Mitral Valve Prolapse and Sudden Cardiac Death: A Systematic Review

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Background—The relationship between mitral valve prolapse (MVP) and sudden cardiac death (SCD) remains controversial. In this systematic review, we evaluate the relationship between isolated MVP and SCD to better define a potential high-risk subtype. In addition, we determine whether premortem parameters could predict SCD in patients with MVP and the incidence of SCD in MVP.

Methods and Results—Electronic searches were conducted in PubMed and Embase for all English literature articles published between 1960 and 2018 regarding MVP and SCD or cardiac arrest. We also identified articles investigating predictors of ventricular arrhythmias or SCD and cohort studies reporting SCD outcomes in MVP. From 2180 citations, there were 79 articles describing 161 cases of MVP with SCD or cardiac arrest. The median age was 30 years and 69% of cases were female. Cardiac arrest occurred during situations of stress in 47% and was caused by ventricular fibrillation in 81%. Premature ventricular complexes on Holter monitoring (92%) were common. Most cases had bileaflet involvement (70%) with redundancy (99%) and nonsevere mitral regurgitation (83%). From 22 articles describing predictors for ventricular arrhythmias or SCD in MVP, leaflet redundancy was the only independent predictor of SCD. The incidence of SCD with MVP was estimated at 217 events per 100 000 person-years.

Conclusions—Isolated MVP and SCD predominantly affects young females with redundant bileaflet prolapse, with cardiac arrest usually occurring as a result of ventricular arrhythmias. To better understand the complex relationship between MVP and SCD, standardized reporting of clinical, electrophysiological, and cardiac imaging parameters with longitudinal follow-up is required. (J Am Heart Assoc. 2018;7:e010584. DOI: 10.1161/JAHA.118.010584.)

Key Words: mitral valve • sudden cardiac death • ventricular fibrillation • ventricular tachycardia

Mitral valve prolapse (MVP) is characterized by the atrial displacement of the mitral valve (MV) leaflet(s) during ventricular systole. The estimated prevalence of MVP is 2.4%, with approximately equal sex distribution. Although most MVP cases are thought to be benign, reported complications include mitral regurgitation (MR) requiring MV surgery, infective endocarditis, stroke, and sudden cardiac death (SCD). The association between MVP and SCD (a potential high-risk MVP subtype) has been reported but the underlying mechanisms remain poorly understood. It is postulated that SCD in individuals with MVP is caused by ventricular arrhythmias (VAs), although this association remains controversial. The initial description of MVP involved cardiac auscultation, cineangiography, and histopathological examination. This led to an abundance of literature describing MVP at autopsy, provoking discussions about a causal relationship between MVP and SCD.

The application of M-mode and 2-dimensional echocardiography for the diagnosis of MVP posed challenges as the identification of MVP shifted from the long axis view, to either a long axis or apical 4-chamber view, and then back to the long axis view as the gold standard for diagnosing MVP. These changes resulted in a significant rise and fall in the prevalence of MVP, with implications for the estimated incidence of SCD.

We aimed to comprehensively evaluate all reported cases of MVP and SCD in the current literature to better characterize the potential high-risk MVP subtype and to determine whether clinical and diagnostic parameters can predict which
patients with MVP were at a higher risk of experiencing SCD. Furthermore, based on published studies, we provide an estimated incidence of SCD in MVP.

Methods
The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure as source data for this systematic review are available from web-based medical libraries.

Case Identification and Search Strategy
We conducted a literature search for cases of MVP with SCD or cardiac arrest in PubMed and Embase on January 1, 2018, using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed search terms were “mitral valve prolapse” AND “cardiac arrest” OR “mitral valve prolapse” AND “sudden cardiac death” OR “mitral valve prolapse” AND “sudden death” OR “mitral valve prolapse” AND “arrhythmia.” Embase search terms were “mitral valve prolapse” AND “heart ventricular fibrillation” OR “mitral valve prolapse” AND “heart arrest” OR “mitral valve prolapse” AND “sudden death” OR “mitral valve prolapse” AND “sudden cardiac death” OR “mitral valve prolapse” AND “heart ventricular tachycardia” OR “mitral valve prolapse” AND “heart arrhythmia” OR “mitral valve prolapse” AND “heart ventricular arrhythmia.”

Titles and abstracts were screened for relevance by 2 reviewers (H.H. and F.J.H.) and bibliographies of all included publications were screened to identify additional references. Screening of the above search result was also conducted to identify articles, which investigated whether patients with MVP had certain clinical, electrophysiological, or imaging predictors that were associated with VAs or SCD. Finally, prospective studies of patients with MVP, which reported SCD outcomes, were included to estimate the incidence of SCD in MVP. Details of the search algorithm are shown in Figure 1.

Included articles were any cases of MVP with SCD or MVP with cardiac arrest and documented rhythm reported in English. Cases of MVP and SCD were separated into isolated MVP (iMVP) and nonisolated MVP (non-iMVP) depending on whether there was another potential cause of death or cardiac arrest. Reports from case series were included if individual patient age and sex could be determined. Cases were excluded if they described VAs that did not result in cardiac arrest or survived cardiac arrest without a documented rhythm. Reports were also excluded if they were published only in abstract form.

Regarding predictors of SCD or VAs, we excluded articles that used healthy patients (as opposed to those with high-versus low-risk MVP) as controls. We also excluded articles with nonsignificant findings or outcomes that were not related to VAs or SCD.

Regarding the incidence of SCD in MVP, we used prospective studies that included a mean patient age older than 18 years, at least 100 patients, and minimum follow-up duration of 24 months.

Statistical Analysis
Continuous data are presented as either medians with interquartile ranges (IQRs) or means with SDs as indicated. Categorical data are presented as absolute numbers and percentages.

Results
In total, 161 cases of MVP with either SCD or cardiac arrest were identified from 79 studies, with 123 cases of iMVP and 38 cases of non-iMVP. A further 22 studies investigated predictors of VAs or SCD. Comprehensive details of all included studies are presented in Tables S1 and S2. There were 3 studies that provided long-term follow-up data regarding SCD in MVP.18-20

Clinical Characteristics in iMVP and SCD
Clinical characteristics of the cases are summarized in Table 1. The age-sex distribution of the index event of cardiac arrest or death is illustrated in Figure 2.
For patients with iMVP, the median age was 30 years (range 6 to 79 years), female sex accounted for 69% of cases, and 61% were SCD cases. The median age for female cases was 28 (IQR, 24–41) years and the median age for male cases was 39 (IQR, 28–53) years. Two cases occurred in individuals younger than 10 (ages 6 and 7), and a further 6 cases in individuals between 10 and 18 years. Activity at the time of cardiac arrest included routine daily activities (46%), exertion related (23%), emotional stress (5%), sleeping (7%), driving (5%), and pregnancy related (4%). Seven cases had cardiac arrest while in the hospital, with 5 occurring in the setting of general anesthesia.

Preceding symptoms included palpitations (58%), syncope (29%), chest pain (31%), dizziness (23%), and fatigue (8%). Only 21% of patients were reported to be asymptomatic before the index event. Three cases had a history of cardiac arrest, although none of these cases overlapped with those who had prior syncope.

Prior medication use was reported in 32 cases, of which 8 (25%) involved patients taking either a β-blocker or digoxin at...
Table 1. Baseline Characteristics in Cases of MVP and SCD or Cardiac Arrest

| Baseline Characteristics | All Cases (N=161) | MVP (N=123) | Non-MVP (N=38) |
|-------------------------|------------------|------------|---------------|
| Age, y                  |                  |            |               |
| Range                   | 6–79             | 6–79       | 8–76          |
| Mean±SD                 | 37±16            | 36±16      | 40±17         |
| Median (IQR)            | 32 (25–51)       | 30 (25–47) | 36 (26–56)    |
| Female sex              |                  |            |               |
|                         | 109 (68)         | 85 (69)    | 24 (63)       |
| SCD                     | 100 (62)         | 75 (61)    | 25 (66)       |
| Circumstances of death  |                  |            |               |
| or cardiac arrest       | n=98             | n=74       | n=24          |
| Sleeping                | 6 (6)            | 5 (7)      | 1 (4)         |
| Normal daily activitya  | 45 (46)          | 34 (46)    | 11 (46)       |
| Exertion or soon afterb | 22 (22)          | 17 (23)    | 5 (21)        |
| Emotional stress        | 6 (6)            | 4 (5)      | 2 (8)         |
| Driving                 | 4 (4)            | 4 (5)      | 0             |
| Anesthesia relatedc     | 6 (6)            | 5 (7)      | 1 (4)         |
| Pregnancy relatedd      | 4 (4)            | 3 (4)      | 1 (4)         |
| Witnessed in hospital   | 5 (5)            | 2 (3)      | 3 (13)        |
| Prior symptoms          | n=71             | n=48       | n=23          |
| Dizziness               | 14 (20)          | 11 (23)    | 3 (13)        |
| Syncope                 | 25 (35)          | 14 (29)    | 11 (48)       |
| Dyspnea                 | 9 (13)           | 5 (10)     | 4 (17)        |
| Chest pain              | 20 (28)          | 15 (31)    | 5 (22)        |
| Palpitations            | 39 (55)          | 28 (58)    | 11 (48)       |
| Fatigue                 | 6 (8)            | 4 (8)      | 2 (9)         |
| None                    | 12 (17)          | 10 (21)    | 2 (9)         |
| Previous cardiac arrest | n=20             | n=14       | n=6           |
| Yes*                    | 8 (40)           | 3 (21)     | 5 (83)        |
| No                      | 12 (60)          | 11 (79)    | 1 (21)        |
| Medication use          | n=57             | n=32       | n=25          |
| Digoxin                 | 7 (13)           | 1 (3)      | 6 (24)        |
| ß-Blocker²              | 16 (28)          | 7 (22)     | 9 (36)        |
| Class 1**               | 10 (18)          | 0          | 10 (40)       |
| Amiodarone             | 1 (2)            | 0          | 1 (4)         |
| Other medications††     | 15 (26)          | 9 (28)     | 6 (24)        |
| Nil                     | 17 (30)          | 16 (50)    | 1 (4)         |

Values are expressed as number (percentage) unless otherwise indicated. MVP indicates isolated mitral valve prolapse; VP, ventricular premature; IQR, interquartile range; SCD, sudden cardiac death.

*Includes deaths at home, work (nonphysical), or during commute.

†One case was after sexual intercourse.

‡Four cases during induction, 1 case during anesthesia reversal, and 1 case during peripheral arterial puncture.

§Two cases were during pregnancy, 1 case during epidural injection, 1 case [classified as nonisolated mitral valve prolapse (non-MVP)] was 2 days postpartum with likely tachycardia-mediated cardiomyopathy caused by permanent junctional reciprocating tachycardia.

Multiple symptoms in some cases.

¶Three cases with documented ventricular tachycardia.

‖Two patients taking sotalol (classified as non-MVP).

**Includes propafenone, procainamide, mexiletine, quinidine, disopyramide, and flecainide.

††Includes amoxicillin, diuretics, antiepileptics, primidone, methyldopa, perindopril, trastuzumab, inhaled glucocorticosteroids, danazol, domperidone, and various psychotropic agents in 3 cases.

A positive family history for SCD was reported in 14% of cases. One case described a possible familial cluster of malignant MVP involving a 14-year-old female with SCD and iMVP, 3 first-degree relatives with SCD (mother aged 36, sister aged 11, and brother aged 12 years who had thickening of his MV) and 3 of 7 remaining siblings with MVP.

Table 1. Continued

| Baseline Characteristics | All Cases (N=161) | MVP (N=123) | Non-MVP (N=38) |
|-------------------------|------------------|------------|---------------|
| Family history of SCD   |                  |            |               |
| Yes                     | 4 (14)           | 3 (14)     | 1 (17)        |
| No                      | 24 (86)          | 19 (86)    | 5 (83)        |

Electrophysiological Findings in iMVP and SCD

Electrophysiological findings for cases of MVP and SCD or cardiac arrest are shown in Table 2.

On baseline ECG, premature ventricular complexes (PVCs) were frequently reported (51%), while T-wave inversion in the inferior leads (24%) and other T-wave changes (19%) were also common. Seven cases described combined inferior and lateral T-wave changes. Normal baseline ECG findings were described in 32% of cases.

Among patients who underwent Holter monitoring, PVCs and couplets were the most common finding (63%), followed by nonsustained VT (29%). No abnormalities were recorded in 8%.

The site of origin of VT or PVCs was available (either reported or interpreted based on published ECG) in 6 cases. Both left and right bundle branch morphologies (in V1) were present with regard to VT or PVC origin. Four cases (all VT) published 12-lead ECGs allowing for interpretation of possible VT origin (Figure 3). Cardiac arrest rhythm was reported in 53 cases and was caused by ventricular fibrillation (VF) (81%), VT (11%), torsades de pointes (4%), and asystole (2%). Six cases documented the initiation of malignant VAs with 5 cases showing PVC-triggered polymorphic VT or VF...
In total, there were 10 cases of autopsy-confirmed MVP (6 with iMVP and 4 with non-iMVP) with documented cardiac rhythm at the time of death, and they all had VF.\textsuperscript{10,22,29,32–38}

Programmed ventricular stimulation was reported for 22 cases using various induction protocols. The findings included sustained VT (5%), nonsustained VT (23%), VF (18%), and no induction of VAs (55%).

Cardiac Imaging Findings in iMVP and SCD

Cardiac imaging findings for cases of MVP and SCD or cardiac arrest are shown in Table 3.

Leaflet involvement was most commonly bileaflet (70%), then posterior leaflet (26%) and anterior leaflet (4%). Severe MR was present in 17% of cases. Six cases reported MV surgery (3 repair and 3 replacement), with 3 cases describing improvement in VAs (follow-up duration ranged from 2 to 3 years), 2 cases describing recurrent VT requiring treatment even after surgery, and 1 case with unreported arrhythmia outcomes.

Two cases reported cardiac magnetic resonance imaging findings, with 1 case reporting anteroseptal and posterior left ventricular wall fibrosis, while the other did not demonstrate late-gadolinium enhancement.

Cardiac Structural Findings in iMVP and SCD

Cardiac structural findings are summarized in Table 4.

Autopsy confirmation of MVP was documented in 73 of the 75 SCD cases. In total, 72 of 73 (99%) cases that commented on the MV described redundant leaflets. Median MV annulus circumference was 126 mm based on 15 cases, while another 2 cases reported a dilated annulus. Median anterior and posterior MV lengths were 30 mm and 25 mm, respectively. Leaflet thickness was not reported in cases of iMVP and SCD. Chordae were described in 45 cases and included generalized abnormalities (62%), rupture (33%), and normal appearance (4%).

Histological abnormalities in the left ventricle were described in 12 of 30 cases (40%), with 3 cases describing fibrosis involving the papillary muscles. From 27 cases that described other cardiac structural findings, 17 cases (63%) had no other abnormal findings, 5 cases (19%) had right ventricular fibrosis, 3 cases (11%) had tricuspid valve prolapse, and 2 cases (7%) had evidence of prior endocarditis.

Nonisolated MVP Cases

For cases of non-iMVP, there were 11 cases with a probable other cause of death or cardiac arrest including anomalous right coronary artery (2), significant left main coronary disease (1), diffuse coronary disease in the setting of pseudoxanthoma elasticum (1), coronary vasospasm (1), previous inferior infarct (1), arrhythmogenic right ventricular cardiomyopathy (1), Brugada syndrome (1), hypertrophic cardiomyopathy (1), dilated cardiomyopathy (1), and postpartum cardiomyopathy (1). There were a further 27 cases with
Table 2. Electrical Findings in Cases of MVP and SCD or Cardiac Arrest

| Electrical Findings                  | All Cases | iMVP     | Non-iMVP |
|--------------------------------------|-----------|----------|----------|
| Baseline ECG changes*               | n=81      | n=59     | n=22     |
| Inferior TWI*                        | 15 (19)   | 14 (24)  | 1 (5)    |
| Other ST-T changes†                  | 16 (20)   | 11 (19)  | 5 (23)   |
| PVCs‡                                | 40 (49)   | 30 (51)  | 10 (45)  |
| Normal                               | 23 (28)   | 19 (32)  | 4 (18)   |
| Atrial fibrillation                  | 9 (11)    | 5 (8)    | 4 (18)   |
| Left ventricular hypertrophy         | 5 (6)     | 2 (3)    | 3 (14)   |
| Other†                               | 9 (11)    | 5 (8)    | 4 (18)   |
| Holter findings                      | n=36      | n=24     | n=12     |
| No PVCs                             | 4 (11)    | 2 (8)    | 2 (17)   |
| PVCs and couplets only               | 20 (56)   | 15 (63)  | 5 (42)   |
| Nonsustained VT                      | 10 (28)   | 7 (29)   | 3 (25)   |
| TDP/VT                              | 2 (6)     | 0        | 2 (17)   |
| Cardiac arrest rhythm                | n=72      | n=53     | n=19     |
| VF                                  | 58 (81)   | 43 (81)  | 15 (79)  |
| VT                                  | 9 (13)    | 6 (11)   | 3 (16)   |
| TDP                                 | 3 (4)     | 2 (4)    | 1 (5)    |
| Asystole                            | 2 (3)     | 2 (4)    | 0        |
| PVS findings                         | n=26      | n=22     | n=4      |
| Normal                               | 13 (50)   | 12 (55)  | 1 (25)   |
| Nonsustained VT                      | 6 (23)    | 5 (23)   | 1 (25)   |
| Sustained VT                         | 2 (8)     | 1 (5)    | 1 (25)   |
| VF                                  | 5 (19)    | 4 (18)   | 1 (25)   |
| Site of origin of PVCs or VT         | n=10      | n=6      | n=4      |
| Left ventricle                       | 3 (30)    | 2 (33)   | 1 (25)   |
| Right ventricle                      | 5 (50)    | 4 (67)   | 1 (25)   |
| Both                                 | 2 (20)    | 0        | 2 (50)   |

Values are expressed as number (percentage). MVP indicates mitral valve prolapse; PVS, programmed ventricular stimulation; SCD, sudden cardiac death; TDP, torsades de pointes; VF, ventricular fibrillation; VT, ventricular tachycardia.

*Multiple changes in some cases.
†All leads (11 cases), lead III (1 case), leads II and III (2 cases), and leads III and aVF (1 case).
‡T-wave inversion (TWI) in lateral leads (7 cases), TWI in V1–V3 (1 case), diffuse changes (1 case), and not specified (7 cases).
§Includes multiple premature ventricular complexes (PVCs) (1), multifocal PVCs (6), bigeminy (3), and couplets (1).
†Includes premature atrial complexes, bundle branch blocks, and accessory pathway (isolated mitral valve prolapse [MVP] cases); Brugada pattern, prolonged QT, left axis deviation, and poor R-wave progression (nonsolated mitral valve prolapse [non-iMVP] cases).

another possible cause of death or cardiac arrest including nonspecific left ventricular hypertrophy or cardiomegaly (12), conduction system fibrosis (2), possible side effect from antiarrhythmic medications (13), and prolonged QTc (3) or a combination of the above. These cases are identified in Table S1.

Predictors of VAs and SCD

We identified 22 articles that reported a heterogeneous group of clinical, electrical, and imaging predictors for MVP and its association with various clinical outcomes. A summary of all studies is presented in Table 53–4,18,39–56 and a full list is presented in Table S2.

Significant multivariate predictors of various outcomes include female sex and anterior mitral leaflet thickness for Lown grade ≥3 complex VAs, QTc dispersion and anterior mitral leaflet length for VT, moderate to severe MR for PVCs and VAs, degree of MVP and anterior mitral leaflet thickness for QT dispersion, and leaflet redundancy for SCD.

Incidence of SCD in MVP

We identified 3 prospective articles that described SCD events in patients with MVP (Table 6).18–20.

Incidence of SCD ranged from 112 to 408 events per 100 000 person-years, with an aggregate incidence of 217 events per 100 000 patient-years (total 13 events in 5985.4 person-years of follow-up). One additional study described a pediatric cohort (mean age, 9.9 years) of patients with MVP with no SCD events during 814 person-years of follow-up.57

Discussion

This systematic review of all identified cases of cardiac arrest in patients with MVP demonstrates the following key features in patients with iMVP and SCD:

1. Clinical characteristics
   a. Median age of 30 years (range 6–79 years) and 69% were female
   b. A total of 47% of cases occurred during physiological or psychological stress

2. Cardiac electrophysiological findings
   a. Frequent PVCs or VAs (92% on Holter monitoring)
   b. VF is the primary rhythm (81%) in cardiac arrest and death

3. Cardiac imaging findings
   a. Predominant (70%) bileaflet MVP
   b. Moderate MR or less in 83%

4. Histopathological findings
   a. Redundant leaflets in 99%
   b. Abnormal chordae in 96%

5. Clinical predictors for SCD in MVP
   a. Lacks robust evidence with heterogenous predictors and end points
   b. Leaflet redundancy is the only independent predictor of SCD in patients with MVP
6. Estimated incidence of SCD in MVP is 217 events per 100,000 person-years

Clinical Characteristics

The median age at time of cardiac arrest or SCD was 30 years, although this was 28 years in females and 39 years in males. The age-sex distribution graph for the cases demonstrated a peak in female cases between 20 and 30 years consistent with previous data relating to iMVP and SCD.3,42 Cases of MVP-related cardiac arrest or SCD in males appeared evenly distributed throughout life.

There appeared to be a disproportionately large number of cases (47%) related to situations of stress (physical, emotional, driving, pregnancy, and in-hospital). The association between increased adrenergic state and complex VAs may provide a plausible explanation as to why autonomic fluctuations may be important in the pathogenesis of iMVP-related SCD.41

Cardiac Electrical Findings

From this large collection of MVP cases with cardiac arrest rhythm, VF appears to be primarily responsible for iMVP-related SCD. Where documented, most were PVC triggered. Only 2 cases described cardiac arrest caused by asystole, with 1 patient having exercise-induced asystole and 1 patient having a likely vagal reaction.58,59 These findings support a primary arrhythmogenic cause of SCD in patients with iMVP.

Common ECG changes included the presence of inferolateral T-wave inversion and PVCs on ECG and the presence of PVCs and VAs on Holter monitoring. However, despite the postulation that inferior T-wave changes on ECG are associated with a potentially high-risk MVP subtype,3,34 prospective evidence is lacking. Similarly, despite reports of a high incidence of PVCs and VAs on Holter monitoring,60 these findings have not been prospectively correlated to SCD events in patients with MVP.

Inducible VAs on programmed ventricular stimulation does not appear to predict SCD events in patients with MVP.61 Two cases in this study reported programmed ventricular stimulation findings before SCD and both cases did not induce VAs.36,62 Additionally, only 1 of 22 cases (5%) had sustained VT during programmed ventricular stimulation, suggesting that arrhythmia initiation is PVC triggered rather than re-entrant scar related. As such, the role of electrophysiological
Figure 4. Documented onset of ventricular arrhythmias. A, Late diastolic premature ventricular complex (PVC)–triggered polymorphic ventricular tachycardia (VT; nonisolated mitral valve prolapse [non-iMVP], patient taking quinidine, reproduced with permission from Elsevier)\textsuperscript{27} B, Possible PVC-triggered polymorphic VT (isolated mitral valve prolapse [iMVP], reproduced with permission from Elsevier)\textsuperscript{28} C, Monomorphic VT with pace termination (non-iMVP, patient taking procainamide, reproduced with permission from Elsevier)\textsuperscript{24} D, Late diastolic couplets triggering polymorphic then fast VT (non-iMVP, patient had arrhythmogenic right ventricular cardiomyopathy, reproduced with permission from Elsevier)\textsuperscript{29} E, Late diastolic PVC–triggered polymorphic VT with varying PVC morphologies in rhythm strip (iMVP, reproduced with permission from Elsevier)\textsuperscript{30} F, (bottom 2 strips), PVC–triggered recurrent VF (iMVP, reproduced with permission from Elsevier).\textsuperscript{31}
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Table 3. Imaging Findings in Cases of MVP and SCD or Cardiac Arrest

| Imaging Findings          | All Cases | iMVP | Non-iMVP |
|---------------------------|-----------|------|----------|
| Leaflet involvement*      | n=83      | n=57 | n=26     |
| Bileaflet                 | 57 (69)   | 40 (70) | 17 (65) |
| Posterior leaflet         | 23 (28)   | 15 (26) | 8 (30)  |
| Anterior leaflet          | 3 (4)     | 2 (4)  | 1 (4)    |
| MR severity               | n=38      | n=23  | n=15     |
| Nil/trivial               | 9 (24)    | 6 (26) | 3 (20)   |
| Mild                      | 12 (32)   | 9 (39) | 3 (20)   |
| Moderate                  | 8 (21)    | 4 (17) | 4 (27)   |
| Severe                    | 9 (24)    | 4 (17) | 5 (33)   |

Values are expressed as number (percentage). iMVP indicates isolated mitral valve prolapse; non-MVP, nonisolated mitral valve prolapse; MVP, mitral valve prolapse; MR, mitral regurgitation; SCD, sudden cardiac death.

*Determination based on either noninvasive imaging reports and/or autopsy reports.

extrastimuli testing in identifying a potential high-risk MVP subtype may be limited.

Cardiac Imaging Findings

The presence of bileaflet prolapse has been associated with an increased rate of VAs and cardiac arrest.\(^5,45\) This is consistent with our findings where a bileaflet phenotype was present in 70% of cases of SCD or cardiac arrest. The association between bileaflet prolapse, mitral annular disjunction, and VAs indicates that mitral apparatus abnormalities likely play a contributory role in the development of malignant VAs.\(^5,3\)

Although prior studies suggest that severe MR is correlated with VAs,\(^5\) we found no association between them. Where degree of MR was reported, the majority (83%) of patients experienced cardiac arrest in the setting of nonsevere MR. Whether surgery on the MV may mitigate risk of cardiac arrest is also unclear. Patients who underwent MV surgery had variable results, including 2 cases that experienced recurrent VAs requiring defibrillator therapy post-MV surgery.\(^5,44\) The lack of systematic reporting and long-term follow-up limits our interpretation.

Other cardiac imaging parameters that may be important include degree of redundancy,\(^18\) mitral annular dilatation,\(^6,3\) mitral annular disjunction,\(^5,3\) and anterior mitral leaflet thickness and length.\(^42,48\) Unfortunately, few studies documented findings in regard to these parameters. Furthermore, although previous work has suggested that radiological myocardial fibrosis may be a trigger for complex VAs in MVP,\(^3,45\) results from cardiac magnetic resonance imaging were only available in 2 studies, limiting interpretation. Studies that prospectively evaluate cardiac imaging parameters with systematic reporting of longitudinal outcomes are required.

Table 4. Cardiac Structural Findings Based on Autopsy Reports, Surgical Reports, or Cardiac Investigations

| Cardiac Structural Findings          | All Cases | iMVP | Non-iMVP |
|--------------------------------------|-----------|------|----------|
| Mitral valve changes                 | n=88      | n=73 | n=15     |
| Redundant leaflet(s)*                | 87 (99)   | 72 (99) | 15 (100) |
| Annulus circumference, mm\(^1\)      | n=19      | n=15 | n=4      |
| Range                                | 96–160    | 100–160 | 96–135   |
| Median, IQR                          | 125 (100–136) | 126 (113–138) | 106 (97–120) |
| Anterior leaflet length, mm          | n=15      | n=13 | n=2      |
| Range                                | 20–35     | 20–35 | 20–28    |
| Median, IQR                          | 30 (25–30) | 30 (25–30) |            |
| Posterior leaflet length, mm         | n=16      | n=13 | n=3      |
| Range                                | 15–30     | 15–30 | 15–30    |
| Median, IQR                          | 25 (20–30) | 25 (20–30) | 28         |
| Chordal changes                      | n=56      | n=45 | n=11     |
| Normal                               | 3 (5)     | 2 (4)  | 1 (9)    |
| Abnormal\(^2\)                       | 37 (66)   | 28 (62) | 9 (82)   |
| Ruptured                             | 16 (29)   | 15 (33) | 1 (9)    |
| Left ventricle histology             | n=40      | n=30  | n=10     |
| Normal\(^1\)                         | 20 (50)   | 18 (60) | 2 (20)   |
| Abnormal\(^1\)                       | 20 (50)   | 12 (40) | 8 (80)   |
| Other cardiac abnormalities          | n=50      | n=27  | n=23     |
| Left ventricular hypertrophy or cardiomegaly | 14 (28)  | 0    | 14 (61)  |
| Right ventricular fibrosis\(^5\)     | 6 (12)    | 5 (19) | 1 (4)    |
| Coronary artery disease\(^\#\)       | 6 (12)    | 0    | 6 (26)   |
| Other\(^**\)                         | 6 (12)    | 5 (19) | 1 (4)    |
| Nil                                  | 18 (36)   | 17 (63) | 1 (4)    |

IQR indicates interquartile range.

*Includes descriptive terms myxomatous, ballooned, thickened, nodose, hooding, voluminous, opaque, and edematous.

\(^2\)Three additional cases reported a dilated annulus without measurement.

\(^3\)Descriptions included elongated, thickened, and/or fused.

\(^4\)Fifteen normal samples were from 1 series (all samples in that series were normal).\(^11\)

\(^5\)Heterogeneous group of descriptors including fibrosis affecting the interventricular septum (3), interstitial fibrosis (5), extensive papillary muscle fibrosis (1), slight papillary muscle fibrosis (2), subendocardial fibrosis affecting the papillary muscles (2), presence of myxomatous material within the papillary muscles (1), multifocal necrosis (3), high-grade left ventricular hypertrophy changes (1), and degenerated elastic fibers (1).

\(^\#\)One case with arrhythmogenic right ventricular cardiomyopathy (nonisolated mitral valve prolapse [non-MVP]).

\(^**\)Includes left main coronary disease (1), anomalous right coronary artery (2), coronary vasospasm (1), prior inferior infarct (1), and significant diffuse coronary disease in the setting of pseudoxanthoma elasticum (1).

\(^**\)Includes tricuspid valve prolapse (3) and previous endocarditis (2) (isolated mitral valve prolapse cases) and significant conduction system fibrosis (1) (non-MVP case).
Cardiac Structural Findings
Where reported, 99% of cases described mitral leaflet redundancy, and MV annulus diameter was dilated compared with population data. Anterior and posterior mitral leaflet length were also greater than otherwise expected. Abnormal chordal findings were present in 96% of cases. The combination of morphological valve distortion and chordal abnormalities are consistent with other autopsy studies of patients with MVP and provide further support that mitral apparatus abnormalities have a contributory role in the development of SCD.

### Table 5. Predictors of VAs or SCD

| Author         | Year | Study population | Predictor/association | Outcome/Endpoint |
|----------------|------|------------------|-----------------------|------------------|
| Gaffney49      | 1979 | MVP              | Higher heart rate     | Clinical severity (combination of symptoms and VAs) |
|                |      |                  | Lower cardiac index  |                   |
| Puddu41        | 1983 | MVP              | Plasma catecholamine level | QTC                |
| Sniezek42      | 1992 | MVP              | Adrenaline excretion | Complex VAs (Lown grade ≥3) |
| Zuppiroli43    | 1994 | MVP              | Female                | Complex VAs (Lown grade ≥3)* |
| Babuty43       | 1994 | MVP              | Age (older)           | Complex VAs (Lown grade ≥3) |
| Naksuk44       | 2016 | MV surgery       | Age (younger)         | PVC reduction post-surgery in BiMVP |
| Fulton45       | 2017 | MVP              | Female                | PVCs from PM |

**Clinical**

- **Electrical**
  - Campbell46 1976 MVP Inferolateral T-wave changes VT (>100bpm for ≥3 beats) or VF
  - Babuty43 1994 MVP Late potentials VT (>3 beats)
  - Bobkowski47 2002 MVP Late potentials VAs (Lown grade ≥1) and VT (>120bpm for ≥4 beats)
  - Akcay48 2010 MVP QTc dispersion VT (>120bpm for ≥3 beats)*

**Imaging**

- Shah49 1982 MVP MR Complex VAs (Lown grade ≥3)
- Nishimura50 1985 MVP Redundant leaflets Sudden death*
- Kligfield5 1985 MVP MR VAs (>1% PVC frequency or exercise induced PVCs/VT or Lown grade ≥4 complex VAs)
- Sanfilippo51 1989 MVP Anterior leaflet thickness MR VAs (≥10 PVCs/hr or VT at ≥100bpm for ≥3 beats)
- Zuppiroli42 1994 MVP Anterior leaflet thickness Complex VAs (Lown grade ≥3)*
- Babuty43 1994 MVP MR Complex VAs (Lown grade ≥3)
- Zouridakis52 2001 MVP MVP degree QT dispersion*
- Turker53 2010 MVP Moderate-severe MR VAs (Lown grade ≥1)*
- Carmon54 2010 MVP Mitral annular disjunction Non-sustained VT (NS)
- Han55 2010 MVP LGE in PM Complex VAs (Lown grade ≥4)
- Akcay48 2010 MVP Anterior leaflet length VT (>120 bpm for ≥3 beats)*
- Sriram56 2013 OHCA BiMVP Appropriate ICD therapies at follow-up
- Basso4 2015 MVP LGE Complex VAs (Lown grade ≥4b or VF)
- Nordhues57 2016 MVP BiMVP All-cause mortality
- Bui58 2017 MVP Myocardial T1 time Complex VAs (Lown grade ≥3)
- Fulton45 2017 MVP BiMVP PVCs from PM

BiMVP indicates bileaflet mitral valve prolapse; bpm, beats per minute; ICD, implantable cardioverter-defibrillator; LGE, late-gadolinium enhancement; MR, mitral regurgitation; MV, mitral valve; MVP, mitral valve prolapse; OHCA, out-of-hospital cardiac arrest; NS, not specified; PM, papillary muscle; PVCs, premature ventricular complexes; QTc, corrected QT; SCD, sudden cardiac death; VAs, ventricular arrhythmias; VF, ventricular fibrillation; VT, ventricular tachycardia.

*Significant result on multivariate analysis; significant univariable predictors are not presented.
abnormal left ventricular histological changes, including 3 cases that specifically described histological abnormalities involving the papillary muscles. Left ventricular fibrosis, especially near the papillary muscles, is described in autopsy patients with MVP and may provide a substrate for the development of VAs. These findings suggest that both diffuse and focal changes within the left ventricle occur in patients with MVP, which may act as a substrate for the development of VAs.

Findings in Non-iMVP
As described, there was a subset of patients with SCD and MVP but also other cardiac abnormalities.

SCD is likely attributable to significant coronary artery disease, dilated or hypertrophic cardiomyopathy, Brugada syndrome, and arrhythmogenic right ventricular cardiomyopathy in cases with these coexistent conditions.

Other coexistent findings are more contentious. Anatomical findings such as mild left ventricular hypertrophy or cardiomegaly at autopsy have been described in relation to MVP and could indicate that pathological changes of the ventricle in otherwise “iMVP” is a contributor to SCD events. Additionally, 13 patients were taking antiarrhythmic medications. It is prudent to consider that while these medications in themselves may have proarrhythmic side effects, these medications were likely administered to treat preexisting VAs in the cases. Finally, findings of prolonged QTc may also reflect underlying repolarization abnormalities in patients with MVP, which has also been previously described.

Challenges in Predicting SCD in Patients With Isolated MVP
Studies investigating premortem predictors of SCD in MVP are limited. One prospective study demonstrated that leaflet redundancy was an independent predictor of SCD. Some controversy surrounds the risk of bileaflet MVP with 1 study suggesting that it was associated with appropriate implantable cardioverter-defibrillator therapies, while another suggested that bileaflet MVP was associated with lower all-cause mortality based on registry data. Premortem predictors of VAs are difficult to validate in the current collection of cases. Some predictors such as leaflet redundancy, bileaflet MVP, and inferolateral T-wave inversion on ECG were only available in approximately half of the case reports, while degree of MR was available for about one quarter of cases. Other potential predictors such as catecholamine levels, late potentials, QT dispersion, anterior mitral leaflet thickness and length, mitral annular disjunction, presence of late-gadolinium enhancement, and myocardial T1 time were either scarcely reported or not reported.

In addition, many studies have used VAs or repolarization abnormalities as surrogate end points for SCD because of the relatively low event rates of SCD. These end points, which include nonsustained ventricular tachycardia, Lown grade VAs of varying degrees, PVC frequency, exercise-induced PVCs, presence of papillary muscle PVCs, PVC reduction post-MV surgery, corrected QT interval, or QT dispersion, are yet to be validated as predictors of SCD in the MVP population.

The heterogeneous nature of these predictors and end points limits comparisons between studies. As such, despite the numerous cases reporting SCD or cardiac arrest in MVP, there is limited evidence that such outcomes can be reliably predicted.

Incidence of SCD in MVP
Our findings suggest that the overall incidence of SCD in MVP was 217 events per 100 000 person-years based on 3 prospective studies, although the presence of leaflet redundancy may signal a higher risk cohort. Extrapolation of data from Nishimura et al suggests an approximate event rate of 998 per 100 000 person-years in patients with evidence of leaflet redundancy.

Comparisons to population data are inherently limited (Figure 5). More recent population-based studies indicate that the incidence of SCD in the general population has decreased from 94 to 97 events per 100 000 person-years in the 1990s to 42 to 53 events per 100 000 person-years in the 2000s, although advances in resuscitation methods may account for some of this difference. Framingham data (involving an older and more male-predominant cohort) suggest that the SCD risk in the general population was ≈130 events per 100 000 person-years.

Table 6. Prospective Follow-Up Studies in MVP With SCD Rates

| Study Author | Patients, No. | Mean Age, y | Females, No. | Mean Follow-Up, y | SCD Events/100 000 Patient-Y, No. |
|--------------|---------------|-------------|--------------|------------------|----------------------------------|
| Nishimura18  | 237*          | 44          | 142          | 6.2              | 408                              |
| Düren19      | 300           | 42          | 164          | 6.2              | 219                              |
| Zuppiroli20  | 316           | 42          | 220          | 8.5              | 112                              |

MVP indicates mitral valve prolapse.

*A total of 97 patients had redundant leaflets—all cases of sudden cardiac death (SCD) occurred in those with redundant leaflets.
Our systematic review indicates that iMVP and SCD predominantly affects young females. The MV leaflets are frequently redundant with bileaflet prolapse, associated chordal abnormalities, and nonsevere MR. Electrophysiological changes include frequent PVCs on Holter monitoring and VF as the predominant cardiac arrest rhythm. Current predictors for SCD events in iMVP lack robust evidence. To better understand the complex relationship between MVP and SCD, standardized reporting of clinical, electrophysiological, echocardiographic, and other cardiac imaging variables with documentation of long-term outcomes is required.

Disclosures

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**Table S1. All Cases Included in Study.**

| Year | Author | Cases | Description |
|------|--------|-------|-------------|
| 1968 | Barlow¹ | 1 | Review of 90 patients with non-ejection systolic click and late systolic murmurs. 1 case of 39M with SCD. (iMVP) |
| 1970 | Trent² | 1 | Report of 63F with MVP and SCD. (non-iMVP) |
| 1971 | Jeresaty³ | 1 | Review of 24 patients with mitral ballooning on angiography. 1 case of 62F with SCD. (iMVP) |
| 1973 | Jeresaty⁴ | 1 | Review of 100 patients with non-ejection click or MVP on left ventriculography. 1 case of 44F with SCD. (iMVP) 1 case of 62F with SCD (repeat case). |
| 1973 | Shappell⁵ | 1 | Report of 27F with MVP and SCD. (non-iMVP) |
| 1974 | Marshall⁶ | 1 | Report of 2 cases (27F and 36F) with MVP and SCD. (1 case iMVP and 1 case non-iMVP) Case of 27F (repeat case). |
| 1975 | Shappell⁷ | 1 | Series of 4 patients with MVP. 1 case of 23F with VF. (iMVP) 2 cases (27F and 36F) of SCD (repeat cases). 1 case of NSVT (not included). |
| 1976 | Jeresaty⁸ | 2 | Summary of 12 cases of MVP and SCD. 2 cases (39F and 40M) included. (both iMVP) 7 cases previously reported. 3 cases of personal communication without individual age or gender (not included). |
| 1976 | Kleid⁹ | 1 | Report of 38F with MVP and SCD. (iMVP) |
| 1976 | Ritchie¹⁰ | 1 | Report of 56M with MVP and VF. (non-iMVP) |
| 1976 | Winkle¹¹ | 5 | Series of 7 patients with MVP and VAs. 3 cases with VF and 2 cases with VT. (4 cases iMVP and 1 case non-iMVP) 2 cases excluded (1 with unmonitored cardiac arrest and 1 NSVT). |
| 1977 | Cobbs¹² | 1 | Report of 39F with MVP and VF. (iMVP) |
| 1977 | Mills¹³ | 2 | Follow-up of 53 patients with MVP. 1 case of 58M with SCD. (non-iMVP) 1 case of 26F with VF. (iMVP) |
| 1978 | Davies¹⁴ | 13 | Review of 90 cases of MVP at autopsy. 13 cases with MVP and SCD (12 cases iMVP and 1 case non-iMVP). |
| 1979 | Forbes¹⁵ | 1 | Report of 25F with MVP and VF on anaesthesia induction. (non-iMVP) |
| 1979 | Watts¹⁶ | 1 | Report of 26F with MVP and VF. (iMVP) |
| 1980 | Anderson¹⁷ | 2 | Report of 2 cases (both 21F) with MVP and SCD. (both iMVP) |
| 1980 | Bennett¹⁸ | 1 | Report of 15F with MVP and TDP. (iMVP) |
| 1980 | Mair¹⁹ | 3 | Series of 3 cases (25F, 29F and 35F) with MVP and SCD. (all iMVP) |
| 1980 | Mautner²⁰ | 2 | Review of 22 patients with MVP and PVCs. 1 case of 51F with VF. (iMVP) 1 case of 50M with VT during anesthesia induction. (iMVP) |
| 1981 | Bharati²¹ | 1 | Report of 45M with MVP and SCD. (iMVP) |
| 1981 | Salmela²² | 1 | Report of 27M with MVP and SCD. (non-iMVP) |
| 1982 | Noneman²³ | 1 | Report of 29M with MVP and VF. (iMVP) |
| 1982 | Vesterby²⁴ | 3 | Series of 3 cases (23F, 68M, 55M) with MVP and SCD. (1 case iMVP and 2 cases non-iMVP) |
| 1982 | Virmani²⁵ | 1 | Review of 30 autopsies in joggers. 1 case of 27M with MVP and SCD. (iMVP) |
| 1983 | Bharati²⁶ | 2 | Series of 3 cases of SCD in teenagers. 2 cases (17M and 19F) with MVP. (both iMVP) |
| Year | Author(s) | Cases | Description |
|------|-----------|-------|-------------|
| 1983 | Chesler | 14 | Series of 14 cases of MVP and SCD. (non-iMVP) |
| 1983 | Conklin | 1 | Report of 22F with MVP and VT during labor. (iMVP) |
| 1983 | Morady | 2 | Series of 31 patients with VAs undergoing EPS. 2 patients (28F and 39F) with MVP and VF. (both iMVP) |
| 1984 | Kemp | 1 | Series of 27 cases with SCD on ambulatory ECG monitoring. 1 case of 31F with MVP. (non-iMVP) |
| 1984 | Pocock | 1 | Report of 24F with MVP and SCD. (non-iMVP) |
| 1985 | Andre-Fouet | 1 | Report of 19M with MVP and SCD. (iMVP) |
| 1985 | Rosenthal | 5 | Series of 20 patients with MVP and VAs. 5 patients with VF. (all iMVP) |
| 1985 | Sakuma | 1 | Report of 54M with MVP, coronary vasospasm and VF. (non-iMVP) |
| 1986 | Casthely | 1 | Report of 7M with MVP and VF during anaesthesia induction. (iMVP) |
| 1986 | Higgins | 1 | Report of 36F with MVP and VT. (non-iMVP) |
| 1986 | Hoffman | 1 | Report of 32F with MVP and VF. (iMVP) |
| 1987 | Broustet | 1 | Report of 28F with MVP and SCD. (non-iMVP) |
| 1988 | Goldhammer | 1 | Report of 46M with MVP and asystole. (iMVP) |
| 1988 | Scala-Barnett | 4 | Series of 4 cases of MVP and SCD. (2 cases iMVP and 2 cases non-iMVP) |
| 1988 | Strasberg | 1 | Report of 27M with MVP and VF. (iMVP) |
| 1988 | Vlay | 1 | Report of 24F with MVP and SCD. (iMVP) |
| 1989 | Abraham | 1 | Report of 33F with MVP and asystole during anesthesia. (iMVP) |
| 1989 | Topaz | 2 | Series of 22 patients with cardiac arrest. 2 patients [19M (also anomalous RCA) and 28M] with MVP. (1 case iMVP and 1 case non-iMVP) |
| 1989 | Martini | 2 | Series of 6 cases with VF. 2 cases (14F and 35M) with MVP. (both iMVP) |
| 1990 | Boudoucas | 9 | Series of 9 patients with MVP and cardiac arrest. (8 cases iMVP and 1 case non-iMVP) |
| 1990 | Corrado | 2 | Series of 22 athletes with SCD. 2 cases (17F and 23M) with MVP. (both iMVP) |
| 1990 | Nelson-Piercy | 1 | Report of 67M with MVP, anomalous RCA and VF. (non-iMVP) |
| 1990 | Sadanianz | 0 | Report of 27M with MVP and SCD (repeat case). |
| 1991 | Dollar | 15 | Review of 56 cases of MVP at autopsy. 15 cases of SCD related to MVP. (14 cases iMVP and 1 case non-iMVP) |
| 1993 | Vohra | 2 | Series of 7 patients with MVP and VAs. 2 cases (28M and 45M) with SCD. (both non-iMVP) |
| 1995 | Martini | 1 | Report of 42F with MVP, ARVC and SCD. (non-iMVP) |
| 1997 | Moritz | 1 | Report of 6F with MVP and VF during anaesthesia induction. (iMVP) |
| 1997 | Wilde | 1 | Report of 34M with MVP and VF. (iMVP) |
| 1998 | Ronneberger | 1 | Report of 8M with MVP and SCD. (non-iMVP) |
| 2000 | Nolte | 1 | Report of 26F with MVP, diffuse CAD due to PXE and SCD. (non-iMVP) |
| 2001 | Cannon | 1 | Report of 25F with MVP and SCD. (iMVP) |
| 2003 | Abello | 1 | Report of 28F with MVP and VF during pregnancy. (iMVP) |
| 2003 | Ciancarmerla | 1 | Report of 49M with MVP and SCD. (iMVP) |
| 2003 | Nishida | 1 | Series of 3 cases of SCD and alcohol abuse. 1 case of 37F with MVP. (non-iMVP) |
| 2004 | Chirachariyavej | 1 | Report of 38M with MVP and SCD. (iMVP) |
| 2004 | Frassati | 3 | Series of 14 cases of SCD in psychiatric patients. 3 cases (22M, 51M and 57M) with MVP. (1 case iMVP and 2 cases non-iMVP) |
| 2005 | Zeidan | 1 | Report of 21F with MVP and VF during anaesthesia reversal. (iMVP) |
| 2007 | Anders | 6 | Series of 6 cases of MVP and SCD. (iMVP) |
| 2007 | Kesavan | 1 | Report of 75F with MVP, CAD and VT. (non-iMVP) |
| Year | Author   | Case Count | Description |
|------|----------|------------|-------------|
| 2007 | Knackstedt | 1          | Report of a 54M with MVP and VF. (iMVP) |
| 2010 | Franchitto | 1          | Report of 25F with MVP and SCD. (iMVP) |
| 2010 | Oliviera  | 1          | Report of 57F with MVP and SCD (also heart failure on trastuzumab). (non-iMVP) |
| 2011 | Rordorf   | 1          | Report of 32F with MVP and VF (also DCM post-partum with PJRT). (non-iMVP) |
| 2014 | Abbadi    | 1          | Report of 26F with MVP and VF. (iMVP) |
| 2014 | Rajani    | 1          | Report of 27F with MVP and TDP. (iMVP) |
| 2015 | Lin       | 1          | Report of 30F with MVP and VT during pregnancy. (iMVP) |
| 2015 | Desai     | 1          | Report of 55M with MVP and SCD. (iMVP) |
| 2015 | Fais      | 1          | Report of 47F with MVP and SCD. (iMVP) |
| 2016 | Ahmed     | 1          | Report of 45M with MVP and VT. (iMVP) |
| 2016 | Vaidya    | 5          | Series of 5 patients with MVP, ICD and history of MV surgery (1 case also had HCM). (2 cases iMVP and 3 cases non-iMVP) |
| 2017 | Cacko     | 1          | Report of 28F with MVP and VF. (iMVP) |
| 2017 | Martini   | 1          | Report of 58M with MVP and VF (also Brugada ECG). (non-iMVP) |
| 2017 | Saha      | 1          | Report of 26F with MVP and VF during pregnancy. (iMVP) |

SCD, sudden cardiac death; MVP, mitral valve prolapse; VF, ventricular fibrillation; NSVT, non-sustained ventricular tachycardia; VAs, ventricular arrhythmias; EPS, electrophysiology study; VT, ventricular tachycardia; TDP, torsade de pointes; PVCs, premature ventricular complexes; RCA, right coronary artery; ARVC, arrhythmogenic right ventricular cardiomyopathy; PXE, pseudoxanthoma elasticum; CAD, coronary artery disease; DCM, dilated cardiomyopathy; PJRT, persistent junctional reciprocating tachycardia, ICD, implantable cardiac defibrillator; MV, mitral valve; HCM, hypertrophic cardiomyopathy
Table S2. Predictors of Ventricular Arrhythmias or Sudden Cardiac Death.

| Author       | Year | Study                        | N (% Female) | Age range | Study population | Diagnostic criteria                  | Predictor/association          | Outcome/Endpoint                                                                 |
|--------------|------|------------------------------|--------------|-----------|------------------|---------------------------------------|-------------------------------|----------------------------------------------------------------------------------|
| Clinical     |      |                              |              |           |                  |                                       |                               |                                                                                  |
| Gaffney80    | 1979 | Prospective Cohort           | 19 (100)*    | 19-46     | MVP              | M-mode or auscultation                | Higher heart rate             | Clinical severity (combination of symptoms and VAs)                             |
| Puddu81      | 1983 | Prospective Cohort           | 15 (67)      | NR        | MVP              | Echo (NS)                            | Plasma catecholamine level    | QTc (supine)                                                                    |
| Sniezek82    | 1992 | Prospective Cohort           | 53 (58)      | 19-52     | MVP              | Echo (LAX)                           | Adrenaline excretion          | Complex VAs (Lown grade ≥3)                                                     |
| Zuppiroli83   | 1994 | Prospective Cohort           | 119 (47)     | 12-78     | MVP              | Echo (LAX)                           | Female                        | Complex VAs (Lown grade ≥3)†                                                   |
| Babuty84     | 1994 | Prospective Cohort           | 58 (50)      | NR        | MVP              | Echo (LAX or A4C)                    | Age (older)                   | Complex VAs (Lown grade ≥3)                                                     |
| Naksuk85     | 2016 | Retrospective Cohort         | 32 (53)      | NR        | BiMVP with MV surgery | N/A                           | Age (younger)                 | Reduction in PVCs post MVR in BiMVP                                            |
| Fulton86     | 2017 | Retrospective Cohort         | 18 (61)      | NR        | MVP              | Echo (LAX)                           | Female                        | PVCs from PM                                                                     |
| Electrical   |      |                              |              |           |                  |                                       |                               |                                                                                  |
| Campbell87   | 1976 | Prospective Cohort           | 20 (65)      | 12-61     | MVP              | Auscultation                         | Inferolateral T-wave changes  | VT (>100bpm for 3 beats) or VF                                                  |
| Babuty84     | 1994 | Prospective Cohort           | 58 (50)      | NR        | MVP              | Echo (LAX or A4C)                    | Late potentials               | Non-sustained VT (≥3 beats and <30 seconds)                                     |
| Bobkowski88  | 2002 | Prospective Cohort           | 151 (77)*    | 5-18      | MVP              | Echo (NS)                            | Late potentials               | VAs (Lown grade ≥1) Non-sustained VT (>120bpm for ≥4 beats and <30 seconds)   |
| Akcay89      | 2010 | Retrospective Case control   | 60 (72)      | NR        | MVP (with vs without VT) | Echo (NS)                     | QTc dispersion                | VT (>120bpm for ≥3 beats)†                                                      |
| Imaging      |      |                              |              |           |                  |                                       |                               |                                                                                  |
| Shah90       | 1982 | Retrospective Cohort         | 88 (60)      | 12-84     | MVP              | M-mode                               | MR                            | Complex VAs (Lown grade ≥3)                                                     |
| Nishimura91  | 1985 | Prospective Cohort           | 237 (60)     | 10-69     | MVP              | Echo (NS)                            | Redundant leaflets            | Sudden death†                                                                   |
| Kligfield92  | 1985 | Prospective Cohort           | 80 (65)*     | 19-72     | MVP              | Echo (NS)                            | MR                            | >1% PVC frequency Exercise induced PVCs and VT                                 |

† Denotes imaging study.
| Author          | Year | Study Type                  | N  | NR | Imaging Method | Parameters                                      | Complex VAs (Lown grade 4)                                                                 |
|-----------------|------|----------------------------|-----|----|----------------|------------------------------------------------|------------------------------------------------------------------------------------------|
| Sanfilippo      | 1989 | Retrospective Cohort       | 22(55)* | NR | MVP            | Echo (LAX or A4C) Anterior leaflet thickness MR Leaflet displacement | VAs (≥10 PVCs/hr or NSVT at ≥100bpm for ≥3 beats)                                        |
| Zuppiroli       | 1994 | Prospective Cohort         | 119(47) | 12-78 | MVP         | Echo (LAX) Anterior leaflet thickness | Complex VAs (Lown grade ≥3)†                                                              |
| Babuty          | 1994 | Prospective Cohort         | 58(50)  | NR | MVP            | Echo (LAX or A4C) MR                         | Complex VAs (Lown grade ≥3) on Holter and exercise test                                  |
| Zouridakis      | 2001 | Prospective Cohort         | 89(71)  | NR | MVP            | Echo (LAX or A4C) MVP degree Anterior leaflet thickness | QT dispersion†                                                                          |
| Turker          | 2010 | Prospective Cohort         | 58(55)  | 16-68 | MVP            | Echo (LAX) Moderate-severe MR VAs (Lown grade ≥1)†                  |
| Carmo           | 2010 | Retrospective Cohort       | 38(47)  | NR | MVP            | Echo (LAX) Mitral annular disjunction | Non-sustained VT                                                                         |
| Han             | 2010 | Retrospective Cohort       | 16(44)* | NR | MVP            | Echo (NS) LGE in PM                | Complex VAs (Lown grade ≥4)                                                             |
| Akcay           | 2010 | Retrospective Cohort       | 60(72)  | NR | MVP (with vs without VT) Echo (NS) Anterior leaflet length | VT (>120bpm for ≥3 beats)†                                                             |
| Sriram          | 2013 | Retrospective Cohort       | 24(67)  | 5-60 | Idiopathic OHCA Echo (NS) BiMVP | Appropriate ICD therapies at follow-up |                                                                                                |
| Basso           | 2015 | Prospective Cohort         | 44(66)  | 24-64 | MVP            | Echo (LAX) LGE (PM, inferobasal wall and total percentage) | Complex VA (Lown grade ≥4b or VF)                                                       |
| Nordhues        | 2016 | Retrospective Case control | 13338 (43)* | NR | BiMVP vs SiMVP | Echo (NS) BiMVP | All-cause mortality (lower in BiMVP)                                                                 |
| Bui             | 2017 | Retrospective Cohort       | 32(34)* | NR | MVP            | CMR Myocardial T1 time | Complex VAs (Lown grade ≥3)                                                                 |
| Fulton          | 2017 | Retrospective Cohort       | 18(61)  | NR | MVP            | Echo or CMR BiMVP LGE in PM | PVCs from PM                                                                                     |

A4C, apical 4 chamber; bpm, beats per minute; BiMVP, bileaflet MVP; ICD, implantable cardiac defibrillator; LAX, long axis; LGE, late gadolinium enhancement; NR, not reported; NS, not specified; OHCA, out of hospital cardiac arrest; PM, papillary muscle; SiMVP, single leaflet MVP.
*Studies also included normal control groups which are not presented
†Significant result on multivariate analysis; significant univariable predictors not presented
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