular arrhythmogenicity.⁶⁹ In the same study, higher levels of transforming growth factor β1 (TGF-β1) were observed in patients with myocardial and papillary muscle fibrosis and a larger, circumferential MAD.⁶⁹ Historically, cytokine TGF-β1 was associated with the development of replacement fibrosis and myxomatous degenerative changes of the mitral valve.

Figure 4. Risk Factors for Sudden Cardiac Death



Management Including Mitral Valve Repair

Ventricular arrhythmias in patients with MVP are treated the same way as in any other patient population. β -Blockers, calcium channel blockers, and other antiarrhythmic agents are used, but without evidence of improved survival. Catheter-based ablation is an important second-line treatment option, and ablation of ventricular ectopy originating from fascicular and papillary muscle foci in bileaflet MVP syndrome was found by Syed et al³¹ to improve symptoms and reduce ventricular ectopic burden. Before the use of ICDs, newer generation antiarrhythmics, and catheter-based ablation, several case series demonstrated surgical correction of myxomatous MVP for ventricular arrhythmias refractory to medical treatment, even in the absence of substantial mitral regurgitation.⁷⁰⁻⁷⁴ After the surgical procedure, these patients experienced a lower incidence of arrhythmias and discontinuation or reduction of antiarrhythmic medications. Postoperative left ventriculography revealed the absence of the rapid-jerking ventricular movements corresponding to the papillary sites.⁷²

The evidence is limited on the efficacy of antiarrhythmic medications in preventing the progression of disease or reducing the risk of arrhythmogenicity or SCD. Placement of an ICD is considered in individuals who experience sustained VT or ventricular fibrillation, and despite limited data on primary prevention of SCD, those with high-risk features may find an ICD advantageous. The lack of an association between the overall arrhythmia burden and the risk of SCD or reduction of risk with interventions, such as ablation of PVC foci or surgical procedure for MVP, needs to be further defined before ablation or surgical procedure could be considered as an exclusive option to reduce the risk of SCD. Our conceptual argument that repetitive stretch-mediated triggered activity and altered myocardial deformation or mechanical dispersion associated with increased papillary muscle tugging underlie arrhythmogenesis in MVP

before the later stage of myocardial fibrosis development is supported by the observation that surgical correction of bileaflet MVP reduces the incidence of malignant arrhythmias and appropriate ICD shocks.⁷⁵ However, whether this intervention is helpful to SCD reduction is not yet known.

Conclusions

As evidence builds of the association of SCD with MVP, the challenge remains designing cost-effective risk stratification models that can identify patients at risk and predict arrhythmogenic events with reasonable accuracy. Moreover, optimum treatment; medical, interventional, or surgical correction of the underlying abnormality; and timing and selection of patients for ICD need to be established.

Use of ICD is known to prevent SCD, but the criteria for cost-effective patient selection need to be defined. Surgical correction of bileaflet MVP has been reported to reduce the incidence of malignant arrhythmias and appropriate ICD shocks, but whether this intervention decreases SCD is unknown. This finding leads to the hypothesis that mitral valve repair and ring annuloplasty minimize the tug and pull on the myocardium and, thereby, the abnormal mechanical forces associated with ventricular arrhythmias. Instead of ICD placement, mitral valve repair as a primary option needs to be explored.

The field of arrhythmogenic MVP is evolving. As new information becomes available, we may be able to identify patients at high risk of SCD at an earlier stage, appropriately selecting patients for primary prevention even before fibrosis. We believe that in the near future, SCD in patients with MVP can be minimized by appropriate patient-selection criteria and that the longevity of these patients can be extended to their full life potential.

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