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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.
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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.[1]

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).[2] 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),[3,4] although this association remains controversial.[1,2,5] The initial description of MVP involved cardiac auscultation, cineangiography, and histopathological examination.[6] This led to an abundance of literature describing MVP at autopsy,[7–11] 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,[12,13] to either a long axis or apical 4-chamber view,[14] and then back to the long axis view as the gold standard for diagnosing MVP.[15] These changes resulted in a significant rise and fall in the prevalence of MVP,[1,16] 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

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Accompanying Tables S1 and S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010584

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Clinical Perspective

What Is New?

- Reported cases of isolated mitral valve prolapse and sudden cardiac death indicate that young females with bileaflet redundant leaflets are predominantly affected.
- Clinical predictors of sudden cardiac death in isolated mitral valve prolapse are lacking.
- The estimated incidence of sudden cardiac death in mitral valve prolapse is 217 events per 100 000 person-years from previous studies.

What Are the Clinical Implications?

- Further work is needed to understand the complex relationship between mitral valve prolapse and sudden cardiac death.
- Standardized reporting of clinical, electrophysiological, echocardiographic, and other cardiac imaging variables with documentation of long-term outcomes is required.

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.[17] 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.

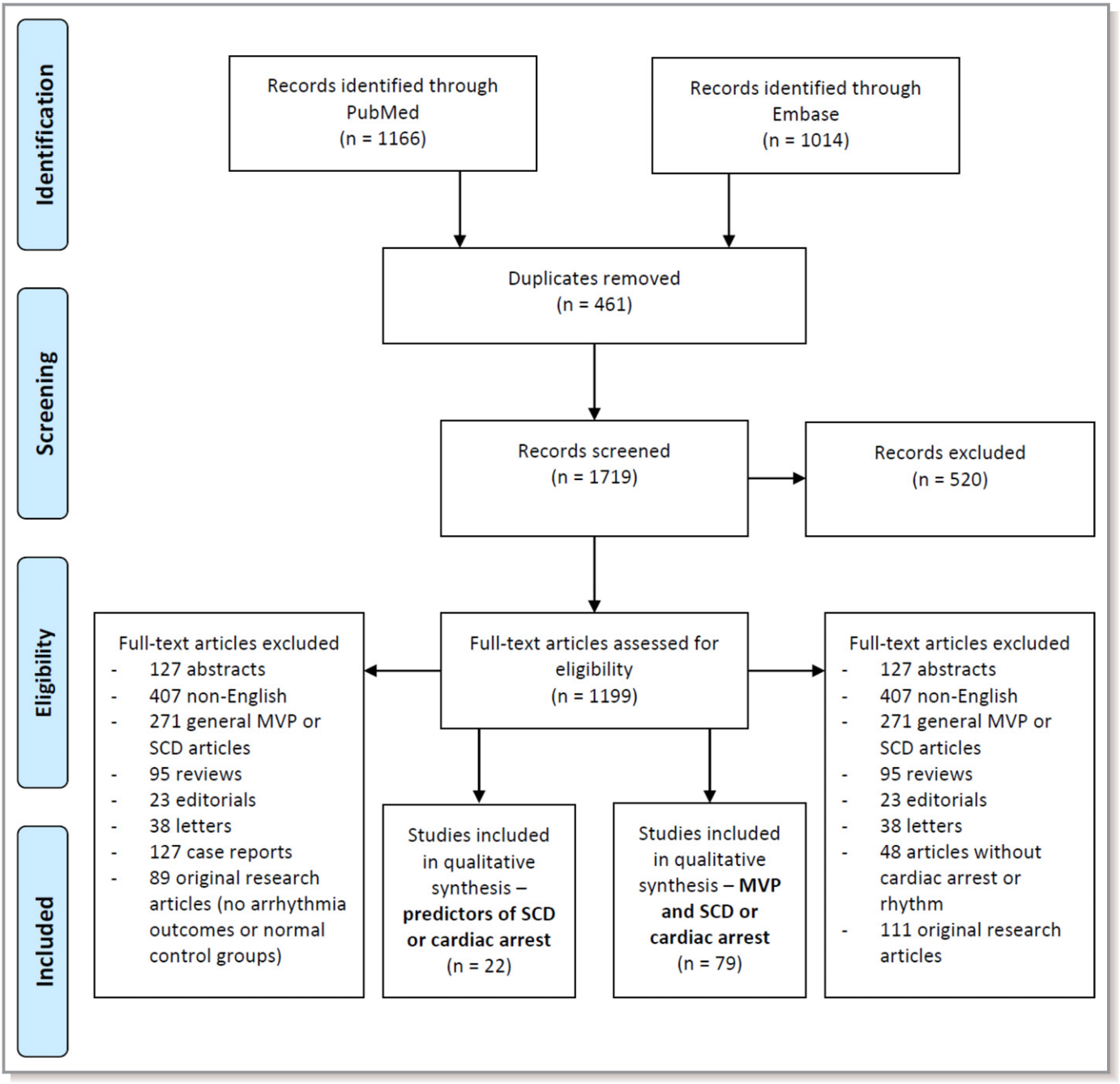

Figure 1. Search algorithm. MVP indicates mitral valve prolapse; SCD, sudden cardiac death.

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)	iMVP (n=123)	Non-iMVP (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 activity*	45 (46)	34 (46)	11 (46)
Exertion or soon after†	22 (22)	17 (23)	5 (21)
Emotional stress	6 (6)	4 (5)	2 (8)
Driving	4 (4)	4 (5)	0
Anesthesia related‡	6 (6)	5 (7)	1 (4)
Pregnancy related§	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)
β-Blocker#	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)
Family history of SCD	n=28	n=22	n=6
Yes	4 (14)	3 (14)	1 (17)
No	24 (86)	19 (86)	5 (83)

Values are expressed as number (percentage) unless otherwise indicated. iMVP indicates isolated mitral valve prolapse; MVP, mitral valve prolapse; IQR, interquartile range; SCD, sudden cardiac death.
*Includes death 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-iMVP]) 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 fibrillation.
#Two patients taking sotalol (classified as non-iMVP).
**Includes propafenone, procainamide, mexilitine, quinidine, disopyramide, and flecainide.
††Includes amoxicillin, diuretics, antiepileptics, primidone, methyldopa, perindopril, trastuzumab, inhaled glucocorticosteroids, danazol, domperidone, and various psychotropic agents in 3 cases.

the time of cardiac arrest or SCD and 50% who were not taking any medications. One patient was taking multiple psychotropic medications,[21] while another case described MVP and SCD in a patient with markedly elevated concentrations of caffeine (from an energy supplement).[22]

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.[8]

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).[23–26] Cardiac arrest rhythm was reported in 53 cases and was caused by ventricular fibrillation (VF) (81%), VT (11%), torsades de pointes (4%), and asystole (4%). Six cases documented the initiation of malignant VAs with 5 cases showing PVC-triggered polymorphic VT or VF

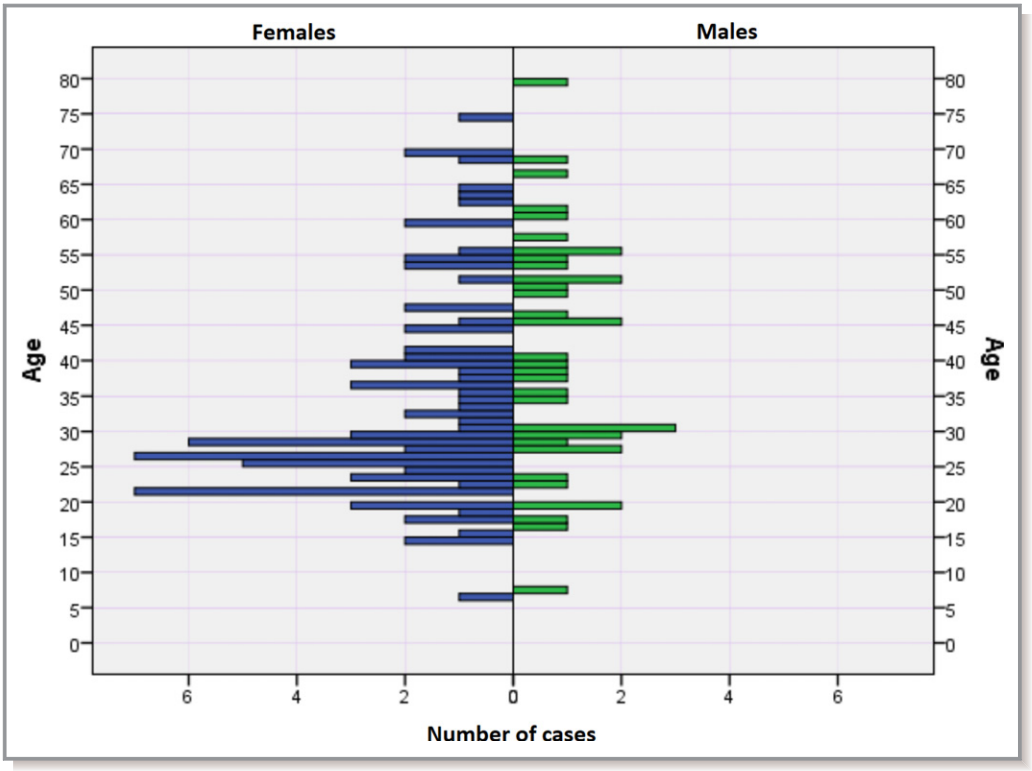

Figure 2. Age at time of death or cardiac arrest in mitral valve prolapse according to sex.

(Figure 4).[24,27–31] 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.[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/VF	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 [iMVP] cases); Brugada pattern, prolonged QT, left axis deviation, and poor R-wave progression (nonisolated 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 5[3–4,18,39–56] 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

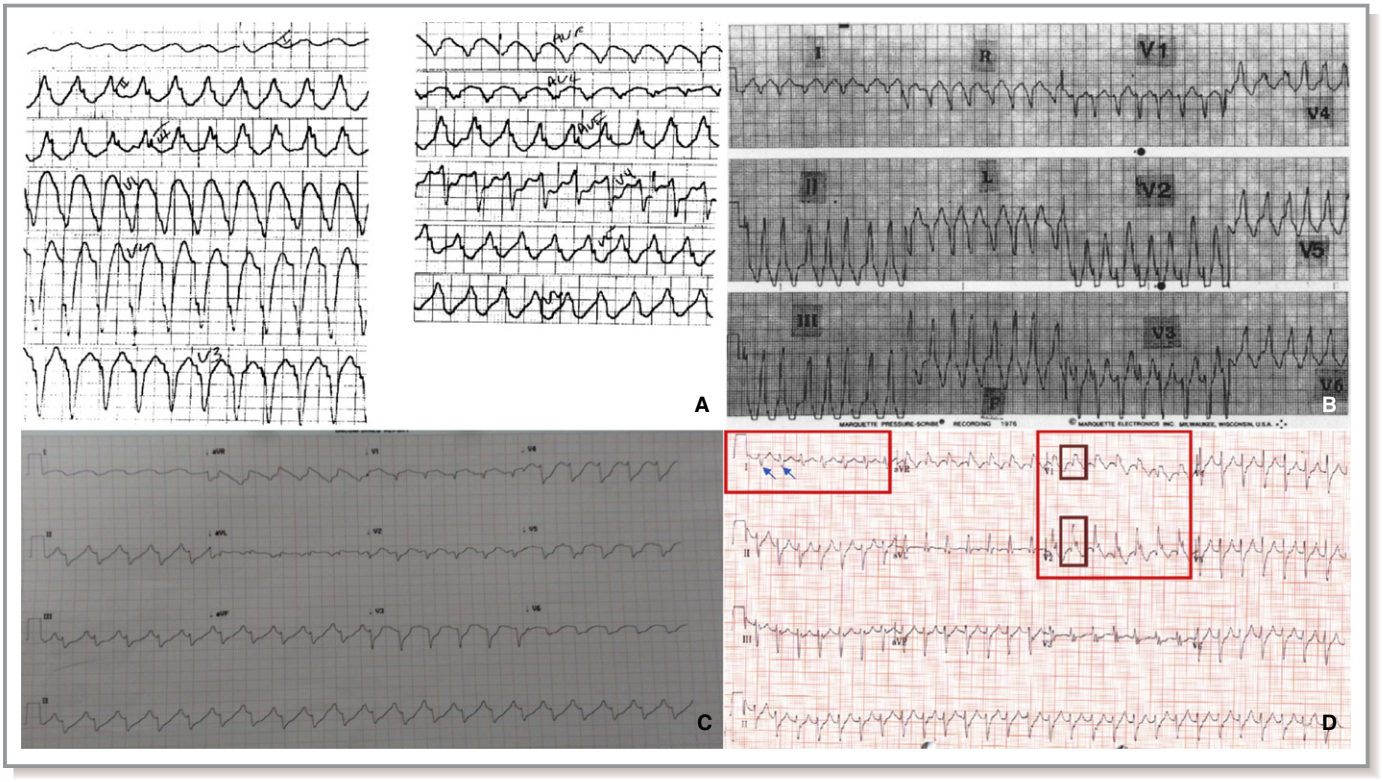

Figure 3. Twelve-lead ECGs of ventricular tachycardia. Left and right bundle morphology interpretation based on V1 appearance. **A**, Left bundle morphology, inferior axis (isolated mitral valve prolapse [iMVP], reproduced with permission from Elsevier).[23] **B**, Left bundle morphology, inferior axis (nonisolated iMVP [non-iMVP], patient taking procainamide, reproduced with permission from Elsevier).[24] **C**, Left bundle morphology, superior axis (iMVP, reproduced with permission from BMJ Publishing Group Ltd.).[25] **D**, Right bundle morphology, superior axis (iMVP, reproduced with permission from Elsevier).[26]

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 reentrant 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)[27] **B**, Possible PVC-triggered polymorphic VT (isolated mitral valve prolapse [iMVP], reproduced with permission from Elsevier)[28] **C**, Monomorphic VT with pace termination (non-iMVP, patient taking procainamide, reproduced with permission from Elsevier)[24] **D**, Late diastolic couplets triggering polymorphic then fast VT (non-iMVP, patient had arrhythmogenic right ventricular cardiomyopathy, reproduced with permission from Elsevier)[29] **E**, Late diastolic PVC–triggered polymorphic VT with varying PVC morphologies in rhythm strip (iMVP, reproduced with permission from Elsevier)[30] **F**, (bottom 2 strips), PVC–triggered recurrent VF (iMVP, reproduced with permission from Elsevier).[31]

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.[3,45] 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.[63]

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.[64] 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,[63] mitral annular disjunction,[63] 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,[4,45] 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†	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‡	37 (66)	28 (62)	9 (82)
Ruptured	16 (29)	15 (33)	1 (9)
Left ventricle histology	n=40	n=30	n=10
Normal§	20 (50)	18 (60)	2 (20)
Abnormal‖	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¶	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, floppy, voluminous, opaque, and edematous.
†Three additional cases reported a dilated annulus without measurement.
‡Descriptions included elongated, thickened, and/or fused.
§Fifteen normal samples were from 1 series (all samples in that series were normal).[11]
‖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-iMVP]).
#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-iMVP case).

Table 5. Predictors of VAs or SCD

Author	Year	Study population	Predictor/association	Outcome/Endpoint
Clinical				
Gaffney[39]	1979	MVP	Higher heart rate Lower cardiac index	Clinical severity (combination of symptoms and VAs)
Puddu[40]	1983	MVP	Plasma catecholamine level	QTc
Sniezek[41]	1992	MVP	Adrenaline excretion	Complex VAs (Lown grade ≥3)
Zuppiroli[42]	1994	MVP	Female	Complex VAs (Lown grade ≥3)*
Babuty[43]	1994	MVP	Age (older)	Complex VAs (Lown grade ≥3)
Naksuk[44]	2016	MV surgery	Age (younger)	PVC reduction post-surgery in BiMVP
Fulton[45]	2017	MVP	Female	PVCs from PM
Electrical				
Campbell[46]	1976	MVP	Inferolateral T-wave changes	VT (>100bpm for ≥3 beats) or VF
Babuty[43]	1994	MVP	Late potentials	VT (≥3 beats)
Bobkowski[47]	2002	MVP	Late potentials	VAs (Lown grade ≥1) and VT (>120bpm for ≥4 beats)
Akcay[48]	2010	MVP	QTc dispersion	VT (>120bpm for ≥3 beats)*
Imaging				
Shah[49]	1982	MVP	MR	Complex VAs (Lown grade ≥3)
Nishimura[18]	1985	MVP	Redundant leaflets	Sudden death*
Kligfield[5]	1985	MVP	MR	VAs (>1% PVC frequency or exercise induced PVCs/VT or Lown grade ≥4 complex VAs)
Sanfilippo[50]	1989	MVP	Anterior leaflet thickness MR	VAs (≥10 PVCs/hr or VT at ≥100bpm for ≥3 beats)
Zuppiroli[42]	1994	MVP	Anterior leaflet thickness	Complex VAs (Lown grade ≥3)*
Babuty[43]	1994	MVP	MR	Complex VAs (Lown grade ≥3)
Zouridakis[51]	2001	MVP	MVP degree Anterior leaflet thickness	QT dispersion*
Turker[52]	2010	MVP	Moderate-severe MR	VAs (Lown grade ≥1)*
Carmo[53]	2010	MVP	Mitral annular disjunction	Non-sustained VT (NS)
Han[54]	2010	MVP	LGE in PM	Complex VAs (Lown grade ≥4)
Akcay[48]	2010	MVP	Anterior leaflet length	VT (>120 bpm for ≥3 beats)*
Sriram[3]	2013	OHCA	BiMVP	Appropriate ICD therapies at follow-up
Basso[4]	2015	MVP	LGE	Complex VAs (Lown grade ≥4b or VF)
Nordhues[55]	2016	MVP	BiMVP	All-cause mortality
Bui[56]	2017	MVP	Myocardial T1 time	Complex VAs (Lown grade ≥3)
Fulton[45]	2017	MVP	BiMVP LGE in PM	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.

Cardiac Structural Findings

Where reported, 99% of cases described mitral leaflet redundancy, and MV annulus diameter was dilated compared with population data.[65] Anterior and posterior mitral leaflet length were also greater than otherwise expected.[66] 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[66,67] and provide further support that mitral apparatus abnormalities have a contributory role in the development of SCD.

There were 30 cases where cardiac histopathological findings were described. Among these, 12 cases reported

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.
Nishimura[18]	237*	44	142	6.2	408
Düren[19]	300	42	164	6.2	219
Zuppiroli[20]	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.

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.[4,68] 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[69] 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.[48,51.]

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.[18] Some controversy surrounds the risk of bileaflet MVP with 1 study suggesting that it was associated with appropriate implantable cardioverter-defibrillator therapies,[3] while another suggested that bileaflet MVP was associated with lower all-cause mortality based on registry data.[55]

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[18] 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,[70–74] 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

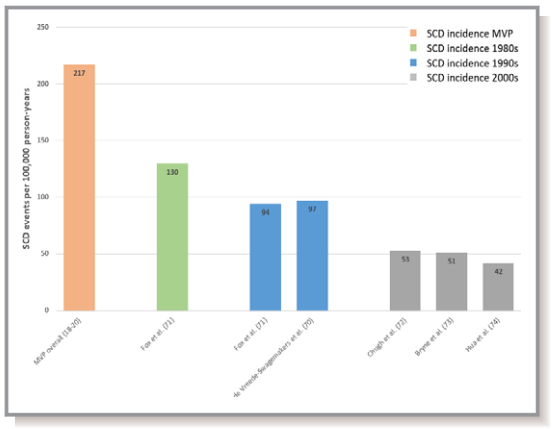

Figure 5. Sudden cardiac death (SCD) incidence in mitral valve prolapse (MVP) versus population studies.

person-years during the 1980s,[71] around the time of the 3 prospective studies.

Limitations

This is the largest systematic review of published cases of MVP and SCD or cardiac arrest. We sought to provide comprehensive insight into clinical, electrical, imaging, and histopathological characteristics. Our results highlight some significant challenges when attempting to characterize a potential high-risk MVP subtype.

The cases that describe MVP and SCD or cardiac arrest span over 50 years. Our understanding of MVP has evolved significantly over that time. Changes in clinical medicine affect the reproducibility of various diagnostic tests, especially echocardiography for the diagnosis of MVP. Information regarding clinical, electrical, imaging, and histopathological characteristics were inconsistently described and are subject to reporting and publication bias. Notably, a lack of systematic reporting regarding these characteristics likely affected their prevalence within this collection of cases.

Further work is required to validate many of the current reported predictors. The disconnect between premortem predictors and available information from SCD cases limits our ability to determine whether these factors may be important in the development of SCD and cardiac arrest.

Finally, despite all the published literature hypothesizing that SCD in MVP is caused by malignant VAs, there are only 6 cases describing autopsy-proven iMVP with documentation of cardiac arrest rhythm. Further correlations of cardiac arrest rhythm with pathological description is warranted.

Conclusions

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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Supplemental Material

Table S1. All Cases Included in Study.

Year	Author	Cases	Description
1968	Barlow[1]	1	Review of 90 patients with non-ejection systolic click and late systolic murmurs. 1 case of 39M with SCD. (iMVP)
1970	Trent[2]	1	Report of 63F with MVP and SCD. (non-iMVP)
1971	Jeresaty[3]	1	Review of 24 patients with mitral ballooning on angiography. 1 case of 62F with SCD. (iMVP)
1973	Jeresaty[4]	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	Shappell[5]	1	Report of 27F with MVP and SCD. (non-iMVP)
1974	Marshall[6]	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	Shappell[7]	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	Jeresaty[8]	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	Kleid[9]	1	Report of 38F with MVP and SCD. (iMVP)
1976	Ritchie[10]	1	Report of 56M with MVP and VF. (non-iMVP)
1976	Winkle[11]	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	Cobbs[12]	1	Report of 39F with MVP and VF. (iMVP)
1977	Mills[13]	2	Follow-up of 53 patients with MVP. 1 case of 58M with SCD. (non-iMVP) 1 case of 26F with VF. (iMVP)
1978	Davies[14]	13	Review of 90 cases of MVP at autopsy. 13 cases with MVP and SCD (12 cases iMVP and 1 case non-iMVP).
1979	Forbes[15]	1	Report of 25F with MVP and VF on anaesthesia induction. (non-iMVP)
1979	Watts[16]	1	Report of 26F with MVP and VF. (iMVP)
1980	Anderson[17]	2	Report of 2 cases (both 21F) with MVP and SCD. (both iMVP)
1980	Bennett[18]	1	Report of 15F with MVP and TDP. (iMVP)
1980	Mair[19]	3	Series of 3 cases (25F, 29F and 35F) with MVP and SCD. (all iMVP)
1980	Mautner[20]	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	Bharati[21]	1	Report of 45M with MVP and SCD. (iMVP)
1981	Salmela[22]	1	Report of 27M with MVP and SCD. (non-iMVP)
1982	Noneman[23]	1	Report of 29M with MVP and VF. (iMVP)
1982	Vesterby[24]	3	Series of 3 cases (23F, 68M, 55M) with MVP and SCD. (1 case iMVP and 2 cases non-iMVP)
1982	Virmani[25]	1	Review of 30 autopsies in joggers. 1 case of 27M with MVP and SCD. (iMVP)
1983	Bharati[26]	2	Series of 3 cases of SCD in teenagers. 2 cases (17M and 19F) with MVP. (both iMVP)

1983	Chesler[27]	14	Series of 14 cases of MVP and SCD. (non-iMVP)
1983	Conklin[28]	1	Report of 22F with MVP and VT during labor. (iMVP)
1983	Morady[29]	2	Series of 31 patients with VAs undergoing EPS. 2 patients (28F and 39F) with MVP and VF. (both iMVP)
1984	Kempf[30]	1	Series of 27 cases with SCD on ambulatory ECG monitoring. 1 case of 31F with MVP. (non-iMVP)
1984	Pocock[31]	1	Report of 24F with MVP and SCD. (non-iMVP)
1985	Andre-Fouet[32]	1	Report of 19M with MVP and SCD. (iMVP)
1985	Rosenthal[33]	5	Series of 20 patients with MVP and VAs. 5 patients with VF. (all iMVP)
1985	Sakuma[34]	1	Report of 54M with MVP, coronary vasospasm and VF. (non-iMVP)
1986	Casthely[35]	1	Report of 7M with MVP and VF during anaesthesia induction. (iMVP)
1986	Higgins[36]	1	Report of 36F with MVP and VT. (non-iMVP)
1986	Hoffman[37]	1	Report of 32F with MVP and VF. (iMVP)
1987	Broustet[38]	1	Report of 28F with MVP and SCD. (non-iMVP)
1988	Goldhammer[39]	1	Report of 46M with MVP and asystole. (iMVP)
1988	Scala-Barnett[40]	4	Series of 4 cases of MVP and SCD. (2 cases iMVP and 2 cases non-iMVP)
1988	Strasberg[41]	1	Report of 27M with MVP and VF. (iMVP)
1988	Vlay[42]	1	Report of 24F with MVP and SCD. (iMVP)
1989	Abraham[43]	1	Report of 33F with MVP and asystole during anesthesia. (iMVP)
1989	Topaz[44]	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[45]	2	Series of 6 cases with VF. 2 cases (14F and 35M) with MVP. (both iMVP)
1990	Boudoulas[46]	9	Series of 9 patients with MVP and cardiac arrest. (8 cases iMVP and 1 case non-iMVP)
1990	Corrado[47]	2	Series of 22 athletes with SCD. 2 cases (17F and 23M) with MVP. (both iMVP)
1990	Nelson-Piercy[48]	1	Report of 67M with MVP, anomalous RCA and VF. (non-iMVP)
1990	Sadaniantz[49]	0	Report of 27M with MVP and SCD (repeat case).
1991	Dollar[50]	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[51]	2	Series of 7 patients with MVP and VAs. 2 cases (28M and 45M) with SCD. (both non-iMVP)
1995	Martini[52]	1	Report of 42F with MVP, ARVC and SCD. (non-iMVP)
1997	Moritz[53]	1	Report of 6F with MVP and VF during anaesthesia induction. (iMVP)
1997	Wilde[54]	1	Report of 34M with MVP and VF. (iMVP)
1998	Ronneberger[55]	1	Report of 8M with MVP and SCD. (non-iMVP)
2000	Nolte[56]	1	Report of 26F with MVP, diffuse CAD due to PXE and SCD. (non-iMVP)
2001	Cannon[57]	1	Report of 25F with MVP and SCD. (iMVP)
2003	Abello[58]	1	Report of 28F with MVP and VF during pregnancy. (iMVP)
2003	Ciancarmerla[59]	1	Report of 49M with MVP and SCD. (iMVP)
2003	Nishida[60]	1	Series of 3 cases of SCD and alcohol abuse. 1 case of 37F with MVP. (non-iMVP)
2004	Chirachariyavej[61]	1	Report of 38M with MVP and SCD. (iMVP)
2004	Frassati[62]	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[63]	1	Report of 21F with MVP and VF during anaesthesia reversal. (iMVP)
2007	Anders[64]	6	Series of 6 cases of MVP and SCD. (iMVP)
2007	Kesavan[65]	1	Report of 75F with MVP, CAD and VT. (non-iMVP)

2007	Knackstedt[66]	1	Report of a 54M with MVP and VF. (iMVP)
2010	Franchitto[67]	1	Report of 25F with MVP and SCD. (iMVP)
2010	Oliviera[68]	1	Report of 57F with MVP and SCD (also heart failure on trastuzumab). (non-iMVP)
2011	Rordorf[69]	1	Report of 32F with MVP and VF (also DCM post-partum with PJRT). (non-iMVP)
2014	Abbadi[70]	1	Report of 26F with MVP and VF. (iMVP)
2014	Rajani[71]	1	Report of 27F with MVP and TDP. (iMVP)
2015	Lin[72]	1	Report of 30F with MVP and VT during pregnancy. (iMVP)
2015	Desai[73]	1	Report of 55M with MVP and SCD. (iMVP)
2015	Fais[74]	1	Report of 47F with MVP and SCD. (iMVP)
2016	Ahmed[75]	1	Report of 45M with MVP and VT. (iMVP)
2016	Vaidya[76]	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[77]	1	Report of 28F with MVP and VF. (iMVP)
2017	Martini[78]	1	Report of 58M with MVP and VF (also Brugada ECG). (non-iMVP)
2017	Saha[79]	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									
	Gaffney[80]	1979	Prospective Cohort	19 (100)*	19-46	MVP	M-mode or auscultation	Higher heart rate Lower cardiac index	Clinical severity (combination of symptoms and VAs)
	Puddu[81]	1983	Prospective Cohort	15 (67)	NR	MVP	Echo (NS)	Plasma catecholamine level	QTc (supine)
	Sniezek[82]	1992	Prospective Cohort	53 (58)	19-52	MVP	Echo (LAX)	Adrenaline excretion	Complex VAs (Lown grade ≥3)
	Zuppiroli[83]	1994	Prospective Cohort	119 (47)	12-78	MVP	Echo (LAX)	Female	Complex VAs (Lown grade ≥3)†
	Babuty[84]	1994	Prospective Cohort	58 (50)	NR	MVP	Echo (LAX or A4C)	Age (older)	Complex VAs (Lown grade ≥3
	Naksuk[85]	2016	Retrospective Cohort	32 (53)	NR	BiMVP with MV surgery	N/A	Age (younger)	Reduction in PVCs post MVR in BiMVP
	Fulton[86]	2017	Retrospective Cohort	18 (61)	NR	MVP	Echo (LAX)	Female	PVCs from PM
Electrical									
	Campbell[87]	1976	Prospective Cohort	20 (65)	12-61	MVP	Auscultation	Inferolateral T-wave changes	VT (>100bpm for 3 beats) or VF
	Babuty[84]	1994	Prospective Cohort	58 (50)	NR	MVP	Echo (LAX or A4C)	Late potentials	Non-sustained VT (≥3 beats and <30 seconds)
	Bobkowski[88]	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)
	Akcay[89]	2010	Retrospective Case control	60 (72)	NR	MVP (with vs without VT)	Echo (NS)	QTc dispersion	VT (>120bpm for ≥3 beats)†
Imaging									
	Shah[90]	1982	Retrospective Cohort	88 (60)	12-84	MVP	M-mode	MR	Complex VAs (Lown grade ≥3)
	Nishimura[91]	1985	Prospective Cohort	237 (60)	10-69	MVP	Echo (NS)	Redundant leaflets	Sudden death†
	Kligfield[92]	1985	Prospective Cohort	80 (65)*	19-72	MVP	Echo (NS)	MR	>1% PVC frequency Exercise induced PVCs and VT

									Complex VAs (Lown grade 4)
	Sanfilippo[93]	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[83]	1994	Prospective Cohort	119 (47)	12-78	MVP	Echo (LAX)	Anterior leaflet thickness	Complex VAs (Lown grade ≥3)†
	Babuty[84]	1994	Prospective Cohort	58 (50)	NR	MVP	Echo (LAX or A4C)	MR	Complex VAs (Lown grade ≥3) on Holter and exercise test
	Zouridakis[94]	2001	Prospective Cohort	89 (71)	NR	MVP	Echo (LAX or A4C)	MVP degree Anterior leaflet thickness	QT dispersion†
	Turker[95]	2010	Prospective Cohort	58 (55)	16-68	MVP	Echo (LAX)	Moderate-severe MR	VAs (Lown grade ≥1)†
	Carmo[96]	2010	Retrospective Cohort	38 (47)	NR	MVP	Echo (LAX)	Mitral annular disjunction	Non-sustained VT
	Han[97]	2010	Retrospective Cohort	16 (44)*	NR	MVP	Echo (NS)	LGE in PM	Complex VAs (Lown grade ≥4)
	Akcay[89]	2010	Retrospective Case control	60 (72)	NR	MVP (with vs without VT)	Echo (NS)	Anterior leaflet length	VT (>120bpm for ≥3 beats)†
	Sriram[98]	2013	Retrospective Cohort	24 (67)	5-60	Idiopathic OHCA	Echo (NS)	BiMVP	Appropriate ICD therapies at follow-up
	Basso[99]	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[100]	2016	Retrospective Case control	11338 (43)*	NR	BiMVP vs SiMVP	Echo (NS)	BiMVP	All-cause mortality (lower in BiMVP)
	Bui[101]	2017	Retrospective Cohort	32 (34)*	NR	MVP	CMR	Myocardial T1 time	Complex VAs (Lown grade ≥3)
	Fulton[86]	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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