Malignant Bileaflet Mitral Valve Prolapse Syndrome in Patients With Otherwise Idiopathic Out-of-Hospital Cardiac Arrest

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Objectives   The aim of this study was to investigate the prevalence of mitral valve prolapse (MVP) and its association with ventricular arrhythmias in a cohort with "unexplained" out-of-hospital cardiac arrest.

Background   Ventricular arrhythmias are an important cause of sudden unexpected death in the young. The role of MVP in sudden unexpected death remains controversial.

Methods   Of 1,200 patients evaluated between July 2000 and December 2009 in the Mayo Clinic's Long QT Syndrome/Genetic Heart Rhythm Clinic, all 24 (16 women, median age 33.5 years) with idiopathic out-of-hospital cardiac arrest (i.e., negative for ischemia, cardiomyopathy, and channelopathy) were reviewed.

Results   All 24 patients had implantable cardioverter-defibrillators (ICDs). Out-of-hospital cardiac arrest was the sentinel event in 22 (92%). Bileaflet MVP was found in 10 (42%). Compared with patients with normal mitral valves, patients with bileaflet MVP: 1) were over-represented by women (9 of 10 [90%] vs. 7 of 14 [50%], p = 0.04); 2) had a higher prevalence of biphasic or inverted T waves (7 of 9 [77.8%] vs. 4 of 14 [29%], p = 0.04); and 3) on Holter interrogation had higher prevalence of ventricular bigeminy (9 of 9 [100%] vs. 1 of 10 [10%], p < 0.0001), ventricular tachycardia (7 of 9 [78%] vs. 1 of 10 [10%], p = 0.006), and premature ventricular contractions originating from the outflow tract alternating with the papillary muscle or fascicular region (7 of 9 [78%] vs. 2 of 10 [20%], p = 0.02). Over a median 1.8 years (range: 0.1 to 11.9 years) from ICD placement, 13 of 24 patients (54%) received appropriate ventricular fibrillation–terminating ICD shocks. Only bileaflet MVP was associated with ventricular fibrillation recurrences requiring ICD therapy on follow-up (logistic regression odds ratio: 7.2; 95% confidence interval: 1.1 to 48; p = 0.028).

Conclusions   The authors describe a "malignant" subset of patients with MVP who experienced life-threatening ventricular arrhythmias. This phenotype is characterized by bileaflet MVP, female sex, and frequent complex ventricular ectopic activity, including premature ventricular contractions of the outflow tract alternating with papillary muscle or fascicular origin.   (J Am Coll Cardiol 2013;62:222–30) © 2013 by the American College of Cardiology Foundation

Sudden cardiac death (SCD) affects 300,000 to 400,000 patients in the United States, and in the majority of cases, a known cause is identified. However, there is a distinct subset

of patients who experience out-of-hospital cardiac arrest (OHCA) but lack clinical evidence of either ischemic cardiomyopathy or nonischemic structural or electrical cardiomyopathies. Identifying this subset of patients with unexplained OHCA is challenging (1).

In this context, the role of mitral valve prolapse (MVP) in sudden unexpected death (SUD) and OHCA remains controversial. MVP has been reported as the only cardiac abnormality at autopsy in certain apparently healthy subjects who died suddenly or were resuscitated successfully from OHCA (2–4). SUD in patients with MVP may stem from ventricular fibrillation (VF) (4,5), but the exact etiology and risk predictors of SUD in MVP are elusive (6). Although single-leaflet MVP is present in 2.4% of the general

population (7), the reported annual rate of SUD in patients with MVP is exceedingly low (3,4). Thus, identifying the small subset of patients with MVP who may be at increased risk for sudden death is difficult. There are case reports and small case series linking SUD and OHCA to MVP, especially in younger female patients with complex ventricular ectopic activity (2,6,8–19).

The prevalence of MVP and ventricular ectopic activity in patients with unexplained OHCA is unclear. Furthermore, there are only a few small reports comparing patients with OHCA with and without mitral valve abnormalities. We report on the prevalence of MVP in a cohort of patients with unexplained OHCA and compare the clinical phenotype of patients with and without MVP.

Methods

Study cohort and study design. For this institutional review board–approved study, 2 investigators (C.S.S., M.E.F.) retrospectively reviewed the electronic medical records of 1,200 consecutive patients seen in the Mayo Clinic's Long QT Syndrome/Genetic Heart Rhythm Clinic between July 2000 and December 2009. All patients who had histories of unexplained OHCA with documented cardiovascular collapse from ventricular tachycardia (VT) or VF that required defibrillation to restore sinus rhythm were included. In all patients, the etiology of OHCA remained elusive after detailed review of histories, previous medical records, and additional investigations. Patients were excluded if: 1) VF or VT was not documented; 2) VT was present without cardiovascular collapse; 3) family history was positive for channelopathy, cardiomyopathy, SUD, or OHCA; or 4) OHCA was attributable to a cardiac channelopathy, Wolff-Parkinson-White syndrome, cardiomyopathy (including arrhythmogenic right ventricular cardiomyopathy), coronary artery disease, congenital coronary artery anomalies, electrolyte derangements, or drugs or medications or was preceded by known depressed left ventricular ejection fraction. None of the included patients had any noncardiac syndromic features or documented family histories of MVP.

Clinical testing. Besides the review of the outside medical records after OHCA, all patients underwent standard investigations, including transthoracic echocardiography (20) and 12-lead electrocardiography. All patients had normal resting corrected QT intervals, and none had electrocardiographic features suggestive of Brugada syndrome or arrhythmogenic right ventricular dysplasia. Most patients underwent additional testing on a discretionary basis, guided by the circumstances of the OHCA and depending on the extent of the primary evaluation, including 24- or 48-h Holter recording, genetic testing for channelopathies, provocative intravenous procainamide or epinephrine testing, exercise stress testing, cardiac computed tomography, cardiac magnetic resonance imaging, electrophysiology study, or coronary angiography. Overall, 20 patients (83%) had genetic testing for channelopathies ordered during the course of their primary

evaluations or performed as part of their Mayo Clinic evaluations (Table 1). Seventeen patients were tested for mutations in the most common long-QT syndrome (LQTS)–associated genes by either the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory or a commercially available LQTS test (21). LQTS genetic testing was performed when a diagnosis of LQTS was considered by the referring physicians. After expert review at our institution, LQTS diagnosis was considered unlikely in this cohort of patients on the basis of detailed clinical histories; normal corrected QT intervals during the resting state, exercise, and recovery; negative results on epinephrine testing when indicated; and negative genetic test results (22,23).

Genetic testing done at the discretion of the referring physicians specifically for deleterious mutations within cardiac sodium channel and/or ryanodine receptor gene for suspected catecholaminergic polymorphic VT yielded negative results in 9 patients.

Significant coronary artery disease and presence of anomalous coronary arteries were excluded on coronary angiography and/or noninvasive imaging (computed tomography or cardiac magnetic resonance). Cardiomyopathy was excluded in part by expert review of cardiac imaging studies showing preserved left ventricular ejection fraction (>50%) and normal ventricular wall thickness.

Blinded to the specific clinical histories and echocardiographic findings, we reviewed the 12-lead electrocardiograms of all OHCA survivors. Ambulatory (24- or 48-h) Holter recordings were available for the majority of patients and were reviewed for density and site of premature ventricular contraction (PVC) origin, type of PVC (singlets, couplets, or triplets), and presence of VT. Complex ventricular ectopic activity was defined as the presence of PVC couplets, ventricular bigeminy, nonsustained VT, or sustained VT. All available 12-lead electrocardiograms were analyzed by 2 investigators (C.S.S., F.F.S.) for age-inappropriate ST-T-segment repolarization changes, including T-wave inversion or biphasic T waves, ST-segment depression or elevation, and J waves.

Blinded to the details of the individual clinical histories as well as the results of echocardiography and other tests (but unblinded to the diagnosis of OHCA), a single investigator (F.C.) retrospectively reviewed all echocardiograms performed and confirmed or revised the echocardiographic findings. The diagnosis of MVP and grading of mitral regurgitation from 1 (trivial) to 4 (severe) were according to standard guidelines. MVP was defined as systolic displacement (>2 mm) of 1 or both mitral valve leaflets into the left atrium beyond the plane of the mitral annulus in a

Abbreviations and Acronyms

LQTS = long QT syndrome

MVP = mitral valve prolapse

OHCA = out-of-hospital cardiac arrest

PVC = premature ventricular contraction

SCD = sudden cardiac death

SUD = sudden unexpected death

VF = ventricular fibrillation

VT = ventricular tachycardia

Table 1	Demographics of OHCA Cohort (n = 24)			
Demographic	**OHCA Cohort**	**Bileaflet MVP**	**No MVP**	**p Value***
n	24/1,200 (2%)‖	10/24 (42%)	14/24 (58%)	—
Age at sentinel event (yrs)	32 ± 15 (median 33.5; range: 5–60)	33 ± 16 (median 34.7; range: 5–60)	32 ± 14 (median 29.4; range: 14–51)	0.84†
Women	16 (67%)	9/10 (90%)	7/14 (50%)	0.04
QTc interval (ms)	430 ± 25	434 ± 22	428 ± 28	0.52§
Cardiac arrest as sentinel event	22/24 (92%)	8/10 (80%)	14/14 (100%)	0.16‡
Activity at time of cardiac arrest	17 wakeful rest, 7 acute emotional or physical stress, 0 sleep	8 wakeful rest, 2 acute emotional or physical stress, 0 sleep	9 wakeful rest, 5 acute emotional or physical stress, 0 sleep	0.65‡
ICD implantation	24/24 (100%)	10/10 (100%)	14/14 (100%)	—
Follow-up after ICD placement (yrs)	3.8 ± 4.1 (median 1.8; range: 0.1–11.9)	7.2 ± 3.5 (median 7.3; range: 2.4–11.9)	1.4 – 2.5 (median 0.7; range: 0.1–5.9)	0.0003†
Patients with appropriate ICD therapies	13/24 (54%)	8/10 (80%)	5/14 (36%)	0.04‡
Genetic testing for channelopathies¶	20/24 (83%)	9/10 (90%)	11/14 (79%)	0.61‡
LQTS types 1, 2, and 3	17/24 (71%)	9/10 (90%)	8/14 (57%)	0.18‡
Isolated testing for *SCN5A* gene mutation	2/24 (8%)	0/10 (0%)	2/14 (14%)	0.49‡
RYR2 gene mutation test	7/24 (29%)	2/10 (20%)	5/14 (36%)	0.65‡
LVEF at presentation	60.3 ± 1.6	60.5 ± 3.1	60.2 ± 1.7	0.92§
No. with abnormal RV size or function	0	0	0	—
RVSP by Doppler echocardiographic estimation (mm Hg)	28.7 ± 5.6 (range: 19–41)	28.6 ± 6.0 (range: 23–41)	28.7 ± 5.6 (range: 19–41)	0.95§
Mitral valve regurgitation	18/24 (75%)	10/10 (70%)	8/14 (57%)	0.02‡
Mild	13/24 (54%)	5/10 (50%)	8/14 (57%)	1.00‡
Moderate	4/24 (17%)	4/10 (40%)	0/14 (0%)	0.02‡
Severe	1/24 (4%)	1/10 (10%)	0/14 (0%)	0.42‡
ST-T repolarization changes#	16/23 (70%)	8/9 (89%)	8/14 (57%)	0.17‡
Inverted/biphasic T wave	12/23 (52%)	7/9 (78%)	4/14 (29%)	0.04‡
J wave	5/23 (22%)	1/9 (11%)	4/14 (29%)	0.62‡
ST-segment depression > 1 mm	1/23 (4%)	1/9 (11%)	0/14 (0%)	0.39‡

Values are n/N (%), mean ± SD, or n (%). *Comparing bileaflet MVP with no MVP. †Wilcoxon rank sum test. ‡Fisher exact test. §Student *t* test. ‖Percent of all patients presenting to the Long QT Syndrome/Genetic Heart Rhythm Clinic. ¶Genetic test results for channelopathies were negative in those who were tested. #One patient with bileaflet MVP had paced rhythm and was excluded from analysis of repolarization changes.

ICD = implantable cardioverter defibrillator; LQTS = long-QT syndrome; LVEF = left ventricular ejection fraction; MVP = mitral valve prolapse; OHCA = out-of-hospital cardiac arrest; QTc = corrected QT; RVSP = right ventricular systolic pressure; *RYR2* = ryanodine receptor type 2; *SCN5A* = sodium channel.

parasternal long-axis view on transthoracic echocardiography, along with thickened (maximal leaflet thickness >5 mm) or myxomatous leaflets during diastole. When advanced quantitative assessment of mitral regurgitation was not available, its degree was assessed on the basis of visual estimation of the regurgitant jet (7,24). Other echocardiographic findings were noted as appropriate. Family echocardiographic screening was not performed in this cohort of patients.

Statistical analysis. JMP version 9.0.1 (SAS Institute Inc., Cary, North Carolina) was used for data analysis. The Shapiro-Wilk goodness-of-fit test was used to determine the distribution of continuous data. Normally distributed data were compared using Student *t* tests. Data not normally distributed were compared using Wilcoxon rank sum tests. Fisher exact tests were used to compare frequency distributions between categorical groups. Statistical significance was taken at a p value ≤0.05.

Results

Patient demographics. Twenty-four of the 1,200 patients (2.0%) had "unexplained" OHCA (16 women [67%]; mean age 32 ± 15 years; median 33.5 years; range: 5 to 61 years;

Table 1). OHCA was the sentinel event in 22 patients (92%). All patients had normal corrected QT intervals (mean corrected QT interval 430 ± 25 ms), and the results of genetic testing for LQTS were negative in the 17 patients tested. Catecholaminergic polymorphic VT genetic test results were negative in the 9 patients tested for that condition, and 16 of the 24 patients had exercise stress test results that were negative for any exercise-induced ventricular ectopic activity that might suggest catecholaminergic polymorphic VT. Ejection fractions were preserved in our patients (mean left ventricular ejection fraction 60.3 ± 1.6%) and were not significantly different between those with and without MVP.

Echocardiography. Bileaflet MVP was present in 10 of 24 patients (42%), and mitral regurgitation was noted to be mild in 5, moderate in 4, and severe in 1 (Fig. 1A, Table 1). Of the remaining patients (58%), none had single-leaflet MVP, and mitral regurgitation was either mild (n = 8) or absent (n = 6). No additional significant echocardiographic anomalies were detected. Of those with bileaflet MVP, 9 of 10 (90%) were female, compared with 7 of 14 (50%) without MVP (p = 0.04). Mitral valves were morphologically normal in all patients without MVP.
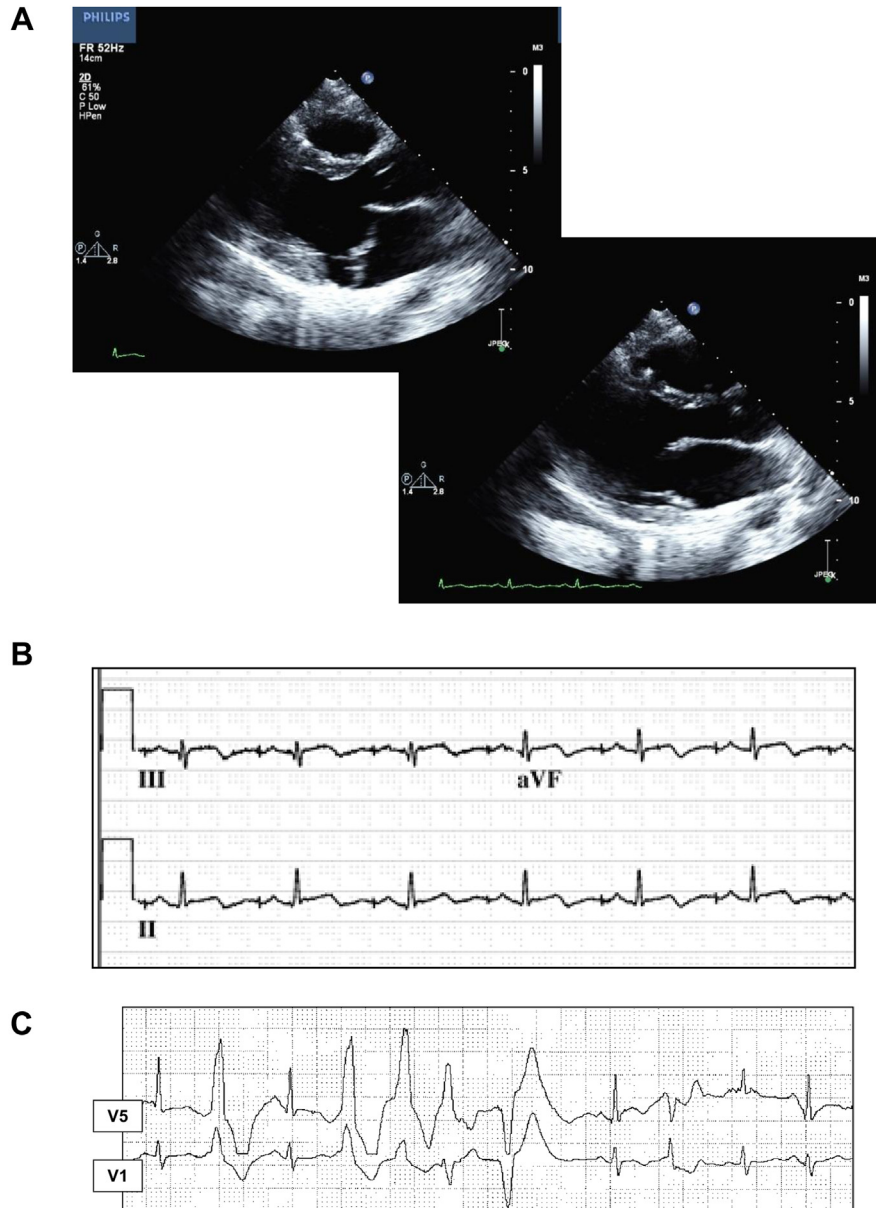
Figure 1   Triad of Sudden Death Pre-Disposing Bileaflet MVP Syndrome

Systolic and diastolic parasternal long-axis view of the heart demonstrating **(A)** bileaflet mitral valve thickening and mitral valve prolapse (MVP), **(B)** T-wave changes in the inferior leads, and **(C)** frequent ventricular ectopic activity with premature ventricular beats of outflow tract origin alternating with papillary muscle or fascicular origin.

Because OHCA was the sentinel event in most patients, it is not surprising that most of these patients did not undergo echocardiography before their sentinel events. One patient had echocardiographically documented bileaflet MVP 51 months before the sentinel event. Another patient with bileaflet MVP underwent echocardiography 5 months before the sentinel event, but the results were unavailable for review. **ST-T repolarization changes.** Age-inappropriate ST-T repolarization electrocardiographic changes were observed in 16 of 24 survivors (67%) of OHCA (Table 1). One

patient with bileaflet MVP had paced ventricular rhythm and was excluded from analysis of repolarization changes. T-wave abnormalities (inverted or biphasic T waves) were more frequent in those with bileaflet MVP (7 of 9 [77.8%]) compared with those without MVP (4 of 14 [29%]) (p = 0.04) (Fig. 1B). The abnormalities were usually noted in the inferior leads. However, the frequency of J waves or ST-segment depression >1 mm was not significantly different between the 2 groups. ST-segment elevation and pathological Q waves were absent in all patients.

Holter results. The prevalence of ventricular ectopic activity in the OHCA survivor cohort is summarized in Table 2. Ambulatory monitoring results were available for 19 of 24 of the OHCA survivors (79%), including 9 of the 10 with bileaflet MVP and 10 of the 14 without MVP. Patients with bileaflet MVP had a significantly higher burden of ventricular ectopic activity (median 67 vs. 23 PVCs/h, p = 0.002) and more frequent ventricular bigeminy (9 of 9 [100%] vs. 1 of 10 [10%], p < 0.0001) and nonsustained or sustained VT (7 of 9 [78%] vs. 1 of 10 [10%], p = 0.006) compared with patients without MVP (Figs. 2A and 2B, Table 2). In 9 patients (7 with bileaflet MVP), we noted PVC configurations of outflow tract origin alternating with papillary muscle or fascicular origin (Fig. 1C). The outflow tract PVCs always originated from the left ventricular outflow tract and in some cases arose from both the left and right ventricular outflow tracts. OHCA survivors with bileaflet MVP more commonly demonstrated such alternating PVC configurations than those without MVP (7 of 9 [78%] vs. 2 of 10 [20%], logistic regression odds ratio: 14; 95% confidence interval: 1.5 to 127; p = 0.02) (Table 2, Fig. 2C).

Electrophysiological study. Three patients with bileaflet MVP underwent invasive electrophysiological assessment of ventricular arrhythmias at our institution. Intracardiac echocardiography, pace mapping, and activation mapping were used. Frequent PVCs of multiple configurations correlating with clinically documented arrhythmias were noted in all patients. The earliest site of origin was mapped to the tips, body, or bases of either the anterior or posterior papillary muscles. At these sites, fascicular signals preceded the local ventricular electrogram during ventricular ectopic activity or tachycardia. In 1 of these patients, there were markedly abnormal regions of slowed conduction in the surrounding myocardium. Two of these patients had PVCs or VT arising additionally from the left ventricular outflow tract and 1 from the septal aspect of the mitral annulus.

Follow-up. All survivors had implantable cardioverter-defibrillators placed after their OHCA. After a median 1.8 years (range: 0.1 to 11.9 years) of follow-up, 13 of 24 (54%; 10 women; median age at diagnosis 39 years; range: 5 to 51 years), patients had received appropriate VF-terminating implantable cardioverter-defibrillator therapy, whereas 11 of 24 (46%; 6 women; median age at diagnosis 22 years; range: 14 to 61 years) patients have not yet had VF recurrence. Only bileaflet MVP was associated with VF recurrences requiring implantable cardioverter-defibrillator therapy on follow-up (logistic regression odds ratio: 7.2; 95% confidence interval: 1.1 to 48; p = 0.028) (Table 3).

Discussion

We observed an increased prevalence of female gender and bileaflet MVP in a cohort of young patients successfully resuscitated from idiopathic OHCA. More than 40% of these OHCA survivors had bileaflet MVP, compared with the 2.4% population prevalence of MVP for which the majority is single-leaflet prolapse (7,25). Ninety percent (9 of 10) of those with bileaflet MVP in this study were women. Compared with the estimated 13% to 17% prevalence of MVP in the general female population aged 20 to 39 years (26), more than half (9 of 16 [56%]) of the young female OHCA survivors had MVP. Again, the MVP detected was bileaflet in all patients, whereas the vast majority of MVP in the general population and female-specific prevalence estimates involves single-leaflet MVP.
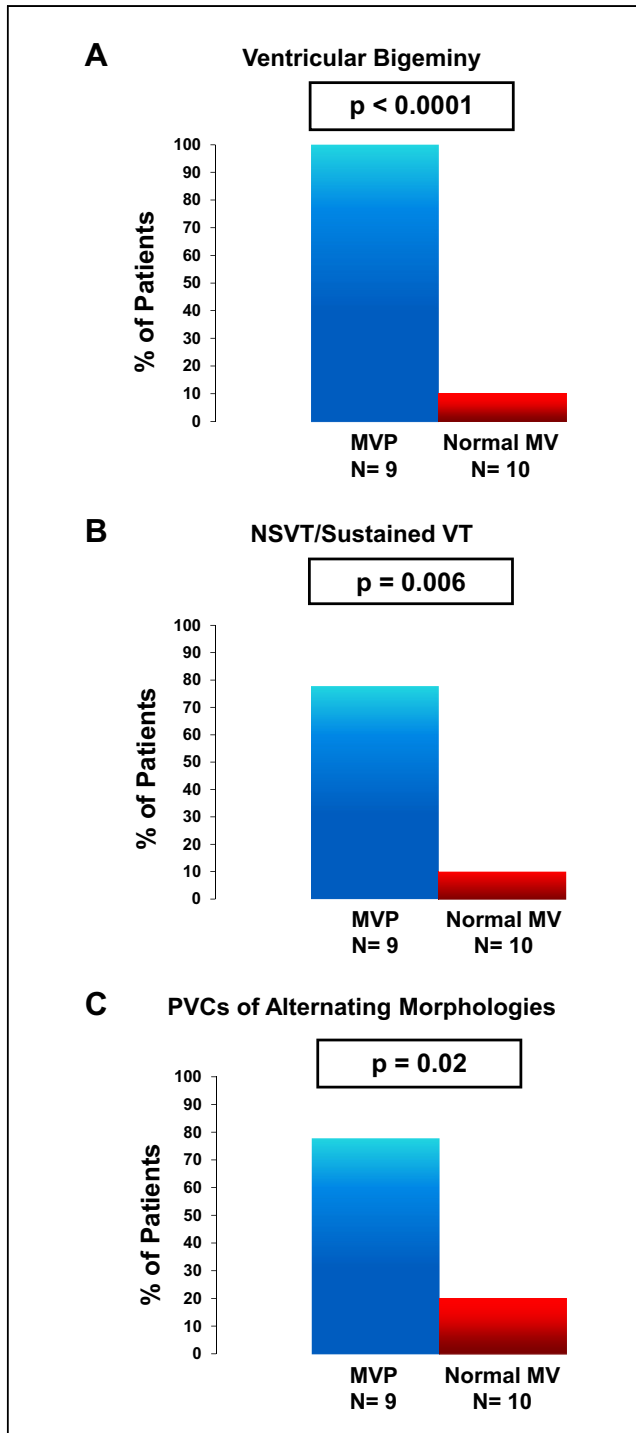
In addition, the hourly PVC burden among our OHCA survivors (136 ± 208; range: 0.8 to 690) was also higher

Table 2	Relationship of Ventricular Ectopic Activity With Bileaflet MVP in OHCA Survivors With Ambulatory Holter Monitoring (n = 19)		
Variable	**Bileaflet MVP (n = 9)**	**No MVP (n = 10)**	**p Value***
PVCs	9/9 (100%)	7/7 (100%)	—
Ventricular ectopic activity burden (PVCs/h)	67 (35–690)	23 (1–258)	0.002†
NSVT/sustained VT	7/9 (78%)	1/10 (10%)	0.006‡
Polymorphic VT	4/9 (44%)	1/10 (10%)	0.14‡
Episodes of NSVT per h	0.3 (0–7.4)	0 (0–0.1)	0.003†
Bigeminal PVCs	9/9 (100%)	1/10 (10%)	<0.0001†
Bigeminal PVCs per h	0.4 (0.05–67.6)	0 (0–0.3)	0.0003†
Ventricular couplets per h	3.0 (0.3–26.5)	0.04 (0–1.6)	0.0015†
Alternating papillary muscle/outflow tract PVCs§	7/9 (78%)	2/10 (20%)	0.02‡
Other sites of PVC origin			
RV free wall	1/9 (11%)	1/10 (10%)	
RV midcavity	2/9 (22%)	1/10 (10%)	
LV midcavity	2/9 (22%)	1/10 (10%)	
Fascicle/papillary muscle alone	0/9 (0%)	1/10 (10%)	
Multiform PVCs	1/9 (11%)	0/10 (0%)	

Values are n/N (%) or median (range). *Comparing bileaflet MVP with no MVP. †Wilcoxon rank sum test. ‡Fisher exact test. §PVCs of alternating morphologies: originating from outflow tract (RV outflow tract alone, n = 0; LV outflow tract alone, n = 4; or RV and LV outflow tracts, n = 5) and papillary muscle or fascicle (n = 9).

LV = left ventricular; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular contraction; RV = right ventricular; VT = ventricular tachycardia; other abbreviations as in Table 1.

A Ventricular Bigeminy

p < 0.0001

% of Patients

MVP
N= 9

Normal MV
N= 10

B NSVT/Sustained VT

p = 0.006

% of Patients

MVP
N= 9

Normal MV
N= 10

C PVCs of Alternating Morphologies

p = 0.02

% of Patients

MVP
N= 9

Normal MV
N= 10

Figure 2   **Ventricular Ectopic Activity and Bileaflet MVP**

(A) Comparison of the burden of ventricular ectopic activity between patients with bileaflet mitral valve (MV) prolapse (MVP) and those with normal MVs. **(B)** Prevalence of nonsustained ventricular tachycardia (NSVT) or sustained ventricular tachycardia (VT) between patients with bileaflet MVP and those with normal MVs. **(C)** Frequency of premature ventricular contractions (PVCs) of alternating configurations (outflow tract alternating with papillary muscle or fascicular region) between those 2 groups.

Table 3   **Association of Patient Characteristics, Ventricular Ectopic Activity, and Bileaflet MVP With Appropriate ICD Therapies on Follow-Up**

Variable	Appropriate ICD Therapies (n = 13)	No Appropriate ICD Therapies (n = 11)	p Value*
Age at sentinel event (yrs)	39 (5–51)	22 (14–61)	0.30†
Women	10/13 (77%)	6/11 (55%)	0.39‡
QTc interval (ms)	435 ± 19	425 ± 31	0.38§
Ventricular ectopic activity burden (PVCs/hr)	43.2 (9.7–690.3)	27.2 (0.8–258.3)	0.17†
NSVT/sustained VT	7/13 (54%)	1/6 (17%)	0.18‡
Polymorphic VT	5/13 (38%)	0/6 (0%)	0.13‡
Episodes of NSVT per hour	0.1 (0–7.4)	0 (0–0.05)	0.088†
Bigeminal PVCs	8/13 (62%)	2/6 (33%)	0.35‡
Bigeminal PVCs per hour	0.08 (0–67.6)	0 (0–0.9)	0.33†
Ventricular couplets per hour	1.1 (0–26.5)	0.1 (0–1.6)	0.10†
Alternating papillary muscle/outflow tract PVCs	6/13 (46%)	3/6 (50%)	1.00‡
Bileaflet MVP	8/13 (62%)	2/11 (18%)	0.047‡

Values are median (range), n/N (%), or mean ± SD. *Comparing bileaflet MVP with no MVP. †Wilcoxon rank sum test. ‡Fisher exact test. §Student *t* test.
   Abbreviations as in Tables 1 and 2.

than in the general population (mean 0.38 PVCs/h, average <5 PVCs/h) (27). We noted an increased frequency of complex ventricular ectopic activity including PVC configurations of the outflow tract alternating with papillary muscle or fascicular origin in OHCA survivors, specifically patients with bileaflet MVP. Biphasic or inverted T waves on electrocardiography were more frequent in our survivors with bileaflet MVP (70%) compared with those without MVP (29%). Our findings suggest that there may be a collective sudden death–pre-disposing syndrome or phenotype characterized in young women with bileaflet MVP, biphasic or inverted inferior T waves, and complex ventricular ectopic activity with alternating outflow tract and papillary muscle or fascicular configurations (Fig. 1).

Previous published reports support our findings. In a small study of only 6 patients with OHCA diagnosed with idiopathic VF, MVP was reported in 2 patients (33.3%) (28). MVP was also noted in 7 of 28 (25%) (29) and 12 of 35 (34.3%) (30) patients with idiopathic VT in 2 separate case series. These studies, however, were limited by the lack of documentation of the exact mitral valve abnormalities, and patients with channelopathies, cardiomyopathies, or ischemia were not necessarily excluded.

When comparing our subset with OHCA and bileaflet MVP with reported cases of SUD (Table 4) or OHCA or malignant ventricular arrhythmias (Table 5) linked to MVP, we note several important similarities. The reported patients were similarly relatively young, more often female (63.2%

Table 4 **Summary of SCDs Linked to MVP Reported in the English Language**

SCDs	Age Range (yrs)	Women	Bileaflet MVP	Complex Ventricular Ectopic Activity	ST-T Repolarization Changes on ECG	Mild or Greater MR	Ref. #
25	9–64	11/16 (68.8%)	7/10 (70%)	—	9/10 (90%)	—	(8,42)
4	29–64	3/4 (75%)	—	—	—	—	(10)
14	14–59 (27 ± 11)	11/14 (78.6%)	11/14 (78.6%)	—	2/7 (28.6%)	—	(38)
17	17–45	12/17 (70.6%)	—	4/13 (30.8%)	6/11 (54.5%)	—	(11)
6	31–70	2/6 (33.3%)	—	—	—	—	(3)
1	—	—	—	—	—	1/1 (100%)	(40)
3	27–70	1/3 (33.3%)	—	—	—	—	(4)
4	26–40	4/4 (100%)	3/4 (75%)	3/4 (75%)	—	—	(13)
15	39 ± 17	10/15 (67%)	—	—	—	1/15 (7%)	(14)
6	—	—	—	—	—	6/6 (100%)	(43)
27	37 ± 10	14/27 (51.9%)	—	—	—	—	(15)
2	28–44	0/2 (0%)	—	—	2/2 (100%)	—	(2)
17	≤35	12/17 (70.6%)	—	—	—	Uncommon	(16,17)
6	17–34	6/6 (100%)			—	—	(6)
6*	8–38	4/5 (80%)	1/1 (100%)	1/1 (100%)	—	—	(9,12,18,19,44)
Total = 153	8–70	91/144 (63.2%)	22/29 (75.9%)	8/18 (44.4%)	19/30 (63.3%)	8/22 (36.4%)	

Values are mean ± SD or n/N (%). Studies are ordered chronologically by date of publication. *Individual case reports of sudden unexplained death (n ≤ 2) linked to MVP are grouped together and presented at the end of the table.

ECG = electrocardiography; MR = mitral regurgitation; MVP = mitral valve prolapse; SCD = sudden cardiac death; — = data were either not obtained or not provided in the primary report.

among patients with SUD, 72.8% among those with OHCA or malignant ventricular arrhythmia), and bileaflet MVP was common (75.9%) in patients with SUD whenever the type of prolapse was documented explicitly. In addition, at least mild mitral regurgitation, complex ventricular ectopic activity, and inferolateral repolarization abnormalities on electrocardiography (Tables 4 and 5) were present in similar frequency to our OHCA cohort. However, much of this information as well as ventricular ectopic activity burden and details on diagnosing and excluding channelopathies, cardiomyopathies, and ischemia were not uniformly reported.

In our cohort, PVCs were universal among OHCA survivors whether or not MVP was present. Given the similar high frequency of PVCs in an MVP population (58% to 89%), healthy controls, or in this cohort, the presence of PVCs alone has little prognostic value (31–33). However, OHCA survivors with bileaflet MVP had a higher PVC burden compared with those without MVP. Complex ventricular ectopic activity (specifically ventricular bigeminy

and/or nonsustained or sustained VT) was more frequent in patients with MVP than those without. Furthermore, the clinical profile of our OHCA survivors with MVP appears to be distinct from a general population of patients with single-leaflet MVP; notably, our cohort demonstrates a higher frequency of female gender (90% vs. approximately 50%) (7), bileaflet prolapse (100% vs. 10%) (25), and nonsustained or sustained VT (78% vs. 18.7%) (4,33).

The exact role of PVC configurations of the outflow tract alternating with papillary muscle or fascicular origin in the genesis of VF is unclear. In a prior study of 10 patients with MVP (3 with bileaflet MVP), PVCs originated from the posterobasal region of the left ventricle in 6. It is possible that PVCs originating close to the prolapsing mitral valve leaflet (basal left ventricle or left ventricular outflow tract region) and adjacent structures such as the left ventricular papillary muscles and fascicles in an alternating fashion could be potential VF triggers (34).

The reason for outflow tract ectopic activity in general in this population is not fully understood from our study.

Table 5 **Summary of OHCA and Malignant Ventricular Arrhythmias Linked to MVP Reported in the English Language**

OHCA/Malignant Ventricular Arrhythmias	Age Range (yrs)	Women	Bileaflet MVP	Complex VE	ST-T Repolarization Changes on ECG	Mild or Greater MR	Ref. #
7	21–61	5/7 (71.4%)	—	2/7 (28.6%)	4/7 (57.1)	—	(45)
4	23–70	3/4 (75%)	—	4/4 (100%)	Very common	—	(37)
2	—	—	—	—	—	—	(46)
5	29–47	3/5 (60%)	—	—	—	—	(47)
9 (2 SUDs)	22–66	7/9 (77.8%)	—	—	—	—	(5)
7	28–90	5/7 (71.4%)	—	6/7 (85.7%)	2/7 (28.6%)	0/7 (0%)	(2)
1	54	1/1 (100%)	1/1 (100%)	—	—	—	(48)
Total = 35	21–90	24/33 (72.8%)	1/1 (100%)	12/18 (66.7%)	6/14 (42.9%)	0/7 (0%)	

Values are range or n/N (%). Studies are ordered chronologically by date of publication.

SUD = sudden unexplained death; VE = ventricular ectopic activity. Other abbreviations as in Tables 1 and 4.

Because outflow tract ectopic activity is the most common type of ectopic activity in structurally normal hearts, this may simply represent the second abnormality (high background rate) in addition to the specific pathology related to the disease (MVP and papillary muscle ectopic activity). Because the left ventricular outflow tract does have a shared region with the mitral annulus (aortic mitral continuity), and because this site is a relatively frequent site of ectopic activity, the ectopic activity from this region may be related to mechanical reasons from the MVP itself. Papillary muscle ectopic activity itself may be related to myocardium or may have conduction system–related origin. Fascicular ectopic activity has also been noted to occur from other locations, including the mitral annulus and the outflow tract. Given the now established relationship between fascicular ectopic activity and triggers for VF, our patients may represent fascicular disease arising from 2 sites in association with bileaflet MVP (35,36).

The estimated rate of SCD in patients with MVP is 16 to 41 per 10,000 per year (0.2% to 0.4% per year) on the basis of prospective data (3,4), and the SCD is attributed to VF (4,5). However, the relationship between MVP and VF in patients without other heart conditions has not been elucidated. Traction on papillary muscles, endocardial friction lesions, coronary microemboli from platelet-fibrin aggregates adjacent to the prolapsing mitral valve leaflet, transient ischemia due to mechanical alterations in coronary blood flow, and increased autonomic tone are proposed mechanisms (37–39). Ectopic impulse initiation in the mitral valve leaflet muscle bundles, secondary to stretching or catecholamine exposure, is also plausible (37). Some have proposed that MVP-related SCD may be linked to the hemodynamic and arrhythmogenic consequences of mitral regurgitation, as opposed to being secondary to the MVP itself (40).

Nishimura et al. (3) identified a redundant mitral valve as a risk factor for adverse outcomes in a prospectively followed asymptomatic or minimally symptomatic cohort of patients with MVP (n = 237). All 6 SCDs in that series occurred among the 97 patients with redundant mitral valves. Campbell et al. (41) identified a high-risk subset (n = 8) with inferolateral ST-T repolarization changes among 17 patients with clinically apparent, echocardiographically documented MVP. VT or VF was seen exclusively in 4 of 8 patients (50%) in this high-risk subset with MVP. Similar electrocardiographic changes were also reported in some MVP-linked cases of SUD and OHCA (Tables 4 and 5). In our cohort of survivors with bileaflet MVP, biphasic or inverted T waves on electrocardiography were present in 70%, usually in the inferior leads.

Study limitations. This study was limited by its retrospective design, a relatively small population of patients with OHCA, and a potential for referral bias. A detailed analysis of the exact interaction between different variables was precluded by limited numbers. Because of the retrospective design, it cannot be determined whether the reported echocardiographic findings, including bileaflet MVP, predated the OHCA.

Conclusions

In this young cohort of survivors with documented OHCA, we identified a potentially "malignant" MVP–ventricular arrhythmia phenotype. It is characterized by young women with bileaflet MVP, biphasic or inverted T waves in the inferior leads, and frequent complex ventricular ectopic activity with documented ventricular bigeminy or VT as well as PVC configurations of outflow tract alternating with papillary muscle or fascicular origin. A new approach to prospectively identify this "malignant" subset of patients is warranted.

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