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PRE- AND POSTMORTEM CHARACTERISTICS OF LETHAL MITRAL VALVE PROLAPSE AMONG ALL COUNTYWIDE SUDDEN DEATHS

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Abstract

Objectives: We sought to investigate the characteristics of mitral valve prolapse (MVP) in a postmortem study of consecutive sudden cardiac deaths (SCDs) up to age 90.

Background: Up to 2.3% of MVPs suffer SCD, but by convention SCD is rarely confirmed by autopsies. In a postmortem study of young persons < 40 years, 7% of SCDs were caused by MVP; bileaflet involvement, mitral annular disjunction (MAD), and replacement fibrosis were common.

Methods: In the San Francisco POST SCD Study, autopsies have been performed on >1000 consecutive WHO-defined (presumed) SCDs ages 18–90 since 2011, 603 adjudicated. Autopsy-defined sudden arrhythmic death (SAD) required absence of non-arrhythmic cause; MVP diagnosis required leaflet billowing. We reviewed 100 pre-mortem echocardiograms to identify additional MVPs missed on autopsy.

Results: Among 603 presumed SCDs, 339 (56%) were autopsy-defined SADs, with MVP identified in 7 (1%). We identified 6 additional MVPs by review of echocardiograms, for a

Address for correspondence: Francesca Nesta Delling, MD, MPH, University of California San Francisco, Smith Cardiovascular Research Building MC3120, 555 Mission Bay Blvd South, Room S352C, San Francisco, CA 94158, Phone: 415-476-2796, Fax: 415-502-7949, Francesca.Delling@ucsf.edu, TWITTER SUMMARY, From: @SF_POSTSCD: MVP prevalence ≥4% of SADs 18–90 years, but half of cases, all monoleaflet, were missed despite thorough autopsy. Lethal MVP in older SADs all had interstitial fibrosis but did not consistently have bileaflet anatomy, replacement fibrosis, or MAD as described in younger SADs.

DISCLOSURES

Dr. Delling is a consultant for Zogenix, although relationship with this company is not relevant to the work described in the manuscript.

prevalence of at least 2% among 603 presumed SCDs and 4% among 339 SADs (p = 0.02 vs 264 non-SADs). All 6 additional MVPs had monoleaflet rather than bileaflet involvement, and mild mitral regurgitation, ruling out hemodynamic cause. Less than half had MAD with replacement fibrosis, but all had multisite interstitial fibrosis.

Conclusions: In a countywide postmortem study of all adult SCDs, MVP prevalence was at least 4% of SADs, but half were missed on autopsy. Monoleaflet MVP was often underdiagnosed postmortem. Compared to young SCDs, lethal MVP in older SCDs did not consistently have bileaflet anatomy, replacement fibrosis, or MAD.

CONDENSED ABSTRACT

Up to 2.3% of individuals with mitral valve prolapse (MVP) suffer sudden cardiac death (SCD), but by convention SCD is rarely confirmed by autopsies. While postmortem studies of MVP are limited to younger SCDs, the POST SCD Study is a countywide postmortem investigation of all adult SCDs up to age 90. In this study, MVP prevalence was at least 4% of autopsy-defined sudden arrhythmic deaths, but half of cases, all monoleaflet, were missed by autopsy. Compared to young SCDs, lethal MVP in older SCDs did not consistently have bileaflet anatomy, replacement fibrosis, or mitral annular disjunction; interstitial fibrosis was universal.

Keywords

Mitral valve prolapse; pathology; sudden cardiac death; arrhythmias

INTRODUCTION

Mitral valve prolapse (MVP) is a common heritable valvulopathy(1,2) affecting over 7 million individuals in the US and over 170 million worldwide.(1,3) MVP is characterized by systolic displacement of one or both mitral leaflets into the left atrium by echocardiography.(4–6) Although MVP is mostly characterized by a benign course,(1) a malignant MVP subtype has been described in association with cardiac arrest or sudden cardiac death (SCD).(7–10)

However, the precise burden of SCD in MVP is unknown due to major limitations of prior studies, nearly all of which employ epidemiologic definitions of SCD that presume cardiac cause. The commonly used World Health Organization (WHO)(11) and the 2016 consensus society guideline(12) definitions of SCD rely on emergency medical services records, death certificates, or conventional criteria rather than autopsies. The yearly incidence of WHO-defined (presumed) SCD in MVP has been estimated between 0.4 and 1.8%, with a prevalence of MVP of 2.3% among presumed SCDs.(7,9,10,13) The lack of autopsy confirmation of cardiac cause of death in these prior investigations may explain the wide range of SCD estimates in MVP. The few postmortem studies of malignant MVP are limited by targeted autopsies in individuals without significant comorbidities and unclear cause of death. (14–19) Another postmortem study on malignant MVP among persons ≤ 40 years(17) did not perform toxicology therefore occult overdose, a substantial contributor to apparent SCDs in the young,(20–22) may have confounded SCDs attributed to MVP. In that study, 7% of SCDs in the young were caused predominantly by bileaflet MVP

without significant mitral regurgitation (MR); replacement fibrosis was common and often associated with mitral annular disjunction (MAD).(17) Other clinical observations suggest that the arrhythmic MVP phenotype may not be restricted to bileaflet MVP with MAD and replacement fibrosis.(23)

Recently, we performed a 5-year prospective medical examiner-based, countywide postmortem study to ascertain the precise incidence and underlying cause of all presumed SCDs up to age 90 in San Francisco County (POstmortem Systematic InvesTigation of Sudden Cardiac Death [POST SCD] Study) and found that only half (55.8%) were autopsy-defined sudden arrhythmic deaths (SADs). Postmortem investigation easily identified non-arrhythmic causes that masquerade as presumed SCD, including occult overdose, cardiac tamponade, electrolyte derangements, intracranial hemorrhage, aneurysm rupture, and pulmonary embolism.(20) In this study, we sought to investigate the unbiased prevalence and clinical characteristics of lethal MVP by pre- and postmortem methods in the POST SCD Study.

METHODS

Study population

The entire metropolitan area of San Francisco County, California (population: 805,235) is served by 10 adult hospitals, 3 emergency medical services agencies and a single Office of the Chief Medical Examiner. As part of the POST SCD Study, all out-of-hospital cardiac arrest deaths ages 18–90 between February 1, 2011 and March 1, 2016 were referred for complete autopsies, including toxicology and histology, as previously described.(20) Those meeting WHO criteria for SCD(11) underwent full adjudication.

Out-of-hospital cardiac arrest deaths were (1) deaths in the field or emergency department if the event was witnessed and/or active resuscitation was performed; or (2) unwitnessed natural deaths if the victim was last observed alive and symptom-free within 24 hours, with no active resuscitation but primary emergency medical services impression of cardiac arrest. Resuscitated out-of-hospital cardiac arrest victims surviving to hospital admission were considered cardiac arrest survivors rather than sudden deaths.

Subjects with the following conditions were excluded: 1) terminal illness (including cancer), 2) end-stage renal disease on dialysis, 3) an identifiable non-cardiac etiology of death at presentation, including evidence of drug abuse/overdose at the scene (i.e., intravenous needles, empty pill bottles), clear life-threatening trauma, homicide, or suicide (with non-sudden death occurring after the acute trauma), and (4) a hospital admission within the prior 30 days for non-cardiac illness or surgical procedure.

The POST SCD Study was approved by the University of California, San Francisco institutional review board and by the review board of all 10 San Francisco County adult hospitals and 3 emergency medical services agencies to obtain medical records.

Postmortem investigation

After excision and dissection, internal organs of the thorax, abdomen, and cranial vault were examined to exclude non-cardiac etiologies. Vitreous chemistries were performed to rule out electrolyte abnormalities. All hearts of presumed SCDs were examined for gross evidence of cardiovascular pathology and coronary artery disease as previously described,(20) including the presence of valvular thickening or calcification. MVP was defined as mitral leaflet redundancy and thickening with billowing toward the left atrium and elongation of chordae tendinae on visual inspection (Figure 1). Since the posterior leaflet is supported by the inferior-posterior wall rather than the posterior wall alone, the term “mural” may be more appropriate (and “aortic” for the anterior leaflet). However, we opted for the classic anterior/posterior mitral leaflet nomenclature which is more widely used. Histology samples were taken from transverse sections at the level of: septum, mid-inferior, mid-superior left ventricular (LV) free wall (including inferior-medial and superior-lateral papillary muscles, respectively). In some instances when MVP was identified on visual inspection, additional samples were taken from a longitudinal section including the posterior mitral leaflet and the inferior-basal LV free wall under the posterior mitral leaflet. In such longitudinal sections, MAD was defined as a separation between left atrial wall at the level of mitral valve junction and the LV free wall.(24,25) Histological sections 5 μm thick were stained with hematoxylin-eosin and Heidenhain trichrome and independently examined by 2 pathologists (E.M. and A.C.).

Interrogation of cardiac implantable electronic devices was performed if present.

Adjudication of cause of death

As previously described,(20) final adjudication of cause of death was established after review of pre-mortem medical records, and detailed autopsy, toxicology and histology findings by a multidisciplinary committee. Sudden arrhythmic death (SAD) required the absence of an obvious cardiac non-arrhythmic (e.g., tamponade or acute heart failure with pulmonary edema) or extra-cardiac cause of death (e.g., acute cerebral accident, electrolyte abnormalities including renal failure, viscous perforation, vascular rupture, pulmonary embolism, hemorrhage, lethal toxicology). Primary cause of death was defined as the “stand alone” etiology of death (most likely, possible, or probable depending on the level of certainty). Contributory cause of death was defined as a secondary etiology which may have contributed to the subject’s sudden death, but was not sufficient as “stand alone” cause of death because other potential alternative causes of death were found on autopsy.

Review of pre-mortem echocardiograms

To identify additional MVP cases possibly missed by autopsy due to its dynamic nature, images from all available transthoracic echocardiograms (TTEs) performed as part of clinical care within 1 year of death were reviewed to assess the presence of MVP, leaflet involvement (mono or bileaflet), MAD, and the degree of MR. MVP was defined as systolic leaflet displacement of one or both leaflets >2 mm beyond the mitral annulus in a parasternal or apical 3-chamber long-axis view (Figure 1).(6) MAD was assessed quantitatively as the separation between the left atrial wall at the level of mitral valve junction and the LV free wall in either the parasternal long-axis view or one of the apical views (Figure

1).(24,25) When quantitative assessment of MR was not available, its severity was based on visual estimation of the regurgitant jet.(26) LV end-diastolic/end-systolic volumes, ejection fraction, and mass were quantified and indexed to body surface area as previously described.(26) Right ventricular dilatation was defined as a basal diameter ≥ 4.2 cm. Right ventricular systolic dysfunction was assessed qualitatively.

Characterization of myocardial fibrosis

Histology sections of MVP cases identified by autopsy and pre-mortem TTE (missed on autopsy) were examined to assess type of fibrosis (patchy replacement vs endoperimysial), location, and qualitative amount of fibrous tissue (mild, moderate, severe). Endoperimysial fibrosis was defined as either endomysial/interstitial fibrosis (between myocardial fibers), or perimysial/perivascular fibrosis (surrounding blood vessels), or a combination of both.

Statistical analysis

We compared subjects with SAD vs non-SAD with regard to demographics, comorbidities (diabetes, hypertension, chronic kidney disease, coronary artery disease, tobacco and alcohol use), and, when available, echocardiographic variables (LV ejection fraction and MVP status). Continuous variables (all non-normally distributed) were expressed as median and quartiles. Categorical data were expressed as number and percentage of total subjects in each group. Differences between the 2 groups were assessed using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. Within the group of subjects diagnosed with MVP as cause of SAD we evaluated demographics, comorbidities, valvular characteristics and fibrosis patterns in those MVP cases identified on autopsy (or both autopsy and pre-mortem TTE), and compared to MVP cases identified on pre-mortem TTE but not apparent on autopsy. Due to the low number of MVP cases overall, and in each of these groups (autopsy vs TTE-diagnosed), a formal statistical comparison was not pursued. For the same reason, we did not run a multivariable model testing the association of MVP with SAD after adjustment for cardiovascular risk factors (well established in prior literature). Analyses used Stata Version 14.2 (StataCorp LP). A 2-tailed $P < 0.05$ was considered statistically significant.

RESULTS

As previously described,(20) 525 presumed SCDs were autopsied and adjudicated for underlying cause during the initial POST SCD study period. At the time of this analysis, 78 additional presumed SCDs were autopsied and added to our cohort for a total of 603 presumed SCDs (Table 1). The mean age of the autopsied presumed SCDs was 62 years, 30% were female. Reflecting the diverse characteristics of San Francisco County, nearly half of cases (269 or 45%) were of non-white race (118 Asian, 92 Black, 43 Hispanic, 16 other).

Of 603 SCDs, 339 were considered SADs based on initial adjudication, 153 had a TTE within 1 year of death, and 100 of those had images available for analysis (50 in the SAD and 50 in the non-SAD group). None of the 53 cases with a pre-mortem TTE report (but no available images) had a diagnosis of MVP. SADs had a higher prevalence of MVP than non-SADs (Table 1 and Figure 2).

MVP and SAD

MVP diagnosed on autopsy.—Based on postmortem criteria alone (prior to retrieval of pre-mortem TTE studies), MVP was adjudicated as cause of SAD in 7 of 603 presumed SCDs (1.0%, all male, ages 49–65, Table 1 and Figure 2). None had obstructive coronary artery disease or hypertrophic/dilated cardiomyopathy. In 5 of the 7 SADs, MVP was considered primary cause of death with “most likely” level of certainty. For the other 2 SADs, MVP was considered contributory to primary causes of death adjudicated with “possible” certainty.

A longitudinal section including the posterior mitral leaflet and the inferior-basal LV free wall under the posterior mitral leaflet (allowing assessment of MAD) was available for 2 of 7 cases. In both cases MVP was considered the primary cause of SAD. One of the 2 cases had bileaflet billowing with MAD; the other had thickening and myxomatous changes of the posterior mitral leaflet with minimal billowing and no MAD on autopsy (Central Illustration).

MVP not apparent on autopsy.—After reviewing digital images available for 100 presumed SCDs with a pre-mortem TTE, we found 6 additional MVPs not identified at autopsy, for a total MVP prevalence of 2% (7 + 6 = 13) among 603 SCDs. All 6 additional MVP cases were associated with SAD, with cause of death revised to primary in one and contributory in the remaining 5 MVP cases. In these 5 cases primary etiologies of SAD were as follows: bicuspid aortic valve (n=1), defibrillator malfunction (n=1) (level of certainty “most likely”) and hypertension (n=3) (“probable”). MVP prevalence was significantly higher for SADs (4% of 339) than non-SADs (0.7% of 264, p = 0.02) for which non-arrhythmic causes of presumed SCD were found (Table 1).

Compared to the 7 SADs with MVP found postmortem, the 6 MVP cases diagnosed by TTE (missed on autopsy) had similar gender, age, comorbidities (including hypertension and diabetes), and family history of SCD (Table 2). LV systolic function was preserved, and the degree of MR was mild. All 6 had monoleaflet MVP (4/6 or 70% posterior/mural), and one of 6 (17%) had MAD.

Gross and histologic autopsy characteristics in SADs due to MVP

Gross findings.—Cardiomegaly was present in only 4 of 13 MVPs with SAD (Table 2), thus significant MR was unlikely in most cases (Table 2). Most MVPs (11 of 13 or 85%) had moderate to severe leaflet thickening (Table 2), although billowing was found only in the MVPs identified on autopsy (Figure 1A). Only 2 of the 7 autopsy-defined lethal MVPs (29%) had monoleaflet (posterior/mural) involvement (Central Illustration).

Histologic findings.—LV fibrosis via Heidenhain trichrome stain was found in all SADs adjudicated due to MVP (either primary or contributory cause).

In the 7 lethal MVP cases diagnosed on autopsy, we found endoperimysial (i.e., interstitial) fibrosis of variable severity involving predominantly the inner and mid inferior-basal wall, superior-lateral and inferior-medial papillary muscles/subjacent LV, and the interventricular septum. In most cases interstitial fibrosis was multisite, even in the SAD with pre-mortem

TTE showing only mild MR. Replacement fibrosis was noted in 3 of 7 (43%) MVPs diagnosed at autopsy (Table 2 and Central Illustration).

In the 6 SADs with MVP diagnosed by TTE but missed by autopsy, endoperimysial (interstitial) fibrosis was found in similar locations as the 7 MVPs diagnosed on autopsy, with multisite involvement in all cases (Table 2).(19) Compared to the 7 MVPs diagnosed on autopsy, replacement fibrosis was found only in 1 of 6 (17%) subjects.

DISCUSSION

We leveraged the POST SCD Study, a systematic postmortem investigation of consecutive SCDs defined by conventional criteria among all adults up to age 90 in an entire metro area, to define the precise, unbiased prevalence and characteristics of lethal MVP in an entire community. Our key findings are as follows (Central Illustration): 1) MVP accounted for 2% of all presumed SCDs, but 4% of SADs when non-arrhythmic causes (i.e., pulmonary embolism, occult overdose, tamponade) of presumed SCD were excluded by autopsy; 2) nearly half of SADs due to MVP were missed after a thorough autopsy, especially if MVP was monoleaflet; 3) in contrast to prior reports in young SCDs, lethal MVP in older SCDs did not consistently have bileaflet anatomy, or MAD; and 4) replacement fibrosis was rare but multisite interstitial fibrosis was common in older SADs due to MVP.

The prevalence of MVP among WHO-defined SCDs in other recent population studies such as the Oregon Sudden Unexpected Death Study is reported to be 2.3%, but only 11% of presumed SCDs in that study were confirmed by autopsy.(10) Therefore, investigators could not assess the pathologic characteristics of lethal MVP.(10) We found a similar prevalence of MVP (2%) when using the WHO definition of SCD in POST SCD, but this prevalence was doubled (4%) when non-arrhythmic causes among these presumed SCDs were excluded by comprehensive postmortem investigation. As applies for other arrhythmic cardiovascular phenotypes,(20) these findings highlight the importance of complete autopsies to improve the specificity and accuracy of SCD diagnosis in MVP.

The lethal MVP cases found in the POST SCD study reflect the large urban, multiethnic population of all adult sudden deaths rather than a targeted sample of younger deaths in Caucasians without comorbidities. Because POST SCD MVP cases were older with common comorbid conditions such as hypertension, alcohol and drug use, and postmortem toxicology was uniformly performed, MVP was adjudicated as a contributory rather than primary cause of death for approximately half of these SADs. Further studies are needed to study the interaction between hypertension, aging, environmental factors, and lethal MVP.

MVP not apparent on autopsy

Based on review of pre-mortem echocardiographic images, we found that MVP diagnosis was not apparent at autopsy in approximately half of MVP cases, all with monoleaflet involvement. We postulate that MVP diagnosis was missed because of the lack of extensive multiscallop involvement typical of Barlow’s disease, the predominant arrhythmic phenotype highlighted in prior postmortem studies of SCDs younger than 40 years.(17,24) Indeed, Barlow’s disease typically occurs at a younger age, even in MVP cases without

arrhythmic complications.(3) In addition, myxomatous involvement of a single scallop or single leaflet may translate into prolapse (a dynamic condition) on TTE, but not prominent billowing on postmortem inspection (a static assessment of the mitral valve). Under-recognition of monoleaflet involvement in lethal MVP cases may explain why isolated bileaflet MVP did not significantly increase the risk of sudden cardiac arrest compared with monoleaflet MVP in a large matched, retrospective cohort study.(27) Prior reports suggest that monoleaflet MVP is associated with arrhythmic risk mainly because of related severe MR.(13) However, in our series MR was mild in 7 of 13 MVPs with SAD and available pre-mortem TTE, suggesting other mechanisms of ventricular arrhythmia beyond hemodynamic triggers such as the multisite interstital fibrosis we found in these cases.

Characteristics of lethal MVP in older adults

In the bileaflet phenotype previously associated with SAD in MVP, autopsies and cardiac magnetic resonance (CMR) imaging with late gadolinium enhancement have revealed focal (replacement) fibrosis.(17,28,29) In postmortem studies of younger individuals, focal fibrosis is often associated with MAD,(24) which is postulated to cause mechanical stretch and scarring of the myocardium.(24) However, in another postmortem investigation, MAD was identified in normal hearts, highlighting the uncertainty surrounding its clinical significance.(30) In our consecutive, unselected series of older sudden deaths, MVP cases with MAD and replacement fibrosis represented the minority (4/13 or 31%) of MVPs with SAD (Table 2), as is the case for living individuals with MVP.(23) In contrast, we found multisite interstitial fibrosis in all MVPs with SAD (Central Illustration), even those without significant MR, and regardless of leaflet involvement. Multisite interstitial fibrosis was found in typical areas of myocardial stretch such as the papillary muscles, subjacent myocardium, and inferior-basal LV, and also areas not easily explained by focal traction such as the interventricular septum, and the right ventricular wall.(19) Multisite interstitial fibrosis may explain why ventricular ectopy is commonly multifocal,(31) and may represent an alternative pattern of fibrosis when replacement fibrosis is absent in MVP with ventricular arrhythmia.(23) Indeed, we have shown that CMR-derived T1 mapping is abnormal in arrhythmic MVP, suggesting the presence of interstitial fibrosis even if late gadolinium enhancement (indicative of replacement fibrosis) is absent, and regardless of MR severity.(23) Because interstitial fibrosis found on autopsy can be detected by CMR in living individuals with MVP, our findings may have important implications for the management and early detection of MVP patients at higher arrhythmic risk.

Novel macroscopic and microscopic features in lethal MVP

In all MVP cases among SADs, including those with MVP not apparent on autopsy and diagnosed on TTE, mitral leaflets were significantly thickened on macroscopic examination, suggesting that primary structural abnormalities of the MV, and not hemodynamics were responsible for the echocardiographic diagnosis of MVP (Figure 1). Moreover, none of these cases had other potential etiologies of leaflet thickening such as chronic kidney disease, diabetes, or annular calcification. Therefore, in cases without multiscallop involvement and billowing where postmortem MVP diagnosis may be problematic, and in situations where no other structural heart disease is identified, mitral leaflet thickening should prompt the pathologist to perform a longitudinal section including the posterior mitral leaflet and

the inferior-basal LV free wall under the posterior mitral leaflet in order to assess for myxomatous changes of the mitral valve leaflets, and for the presence of MAD. This section, not routinely performed during standard autopsies, would increase the diagnostic yield of standard transverse sections, especially when MVP-related patterns of fibrosis are revealed. Moreover, prior postmortem and imaging studies have shown that the atrioventricular junction is not a continuum, suggesting the junction should be sampled more extensively rather than just with a solitary section.(25,30)

Limitations

As expected in a population-based study, the overall number of MVP cases in our sample was small. Thus, we may have had limited power to discern differences. However, our findings reflect the entirety of lethal MVPs in a diverse community. Second, because POST SCD is not a cohort study, pre-mortem TTEs were performed only as part of typical care and were not available in all adjudicated SCDs. Third, we did not compare burden of fibrosis quantitatively between SADs with and without MVP. However, prior literature has already demonstrated a higher mean fibrous tissue area in MVPs compared to age and gender-matched controls.(17,18) Fourth, staining of the right ventricular wall sections was not obtained routinely as in other postmortem studies,(19) thus limiting the assessment of right ventricular fibrosis. Finally, as MVP was not diagnosed on visual inspection in half of our MVP sample, and a dedicated longitudinal section including the posterior mitral leaflet and the inferior-basal LV was not obtained, MAD assessment was not available in all MVP cases with SAD.

CONCLUSIONS

In a 5-year postmortem study of all adult SCDs up to age 90 in an entire metro area, MVP prevalence was at least 4% of SADs, but half of MVP cases were not apparent on autopsy. Postmortem methods often missed MVPs with single leaflet involvement. Contrary to postmortem studies in younger SCDs, lethal MVP in older SCDs did not consistently have bileaflet anatomy, or MAD. Multisite interstitial fibrosis was common among lethal MVP cases, while replacement fibrosis was rare.

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ABBREVIATION LIST

MVP	mitral valve prolapse
SCD	sudden cardiac death
MR	mitral regurgitation

WHO	World Health Organization
POST SCD	POstmortem Systematic InvesTigation of Sudden Cardiac Death
SAD	sudden arrhythmic death
MAD	mitral annular disjunction
LV	left ventricular
TTE	transthoracic echocardiogram
CMR	cardiac magnetic resonance

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CLINICAL PERSPECTIVES

Clinical Competencies:

Our study demonstrates that MVP in individuals > 40 years is often missed as a cause of SAD despite a thorough autopsy, and does not consistently have bileaflet anatomy, MAD, or replacement fibrosis previously described in younger SADs. In contrast, we found histologic interstitial fibrosis in all lethal MVPs > 40 years.

Translational Outlook Implications:

Interstitial fibrosis identified postmortem in lethal MVPs is present despite the lack of significant MR. Because interstitial fibrosis can be detected by CMR in living MVPs, early identification of MVPs at highest risk of SAD is possible, even if traditional arrhythmic features are not present.

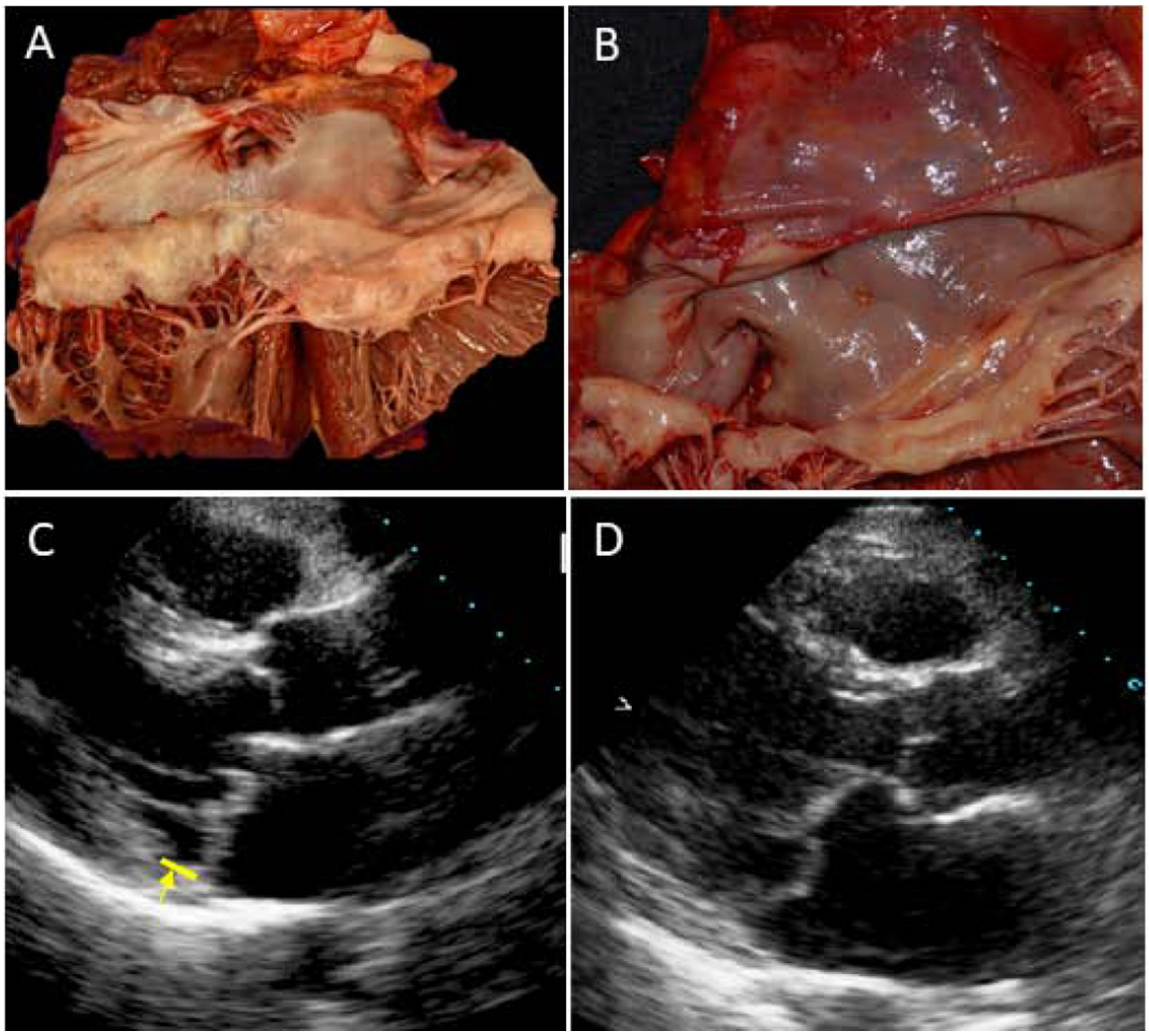


Figure 1.

Gross findings of mitral valve prolapse associated with sudden arrhythmic death with corresponding pre-mortem echocardiographic images. A) Pathologic specimen of MVP demonstrating severe thickening and billowing of both mitral leaflets. C) Echocardiographic image showing bileaflet systolic displacement beyond the mitral annulus and mitral annular disjunction (MAD) (arrow). B) Gross findings of MVP with leaflet thickening but no significant billowing, and D) corresponding echocardiographic image of posterior mitral valve prolapse without MAD.

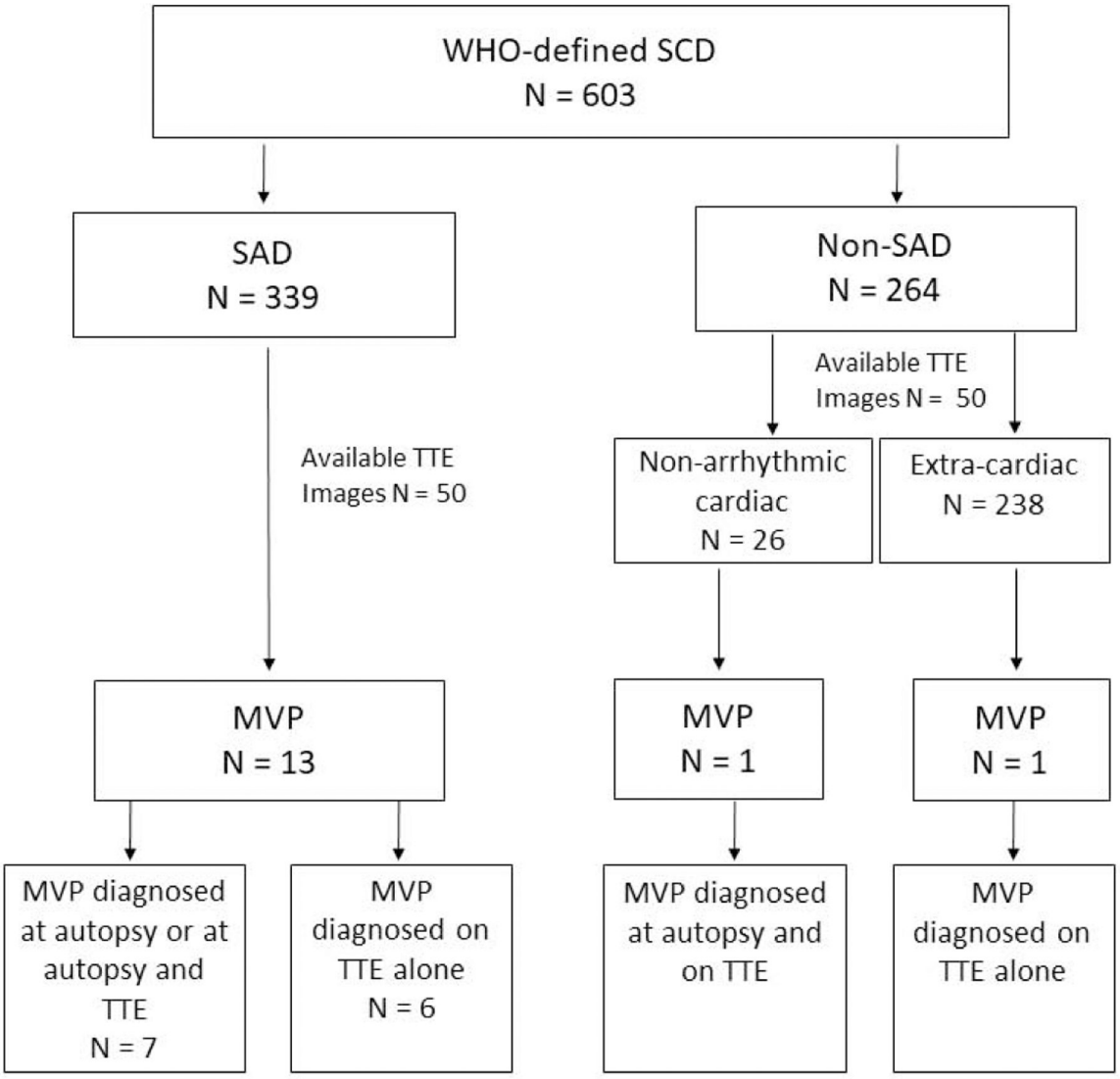
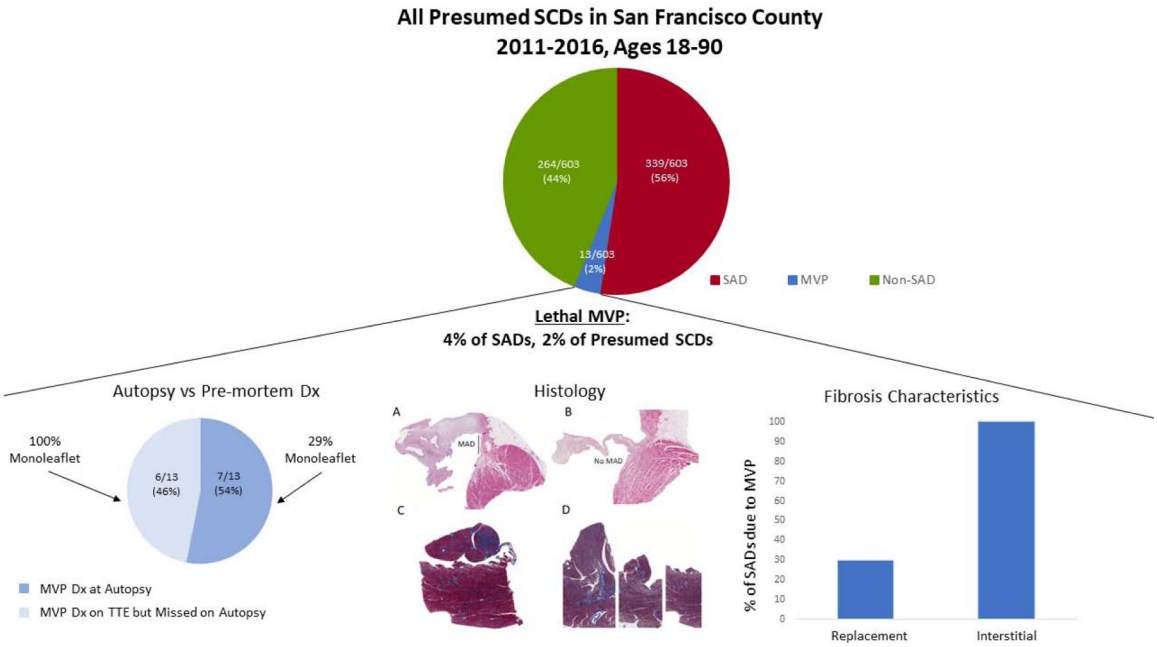


Figure 2.

Identification of lethal mitral valve prolapse (MVP) in the San Francisco POST SCD Study (POstmortem Systematic InvesTigation of Sudden Cardiac Death). WHO = World Health Organization; TTE = transthoracic echocardiogram; SAD = sudden arrhythmic death.



Central Illustration.

Epidemiology and characteristics of lethal mitral valve prolapse (MVP) among all presumed sudden cardiac deaths (SCDs) in San Francisco county, 2011–2016. (Top) MVP prevalence was 2% of all presumed SCDs, and 4% of sudden arrhythmic deaths (SADs) when non-arrhythmic causes were excluded by autopsy. (Bottom, Left) Nearly half of SADs due to MVP were missed after a thorough autopsy, especially if MVP was monoleaflet. (Bottom, Middle) Histology of lethal MVP is not unique: (A) Bileaflet MVP with severely myxomatous/thickened leaflets, mitral annular disjunction (MAD), and replacement fibrosis in the inner/mid basal inferior left ventricle (LV); (C) in the same subject, trichrome section demonstrating patchy replacement-type fibrosis in the inferior-medial papillary muscle and endoperimysial (interstitial) fibrosis in the subjacent LV wall. B) Posterior MVP with thickened leaflets, but without MAD or replacement fibrosis; D) Multisite endoperimysial fibrosis as shown (from left to right) in the superior-lateral papillary muscle/subjacent LV wall, inferior-medial papillary muscle/subjacent LV wall, and interventricular septum. (Bottom, Right) Replacement fibrosis was rare but multisite interstitial fibrosis was universal. Dx = diagnosis.

Table 1.

Baseline Characteristics of Presumed Sudden Cardiac Death Population

	Non-SAD N=264	SAD N=339	*P* value
Demographics			
Age, years (IQR)	60 (52 – 71)	64 (54 – 74)	0.02
Male, n (%)	165 (63)	257 (76)	<0.001
BMI, Kg/m^2 (IQR)	26.5 (23 – 31)	27.8 (24 – 33)	0.01
Non-white race, n (%)	123 (47)	144 (42)	0.31
Medical History			
Diabetes, n (%)	58 (22)	79 (23)	0.77
Hypertension, n (%)	134 (51)	199 (59)	0.06
Tobacco use, n (%)	109 (41)	126 (37)	0.31
CAD, n (%)	37 (14)	79 (23)	0.005
CKD, n (%)	32 (12)	38 (11)	0.80
Medication use			
Antiarrhythmics, n (%)	23 (9)	25 (7)	0.55
Beta-blockers, n (%)	65 (25)	121 (36)	0.003
Calcium-channel blockers, n (%)	40 (15)	49 (14)	0.81
ACE-inhibitors, n (%)	63 (24)	98 (29)	0.16
ARBs, n (%)	20 (8)	29 (9)	0.66
MVP status			
MVP, n (%)	2 (0.7)	13 (4)	0.02
Diagnosed on autopsy or TTE + autopsy, n (%)	1	7	
Diagnosed on TTE only, n (%)	1	6	
Echocardiography			
Available images, n (%)	50 (19)	50 (15)	0.17
LVEF, median (IQR)	60 (53 – 65)	57 (35 – 63)	0.13
LVEF, n (%)			0.005
<=25	6 (12%)	9 (18%)	
>25–35	2 (4%)	4 (8%)	
>35–50	5 (1%)	7 (14%)	
>50	37 (74%)	30 (60%)	

SAD indicates sudden arrhythmic death; Non-SAD were presumed SCDs for which an extra-cardiac (e.g., pulmonary embolism, hemorrhage, lethal toxicology) or non-arrhythmic (tamponade, acute heart failure) cause of death was found, for which a pacemaker or defibrillator would not have rescued the victim. BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; MVP, mitral valve prolapse; TTE, transthoracic echocardiography; LVEF, left ventricular ejection fraction. Data shown as median (interquartile range or IQR) and n (%). $P < 0.05$ for significance.

Table 2.

MVP as cause of sudden arrhythmic death: comparison between autopsy- and echo-diagnosed MVP cases

	MVP on autopsy or autopsy + TTE N = 7	**MVP on TTE alone (missed on autopsy) N = 6**
Age, years (IQR)	60 (49–66)	68 (54–80)
Male, n (%)	5 (71)	5 (83)
Non-white race, n (%)	2 (29)	1 (17)
MVP as primary cause of SAD, n (%)	5 (71)	1 (17)
MVP as contributory cause of SAD, n (%)	2 (29)	5 (83)
Medical History		
Diabetes, n (%)	0 (0)	0 (0)
Chronic kidney disease, n (%)	0 (0)	0 (0)
Hypertension, n (%)	2 (29)	3 (50)
Tobacco use, n (%)	3 (43)	2 (33)
Drug use, n (%)	1 (14)	0 (0)
Obstructive CAD, n (%)	0 (0)	0 (0)
Family History		
SCD with unknown MVP status	0 (0)	1 (17)
Documented MVP	1 (14)	0 (0)
SCD + documented MVP	1 (14)	0 (0)
ECG characteristics		
Pre-mortem 12-lead ECG available	4 (57)	5 (83)
LBBB	1	1
Inverted or biphasic T waves in inferior ECG leads	3	1
Pre-mortem ambulatory ECG monitoring	0	0
Echocardiographic characteristics		
Pre-mortem TTE available, n (%)	3 (43)	6 (100)
LVEF, % (IQR)	58 (54–69)	64 (50–78)
MVP leaflet involvement		
Bileaflet	1	0
Posterior	2	3
Anterior	0	2
Prior mitral valve repair	0	1 *
≥ Moderate mitral regurgitation	2	0
Mitral annular disjunction	2	1
Length, mm	0–8	0–7
Tricuspid valve prolapse	0	2
Right ventricular dilatation	0	0
Right ventricular systolic dysfunction	0	0
Gross autopsy findings		

	MVP on autopsy or autopsy + TTE N = 7	MVP on TTE alone (missed on autopsy) N = 6
Cardiomegaly, n (%)	3 (43)	1 (17)
Thick mitral valve leaflets, n (%)	7 (100)	6 (100)
Mild	0 (0)	2 (33)
Moderate to severe	7 (100)	4 (67)
Histologic autopsy findings		
Replacement fibrosis, n (%)	3 (43)	1 (17)
Inferior-basal LV	1	0
SLPM and subjacent LV wall	0	0
IMPM and subjacent LV wall	2	1
Endoperimysial fibrosis, n (%)	7 (100)	6 (100)
Inferior-basal LV (mild/mod/severe)	1 (1/0/0)	0 (0/0/0)
SLPM and subjacent LV (mild/mod/severe)	2 (1/1/0)	4 (1/3/0)
IMPM and subjacent LV (mild/mod/severe)	3 (0/0/3)	4 (0./2/2)
Septum (mild/mod/severe)	2 (1/1/0)	3 (2/1/0)

MVP indicates mitral valve prolapse; TTE, transthoracic echocardiogram; SAD, sudden arrhythmic death; CAD, coronary artery disease; SCD, WHO-defined (presumed) sudden cardiac death; ECG, electrocardiogram; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; SLPM and IMPM, superior-lateral and inferior-medial papillary muscle.

* posterior MVP prior to mitral valve repair. Data shown as median (interquartile range or IQR) and n (%).