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Mitral Valve Prolapse and Sudden Cardiac Arrest in the Community

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Abstract

Background—Mitral valve prolapse (MVP) is relatively common in the general population with recently reported prevalence of 1% and familial clustering (Framingham Heart Study). However, the association with ventricular arrhythmias and sudden cardiac arrest (SCA) remains controversial.

Objective—To ascertain the frequency of MVP among SCA cases in the community and characterize the clinical profile of SCA cases with MVP

Methods—SCA cases were prospectively identified in the population-based, Oregon Sudden Unexpected Death Study (population approximately 1 million). Presence of MVP was identified from echocardiograms performed prior but unrelated to the SCA event. The detailed clinical profile of SCA cases with MVP was compared to those without MVP to identify potential differences.

Results—729 SCA cases were evaluated over a 12 year period (69.5 ± 14.8 years; 64.6% male). MVP was seen in 17 cases pre-arrest (2.3%; 95% CI 1.2 to 3.4%). Mitral regurgitation (MR) was present in 14 (82.3%) MVP-SCA cases, and was moderate or severe in 10 (58.8%). Compared to cases *without* MVP, MVP-SCA cases were younger (60.9 ± 16.4 vs 69.7 ± 14.7; p=0.02), with fewer risk factors (diabetes 5.9% vs 46.4%; p=0.001; hypertension 41.2% vs 78.9%; p=0.001) or known coronary disease (29.4% vs 65.6%; p<0.001).

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Conclusion—MVP was observed in a small proportion (2.3%) of SCA cases in the general population, suggesting a low risk overall. Since MVP-SCA cases were characterized by younger age and relatively low cardiovascular comorbidity, a focus on imaging for valve structure/insufficiency, as well as genetics could aid future risk stratification approaches.

Keywords

Mitral valve prolapse; sudden cardiac arrest; risk

Introduction

Mitral valve prolapse (MVP) has been reported as a relatively common finding in the general population[1, 2]. A recent analysis from the Framingham cohort showed a prevalence of 1% with almost equal sex distribution and familial clustering[1]. Patients with relatively non-specific symptoms such as palpitations and atypical chest pain who are found to have MVP, continue to represent a major clinical conundrum for the practicing cardiologist.[3]

The existing literature continues to generate significant controversy regarding this condition. Several studies indicate that a subset of patients may suffer adverse outcomes, with sudden cardiac arrest (SCA) potentially the most devastating of these. SCA has been described as one of the possible outcomes on follow-up in MVP[4, 5] and several instances of SCA in young patients with MVP have been reported[6, 7]. Additionally, occurrence of ventricular arrhythmias on resting or ambulatory electrocardiograms is reported to be higher among patients with MVP[8, 9] though some studies have disputed this finding[10]. Conversely, other natural history studies indicate that MVP may have a benign prognosis[2, 4]. Considering the fact that MVP is a common, often incidental diagnosis in the community, the extent to which MVP contributes to excess SCA risk therefore continues to remain unclear. It is conceivable that a rare complication of a relatively common condition may account for a sizeable number of events. Thus it is worthwhile to examine the relevance of MVP vis-à-vis SCA in the general population. Population-based studies looking at the prevalence of MVP among SCA cases are scarce. In the ongoing Oregon Sudden Unexpected Death Study (Oregon-SUDS), we have systematically collected data on SCA in the community over a period of 13 years. We sought to ascertain the frequency of MVP among SCA cases in the general population and characterize the clinical profile of SCA cases with MVP.

Methods

Study Population

Details of case and control ascertainment in the Oregon-SUDS have been published earlier[11, 12]. The Oregon-SUDS is an ongoing, prospective study of SCA in the Portland, Oregon metropolitan area (population approximately 1 million) presently in its 14th year. Briefly, multiple-source surveillance, which includes first responders (Portland fire department and ambulance service), local hospital emergency rooms and the County Medical Examiner's office, is used to track cases of out-of-hospital cardiac arrest. Detailed emergency medical services (EMS), hospital and autopsy (where available) records are retrieved and all data are analyzed and SCA cases adjudicated by a 3-physician team. SCA

is defined as a sudden, unexpected, pulseless state of cardiac etiology, occurring rapidly after symptom onset when witnessed or within 24 hours of the subject being last seen in the usual state of health when unwitnessed. Non-cardiac causes such as drug overdose, trauma, chronic terminal illness, hospice patients, pulmonary embolism etc. are excluded by the adjudication process. Survivors of cardiac arrest are also included as SCA cases. All SCA cases undergo detailed phenotyping through individual review of all available medical records by physician researchers.

Informed consent is obtained from all SCA survivors prior to inclusion in the study. The present analysis was restricted to cases (2002–14) with appropriate pre-arrest echocardiograms available.

Clinical and Echocardiographic information

Information on clinical and demographic variables was obtained from medical records. Information on the presence of MVP and the left ventricular ejection fraction (LVEF) was obtained from the echocardiogram which was closest but unrelated to the SCA event. MVP was defined as a documented echocardiographic diagnosis of MVP by the interpreting cardiologist. Presence and severity (mild, moderate or severe) of mitral regurgitation (MR) was similarly obtained from the cardiologist's report. Severe LV systolic dysfunction was defined as an LVEF of ≤ 35%.

Statistical Analysis

Independent samples t-tests and chi-square or Fisher's exact tests were used to compare continuous (expressed as mean and standard deviation) and categorical (expressed as n, percentage) variables respectively. SCA cases with MVP were compared to SCA cases without MVP to identify any distinguishing characteristics of the former. A two-tailed p value of ≤ 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 21.0 (SPSS, IBM Corporation, New York).

The study protocol was approved by the institutional review boards and ethics committees of all participating hospitals.

Results

Prevalence of MVP in the SCA Population

Over a 12 year period, out of 3040 SCA cases, 729 cases with relevant echocardiograms were analyzed. The differences between subjects with and without echocardiograms are shown in Supplemental table 1. Cases that had echocardiograms were more likely to be older and have known cardiovascular risk factors. The mean time between performance of echocardiography and SCA event was 654 ± 788 days; 80% of the echocardiograms were performed within three years prior to the event. The clinical, demographic and echocardiographic characteristics of the 729 selected cases are summarized in Table 1. Mean age was 69.5 ± 14.8 years, with 64.6% males. Diabetes and hypertension was present in 45.5% and 78.0% of the cases respectively and 27.3% were smokers. The mean LVEF was

48.2 ± 16.8% and severe LV systolic dysfunction (LVEF ≤ 35%) was seen in a little over quarter of the cases (28.0%).

Overall, there were 17 SCA cases with diagnosed MVP prior to cardiac arrest, which accounted for 2.3% overall of SCA cases (95% CI 1.2 to 3.4%). Out of the 17 patients, an indication for echocardiography was clearly documented in 11 cases. The predominant reason was clinically suspected valve disease (7/11). Other indications included acute coronary syndrome, clinical heart failure and assessment of LV function. Mitral regurgitation (MR) was present in 14 of the 17 cases (82.3%). The severity of MR was mild in 4 (23.5%), moderate in 6 (35.3%) and severe in 4 (23.5%); thus over half (58.8%) of the MVP cases had moderate or severe MR. Five patients out of the 17 (29.4%) had potential high risk features in the form of redundant/thickened valve leaflet(s) which was documented echocardiographically in four cases and at postmortem in one case.

Important Clinical Characteristics of the MVP-SCA Cases

Table 2 outlines some of the important clinical characteristics of the 17 MVP-SCA cases. Most cases (12 out of 17; 70.6%) presented with ventricular fibrillation/tachycardia (VF/VT) as the arrest rhythm. SCA occurred during physical activity in 4 cases (23.5%). Return of spontaneous circulation (ROSC) was achieved in 7 (41.1%) cases and all 7 survived to hospital discharge; thus the survival rate in this group was better compared to SCA in the overall population. Documentation of some electrocardiographic arrhythmia prior to the SCA event was seen in about half of the cases (8 out of 17; (47%) and these comprised of premature ventricular/atrial complexes in 5 cases and atrial fibrillation/flutter in 4 cases. One of the subjects had a prior ablation procedure. Majority of the cases (15 out of 17; 88.2%) did not have an autopsy, which is in line with most population-based SCA series. Of the two cases that had an autopsy, high risk features in the form of a redundant, thickened mitral valve was noted in one case.

Comparison of SCA Cases with and without MVP

We compared the clinical characteristics of SCA cases with and without MVP (Table 3). Cases with MVP were younger (60.9 ± 16.4 vs 69.7 ± 14.7 years; p=0.02), less likely to have diabetes (5.9% vs 46.4%; p=0.001), hypertension (41.2% vs 78.9%; p=0.001), chronic kidney disease (11.8% vs 35.2%; p=0.04) or known CAD (29.4% vs 65.6%; p<0.0001). Sex and race distribution was not significantly different. The mean LVEF tended to be slightly higher among patients with MVP (54.2 ± 14.7% vs 48.1 ± 16.9%; p=0.14) and MVP patients were less likely to have severe LV dysfunction (6.7% vs 28.5%; p=0.08) which did not reach statistical significance. The mean LV diameter was similar between the two groups (54.7 ± 7.3 vs. 51.8 ± 10.6 mm; p=0.38). While significant (moderate or severe) MR was seen in 58.8% of MVP cases, it was noted in only 23.9% of non-MVP cases (p=0.02). As the MVP-SCA cases were younger with fewer cardiovascular risk factors, they were less likely to be on some cardiac drugs such as ACE inhibitors, anti-platelets and lipid lowering drugs. There was no significant difference in the proportion of cases with and without MVP who were on QT prolonging drugs. The mean QTc was also not significantly different between the two groups.

Discussion

In this community-based study, MVP was observed in 2.3% of SCA cases overall. SCA cases with MVP were distinguished by younger age and lesser prevalence of cardiovascular risk factors as well as known CAD. Most MVP cases had associated MR and the presence of moderate or severe MR was much more likely in cases with MVP.

The prevalence of MVP in our SCA population is similar to the prevalence of 2.4% reported by Freed and colleagues in the general population in the Framingham offspring cohort[2]. This suggests that the occurrence of MVP among SCA cases in the community may not be significantly increased from what is expected in the general population. Should we interpret this as lack of evidence for a potential link between MVP and SCA? While there are no recent studies and a relative lack of community-based evaluations, the MVP-SCA association has been reported in several early studies. In a prospective follow-up of 237 patients with MVP, Nishimura et al. reported SCA in 2.5%[4], and the congruence with our findings is striking. However, another early study reported occurrence of SCA in 1% of the population[5]. Extrapolations of annual incidence of SCA, especially from the former study suggest that the SCA burden in MVP patients may be higher than that in the general population, though the present study was not designed to answer this question. It has been suggested that MVP could potentially account for an even greater proportion of SCA among young subjects. Basso and colleagues evaluated 200 cases of SCA in the young (≤ 35 years) and reported that MVP was observed in 10% of cases[13]. Autopsy series have described several cases of SCA where MVP was the sole abnormality documented[6, 7], which lends further support to the hypothesis that there may be a small but definite risk of SCA unique to MVP. Additionally, a “malignant” form of MVP has been described with a predisposition for frequent ventricular arrhythmias and sudden death[14].

The exact mechanism(s) linking MVP to SCA is not known; however several possibilities have been advanced. Valve leaflet dumping in diastole or traction on papillary muscles could serve as a mechanical trigger for ventricular arrhythmias. Redundant and thickened leaflets have been identified as a risk factor for SCA in MVP[15, 16]. Endocardial friction lesions in the left ventricle may serve as a focus of arrhythmias as well[7, 16]. Some pathology studies have indicated that a cardiomyopathic process accompanying MVP may play a role[17, 18]. In a study of patients with ventricular tachycardia (VT) and no history of heart disease, MVP was seen in 25% of cases and these cases were characterized by increased endomyocardial fibrosis[19]. Alterations in repolarization including increased QT interval as well as QT dispersion have been documented in MVP and may have a potential role in arrhythmogenesis[20, 21]. Further, QT dispersion was found to be related to the degree of prolapse and leaflet thickness, providing a mechanical correlation for electrical disturbances in MVP[22]. A role for increased autonomic tone has been proposed with relatively higher catecholamine excretion in MVP patients with ventricular arrhythmia[23]. Wilde and colleagues performed detailed mapping studies on a patient with MVP and VT and concluded that delayed afterdepolarization-induced triggered activity was the mechanism, with stretch and fibrosis of the papillary muscles contributing to the origin of the arrhythmia[24].

Identification of the MVP patient potentially at high risk for SCA is a desirable goal and different studies have identified different risk factors, though valve leaflet length and thickness have been consistently found to be related across studies[15, 16, 25, 26]. Basso and colleagues recently performed an elegant study involving autopsy and imaging. In MVP cases that had SCD, they demonstrated fibrosis of the papillary muscles and infero-basal left ventricular wall, and proposed myocardial stretch by leaflet prolapse as a possible mechanism. Furthermore, they reported that late gadolinium enhancement identified on cardiac magnetic resonance imaging may help identify this substrate[27, 28]. Some studies have suggested that ventricular arrhythmias may be more frequent in MVP when MR is present[29, 30]. This could reflect hemodynamic consequences of volume overload; however it is noteworthy that the mean LVEF was normal and LV diameter not significantly increased in the MVP cases compared to the cases without MVP in our population. Additionally, it has been proposed that a subset of young patients with isolated MVP and SCA may actually have less MR[31]. Certain studies have found women to be at higher risk[26, 31] though we did not find this in the present study. Using signal-averaged ECG, an increased frequency of late potentials has been identified in MVP patients[19]; however the utility in risk prediction is unclear[32]. Similarly, programmed electrical stimulation does not appear to be conclusively helpful[33, 34]. The potential of biomarkers[35] and genetic studies[36] to identify high risk individuals is likely to be tested in the future, especially with the recent findings related to familial clustering. Thus, while there are several potential predictors, more focused investigation is needed to establish underlying mechanisms and clinically relevant risk stratification in the patient with symptomatic MVP.

Limitations

Potential strengths of the present analysis are the population-based design, with detailed phenotyping of SCA cases. However a study of this nature is subject to certain inherent limitations. We restricted our study population to those with echocardiograms available (729 out of 3040 SCD cases) which would create some bias as cases with potentially higher cardiovascular risk profile are more likely to be screened. This may inflate the observed prevalence of structural heart disease including MVP; however this was necessary given the nature of the problem being evaluated. The prevalence rate of MVP among SCA cases reported in this study needs to be interpreted with caution and more studies in diverse populations are needed. Even among SCA cases, potentially more severe cases with clinical manifestations may have preferentially undergone echocardiograms; therefore, cases may be enriched with more severe features such as mitral regurgitation. Owing to the community-based nature of the study, we did not have direct access to actual digital echocardiograms for independent review and relied on physician documentation. However, the documented interpretation of the reading cardiologist was considered and is likely to be reasonably accurate and moreover reflects the real-world scenario for MVP diagnosis. Therefore, for this analysis, the diagnosis of MVP was pre-defined by echocardiography, and not by postmortem examination which was performed in 552 of 3040 SCD cases (18%). Accordingly, for 2 of the 17 MVP cases, post-mortem examination findings were also available. Due to the limited number of SCA cases with MVP, findings regarding characteristics of MVP cases should be interpreted with caution. However this analysis is

one of the first to report the prevalence of MVP among SCA in the community and serves as a first step to explore potential links between MVP and SCA with further prospective studies.

Conclusion

MVP was present in 2.3% of SCA cases in this population-based study. SCA cases with MVP were younger and less likely to have cardiac or non-cardiac disease conditions. Future prospective studies that focus on imaging for valve structure/insufficiency as well as genetic propensity are likely to have the most yield for SCA risk stratification of the MVP patient.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

MVP	Mitral valve prolapse
SCA	Sudden cardiac arrest
CAD	Coronary artery disease
EMS	Emergency medical services
LVEF	Left ventricular ejection fraction
MR	Mitral regurgitation
VT	Ventricular tachycardia

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Clinical Perspectives

Mitral valve prolapse (MVP) is a common condition in the community and is often encountered by clinicians in asymptomatic individuals. The issue of an association between MVP and sudden cardiac arrest (SCA) continues to generate controversy with several reports suggesting a potential link in limited series. However, the extent to which MVP is found among SCA cases in the general population and the characteristics of such cases have not been well described. In the Oregon-SUDS, a community-based study of SCA in a population of 1 million, we found that MVP was seen in 2.3% of SCA cases in the community. We described the characteristics of the SCA cases with MVP and found that compared to SCA cases without MVP, MVP-SCA cases were likely to be younger with fewer cardiovascular risk factors. Our study adds further to the evolving concept that there may be a subset of MVP cases that are prone to serious ventricular arrhythmias and SCA. Improved recognition of this subgroup could help identify MVP patients potentially at risk for SCA and intervene appropriately. However further studies are needed to investigate whether modalities such as imaging and genetic evaluation can help in risk stratification for SCA in these challenging group of patients.

Table 1

Demographic, Clinical and Echocardiographic characteristics

	SCA Cases (n=729)
Age (yrs)	69.5 ± 14.8
Male n (%)	471 (64.6)
Body Mass Index (kg/m^2)	30.2 ± 9.0
Diabetes n (%)	331 (45.5)
Hypertension n (%)	568 (78.0)
Cholesterol (mg/dL)	169.3 ± 46.3
Smoking n (%)	154 (27.3)
MVP n (%)	17 (2.3)
Mean LVEF (%)	48.2 ± 16.8
LVEF ≤ 35% n (%)	197 (28.0)

Body mass index available for 632 cases

Cholesterol available for 414 cases

Smoking status available for 563 cases

MVP- Mitral valve prolapse, LVEF- Left ventricular ejection fraction

Table 2

Important Clinical Characteristics of the MVP-SCA Cases

Case no.	Age/sex	Arrest rhythm	Preceding symptoms	Physical activity/exercise at time of SCA	ROSC	STHD	Arrhythmia on ECG/Holter	Autopsy
1	73/F	VF/VT	Feeling of chest pressure	No	No		PACs, PVCs	Not done
2	83/F	Unknown	No information	No	No		none	Not done
3	60/M	VF/VT	None	Yes	No		none	Not done
4	78/M	VF/VT	None	No	Yes	Yes	PVCs	Not done
5	39/M	VF/VT	None	Yes	Yes	Yes	none	Not done
6	82/M	Unknown	No information	Unknown	No		AF, PVCs	Not done
7	44/F	VF/VT	No information	Yes	Yes	Yes	PVCs	Not done
8	53/M	VF/VT	No information	No	No		none	Not done
9	67/M	VF/VT	No information	No	Yes	Yes	none	Not done
10	29/M	VF/VT	None	Yes	No		none	Thickened, billowing mitral valve, marked LVH; cardiomegaly
11	55/M	VF/VT	“indigestion ”, fatigue	No	No		AF	Not done
12	67/M	Asystole	No information	No	No		PVCs	Not done
13	82/M	VF/VT	No information	No	Yes	Yes	AF	Not done
14	57/F	VF/VT	None	No	Yes	Yes	none	Not done
15	40/F	Unknown	Palpitations; headache	No	No		none	very small coronary arteries 1 mm or less
16	69/M	VF/VT	No information	Unknown	Yes	Yes	Atrial flutter; status post ablation	Not done
17	57/M	Asystole	No information	No	No		none	Not done

SCA- Sudden cardiac arrest

PAC- Premature atrial complex

PVC- Premature ventricular complex

AF- Atrial fibrillation

ROSC- Return of spontaneous circulation

STHD- Survival to hospital discharge

VF/VT- Ventricular fibrillation/tachycardia

LVH- Left ventricular hypertrophy

Table 3

Comparison of SCA cases with and without MVP*

	MVP (n=17)	No MVP (n=712)	p value
Age	60.9 ± 16.4	69.7 ± 14.7	0.02
Male	12 (70.6)	459 (64.5)	0.60
White	14 (82.4)	599 (84.7)	0.73
Body Mass Index	27.0 ± 5.8	30.3 ± 9.1	0.18
Hypertension	7 (41.2)	561 (78.9)	0.001
Diabetes	1 (5.9)	330 (46.4)	0.001
Known CAD	5 (29.4)	467 (65.6)	<0.0001
Chronic Kidney disease	2 (11.8)	250 (35.2)	0.04
LVEF	54.2 ± 14.7	48.1 ± 16.9	0.14
LVEF ≤ 35%	1 (6.7)	196 (28.5)	0.08
Left atrial diameter (mm)	45.0 ± 8.7	44.9 ± 10.1	0.98
LV Diameter (mm)	54.7 ± 7.3	51.8 ± 10.6	0.38
Moderate or severe MR	10 (58.8)	170 (23.9)	0.02
Beta Blockers	9 (52.9)	404 (59.0)	0.62
ACE Inhibitors	4 (23.5)	338 (49.3)	0.05
ARBs	1 (5.9)	65 (9.5)	1.0
Anti-arrhythmic drugs	2 (11.7)	219 (32.0)	0.11
Antiplatelets	7 (41.2)	510 (74.4)	0.002
Lipid lowering drugs	2 (11.7)	337 (49.2)	0.002
QT prolonging drugs	5 (29.4)	334 (48.7)	0.11
QTc	429.3 ± 33.1	459.0 ± 40.6	0.35

* Data presented as mean ± SD and as n (%).

SCA- Sudden cardiac arrest, MVP- Mitral valve prolapse, CAD- Coronary artery disease, LVEF- Left ventricular ejection fraction, LV- Left ventricle, MR-Mitral regurgitation, ACE-Angiotensin converting enzyme, ARB-Angiotensin receptor blocker, QTc- corrected QT interval QTc information available for 6 MVP cases and 285 non-MVP cases.

Information on medications was available for 685 non-MVP cases