Arrhythmic Mitral Valve Prolapse and Sudden Cardiac Death

Running title: Basso et al.; Arrhythmic Mitral Valve Prolapse

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Abstract

Background—Mitral valve prolapse (MVP) may present with ventricular arrhythmias and sudden cardiac death (SCD) even in the absence of hemodynamic impairment. The structural basis of ventricular electrical instability remains elusive.

Methods and Results—A) The Cardiac Registry of 650 young adults (≤40 yrs) with SCD was reviewed and cases with MVP as the only cause of SCD were reexamined. Forty-three MVP cases (26 female, age range 19-40, median 32 yrs) were identified (7% of all SCD, 13% of women). Among 12 with available ECG, 10 (83%) had inverted T waves on inferior leads and all right bundle branch block ventricular arrhythmias. A bileaflet involvement was found in 70%. LV fibrosis was detected at histology at the level of papillary muscles in all and infero-basal wall in 88%. B) MVP patients with complex ventricular arrhythmias (N=30) and without (controls, N=14) underwent a study protocol including contrast-enhanced cardiac magnetic resonance (CE-CMR). Patients with complex ventricular arrhythmias (22 female, age range 28-43, median 41 yrs), either right bundle branch block-type or polymorphic, showed a bileaflet involvement in 70% of cases. LV late-enhancement was identified by CE-CMR in 93% vs. 14% of controls (p<0.001), with a regional distribution overlapping the histopathology findings.

Conclusions—MVP is an under-estimated cause of arrhythmic SCD, mostly in young adult women. Fibrosis of papillary muscles and infero-basal LV wall, suggesting a myocardial stretch by the prolapsing leaflet, is the structural hallmark and correlates with ventricular arrhythmias origin. CE-CMR may help to identify this concealed substrate for risk stratification.

Key words: arrhythmia (mechanisms), mitral valve, sudden cardiac death, arrhythmia, pathology, cardiac magnetic resonance imaging, mitral valve prolapse
Introduction

Mitral valve prolapse (MVP) is the most common valve disease with an estimated prevalence of 2-3% in the general population\(^1\). Although MVP is generally regarded as a benign condition\(^2,3\), the outcome is widely heterogeneous and complications such as mitral regurgitation, atrial fibrillation, congestive heart failure, endocarditis and stroke are well known. Ventricular arrhythmias and sudden cardiac death (SCD) have been even reported\(^4-7\).

From a pathologic anatomy viewpoint, accumulation of proteoglycans (myxomatous mitral valve) is the most common cause of MVP, accounting for leaflet thickening and redundancy, chordal elongation, interchordal hoodings and anular dilatation\(^8\). While these valve abnormalities well explain mitral regurgitation and mechanical complications due to enhanced extensibility, the pathogenesis of ventricular arrhythmias/SCD in MVP remains controversial.

The estimated rate of SCD in MVP ranges from 0.2% to 0.4% per year on the basis of prospective follow-up studies\(^4\). Left ventricular (LV) dysfunction due to severe mitral regurgitation identifies a patient subgroup at high risk of SCD\(^9\). However, life-threatening ventricular arrhythmias occur also in MVP patients with trivial or absent mitral regurgitation\(^10\). Previous pathology studies of SCD mostly focused on the mitral valve or conduction system abnormalities as cause of electrical instability\(^8,11-17\), while the demonstration of a myocardial source of arrhythmias remained elusive\(^18-20\).

The aim of our report is to demonstrate that MVP is a significant cause of SCD and life-threatening arrhythmias in young adults due to an underlying myocardial substrate, which is detectable by contrast-enhanced cardiac magnetic resonance (CE-CMR) and may serve for risk stratification and SCD prevention.
Material and Methods

Study populations

A) SCD victims with MVP

In the time interval 1982-December 2013, all the hearts of SCD victims ≤40 years old occurring in the Veneto Region, North East Italy (geographic area 18,368 km², overall population 4,857,210 according to the Italian Census Bureau 2011), were collected, pathologically investigated and preserved. SCD is herein defined as witnessed sudden and unexpected death occurring within 1 hour of the onset of symptoms or death of an individual who had been seen in stable condition <24 hours before being found dead21,22. Demographic, clinical and pathologic data were recorded in the electronic database of the Registry of Cardio-cerebro-vascular pathology which acts as referral center for SCD of the North-East of Italy.

Charts were evaluated for age, sex, symptoms and clinical history. All the hearts were reexamined carefully according to a standardized protocol21. SCD cases were selected in whom MVP due to myxomatous valve disease was the only cardiac abnormality found at autopsy. Myxomatous valve disease is defined as increased leaflet length and redundancy, with interchordal hoodings and leaflet billowing toward the left atrium and chordae tendineae elongation8. In the absence of extracardiac (cerebral, respiratory) or mechanical cardiovascular explanations, the cause of death was considered cardiac arrhythmic.

Exclusion criteria were clinical and/or pathologic evidence of more than mild mitral regurgitation. Hearts from 15 sex and age-matched patients (10 females, mean age 30 years, range 18–40), who died suddenly for extracardiac causes (8 cerebral and 7 respiratory), served as controls.

B) MVP patients with complex ventricular arrhythmias

The study included consecutive patients, referred to the Cardiology Clinic, from January 2010 to
December 2013, with complex ventricular arrhythmias detected on the basis of 12-lead 24-hour Holter monitoring and echocardiographic diagnosis of MVP, defined as >5 mm thickening and >2-mm displacement of one or both mitral leaflets into the left atrium as viewed in the LV outflow tract orientation\(^2\). Twelve-lead ECG 24 hours Holter was requested due to the presence of either arrhythmic symptoms or 12-lead ECG changes. Complex ventricular arrhythmias consisted of ventricular fibrillation (VF) and ventricular tachycardia (VT), either non-sustained or sustained\(^2\). Complex ventricular arrhythmias patients were further sub-divided into two groups, i.e. those with 3 ventricular premature beats (VPB) run and those >3 VPB run.

The control group consisted of MVP patients with minor ventricular arrhythmias, i.e. isolated VPB, couplets and bigeminal VPB.

Exclusion criteria were significant mitral regurgitation, tricuspid dysplasia or regurgitation, cardiomyopathies or congenital heart abnormalities, hemodynamic unstable conditions and contraindication to CMR. The study was approved by the institutional review board, and all patients gave informed consent.

Protocols of investigation.

A) Pathologic anatomy study

Formalin-fixed hearts were restudied according to a protocol previously reported\(^2\). Leaflet involvement (whether anterior, posterior or bileaflet) and the presence of endocardial fibrous plaque (friction lesion) on the LV infero-basal wall were assessed. Multiple samples of the LV and right ventricular free walls and septum, including the papillary muscles (PMs), were obtained for histology. Additional samples were taken in the LV infero-basal free wall, underneath the posterior mitral leaflet. Five \(\mu\)m-thick sections were stained with Hematoxylin-Eosin, Weigert-van Gieson, Heidenhain trichrome and Alcian-PAS. Morphometric analysis was
performed using an Image-Pro Plus program (Version 4.0. Media Cybernetics, MD, USA) to quantify the fibrous tissue percent area of LV myocardium on Heidenhain trichrome stained sections at 25x magnification. Mean cardiomyocytes diameter was calculated on Haematoxylin-eosin stained sections at 400x magnification. Quantitative analysis was performed by two blind expert pathologists (CB, SR) with an interobserver variability <5%.

B) Clinical study

All patients underwent cardiovascular evaluation including history, physical examination, 12-lead electrocardiogram (ECG), 2D-transthoracic echocardiography, 12-lead 24-hour Holter monitoring and CE-CMR. Coronary angiography was performed in selected cases. The 12-lead ECG at rest and the 24-hour Holter monitoring were independently assessed as previously reported25 by two experienced observers (MDL and DC) who were blinded to patient data.

Nou-sustained VT was defined as ≥ 3 consecutive VPBs with a rate > 100 bpm that lasted <30 seconds during 24-hour Holter monitoring. Sustained VT was defined as tachycardia originating in the ventricle with rate >100 beats/minute and lasting >30 seconds or requiring an intervention for termination.

Cardiac magnetic resonance was performed on a 1.5-Tesla scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany). All patients underwent detailed CE-CMR study protocol as previously described25. The presence and location of late gadolinium enhancement (LGE) were independently assessed by two experienced observers (MPM and BG) who were blinded to clinical data. To exclude artifact, LGE was deemed present only if visible in two orthogonal views (long-axis and short-axis). LGE was identified using a signal intensity threshold of >5SD above a remote reference region and quantified according to a previously reported method.
Statistical Analysis

Data are expressed as mean value±standard deviation or median with 25 to 75 percentiles for normally distributed and skewed variables, respectively. Normal distribution was assessed using Shapiro-Wilk test. Categorical differences between groups were evaluated by the chi-square test or the Fisher exact test as appropriate. Paired and unpaired t test were used to compare normally distributed continuous variables respectively obtained from the same patient and different patients; Wilcoxon signed rank test (same patient) and Wilcoxon rank sum test (independent samples) were used for skewed continuous variables.

A p value <0.05 was considered significant. The minimal detectable effect at a significance level of 5% and power at 80% is equal to 1 (with non parametric test) for quantitative variables (Cohen’ Effect); for binary data an odds ratio of at least 10 can be detected if the proportion of the characteristic test is equal to 10% in the no complex ventricular arrhythmias group (Fisher’s exact test). Statistics were analyzed with SPSS version 19 (SPSS Inc, Chicago, IL).

Results

A) SCD victims with MVP

Among 650 consecutive young SCDs recorded in the Veneto Region Registry, 43 cases (26 females, median age 32 years, range 19-40) with MVP due to myxomatous valve disease were identified. They represent 7% of all SCD cases and 13% of women who died suddenly, being the first structural cause in the latter group. Main clinical and pathologic data are reported in Table 1. SCD occurred mostly at rest or during sleep (N=35, 81%). Twenty (47%) had an in vivo diagnosis of MVP, with auscultatory click in 18 (90%) and palpitations in 14 (70%). Nine (21%)
were under beta-blockers therapy due to non sustained ventricular arrhythmias. ECG was available in 12 (28%), showing negative/isodiphasic T waves on inferior lead in 10/12 (83%) (Figure 1A,B); all had right bundle branch block (RBBB) morphology (100%) ventricular arrhythmias.

In SCD cases with MVP, valve leaflets were redundant, thick and elongated, with either isolated posterior (N=13, 30%) or bileaflet (N=30, 70%) involvement (Figure 1C). The involvement of the posterior leaflet was diffuse in 23 (53%) and confined to the medial scallop in 20 (47%). Endocardial fibrous plaques in the postero-lateral wall were found in 25 (58%).

Microscopic examination of the LV myocardium showed an increased endo-perimysial and patchy replacement-type fibrosis at the level of PMs and adjacent free wall in all (Figure 1D,E and Figure 2). Similar findings, with a subendocardial-midmural layer distribution, were detected in the infero-basal wall, underneath the posterior mitral valve leaflet, in 38 cases (88%). The mean fibrous tissue percent area in MVP SCD victims was 30.5% at the level of PMs and 33.1% in the infero-basal wall myocardium (vs. 6.3% and 6.4% in controls, p<0.001). In the same areas, the cardiomyocytes showed increased diameter (19.2±6.0 micron vs. 12.8±0.4, p<0.001) and dysmorphic and dysmetric nuclei.

**B) MVP patients with complex ventricular arrhythmias**

The baseline clinical and CMR findings are summarized in Table 2. Fourteen MVP patients with or without minor ventricular arrhythmias (i.e. isolated VPB, couplets and bigeminal VPB) served as controls.

Thirty MVP patients (22 female, median age 41) with complex ventricular arrhythmias, i.e. ≥1 VF (N=2, who had also non-sustained VT) and VT (N=28) - either non-sustained (N=27) or sustained (N=1)- were collected. VT of LV origin (RBBB morphology) was present in all,
with either inferior (43%) or superior (87%) axis. Among the 27 patients with non-sustained VT, the mean length was 4 beats (ranging 3-11 beats). Complex ventricular arrhythmias occurred at rest in 26/30 (87%). All patients had normal QTc (mean 423, range 409-440). Exercise stress test, performed in 20, was negative for effort-induced ventricular arrhythmias.

Bileaflet MVP was present in 21 (70%) patients with complex ventricular arrhythmias vs. 5 (36%) controls (p=0.031).

On post-contrast sequences, LV-LGE was identified in 28 (93%) vs. 2 (14%) (p<0.001). By dividing the MVP population with complex ventricular arrhythmias into two sub-groups, 20 patients had 3 VPB run and 10 patients >3 VPB run (p>0.05). In MVP patients with complex ventricular arrhythmias, no difference was found in terms of LV-LGE when comparing those with 3 VPB run and those >3 VPB run (p>0.05).

The LGE was localized on the PMs in 25 patients (83%), with a mid-apical distribution in 16 and/or basal adjacent free wall in 24 cases; and on the LV infero-basal segment, underneath the posterior leaflet, in 22 (73%) (Figure 3A-D). A focal endocardial LGE in the same region, featuring a fibrous plaque, was found in 12 patients (40%).

The median LV LGE % was 1.2 in MVP with complex ventricular arrhythmias vs. 0 in MVP without (p<0.01).

Two MVP patients experienced aborted SCD due to VF, despite beta-blocker therapy due to previous sustained VT. Detailed invasive and non-invasive evaluation ruled out cardiac causes other than MVP. Both had RBBB pattern ventricular arrhythmias with superior axis and T waves abnormalities on inferior leads. CE-CMR, performed 6 and 10 months before aborted SCD, revealed LV LGE of PMs and infero-basal wall (Figure 3 E,F). Both patients received an implantable cardioverter defibrillator (ICD).
One patient had pre-syncopal episodes despite bisoprolol therapy. She underwent electrophysiological study with induction of sustained VT with the same RBBB morphology of VPBs (Figure 4A-C). The CE-CMR showed a non-ischemic LGE pattern in the LV infero-basal wall (Figure 4D). She also underwent ICD implantation.

Of the three patients with ICD (mean follow-up 10 months), two had non sustained-VT: one patient with spontaneous interruption and the other requiring anti-tachycardia pacing.

**Discussion**

MVP is an under-recognized cause of SCD in young adults, accounting for 7% of total fatal events and 13% of female victims in our large Cardiac Registry experience. The patient with MVP and ventricular arrhythmias at risk of SCD is usually a young adult woman, with a mid-systolic click at auscultation, bileaflet involvement of the mitral valve, T wave abnormalities on inferior leads, RBBB-type or polymorphic ventricular arrhythmias on ECG. Clear-cut evidence of a substrate of electrical instability in MVP is herein provided for the first time and consists of myocardial scarring targeting the PMs and the infero-basal LV free wall, underneath the posterior leaflet, well in keeping with the site of origin of RBBB-type ventricular arrhythmias. The LV myocardial fibrosis observed at histology in SCD victims was then confirmed in the clinical arm of the study, with evidence of LGE at CE-CMR in arrhythmic MVP patients, thus pointing to a promising role of this non invasive technique for risk stratification beyond traditional prognostic markers.

**MVP: an underappreciated cause of SCD**

The absence of uniform diagnostic criteria of MVP in the general and forensic pathology practice and the frequent consideration of this valve disease as an uncertain cause of SCD are major
obstacles to provide data on the real burden of MVP based upon a metanalysis of published studies. With these shortcomings, the prevalence of MVP in pathology series of SCD in the young ranges from 0 to 24%. By adopting strict criteria for definition of myxomatous mitral valve, in the Veneto Region SCD Registry MVP accounted for 7% of all cases in young adults (<40 years) and 13% among women, representing the first structural cause in the latter group. The diagnosis can be easily established at macroscopic examination and then confirmed by routine histology, but it might be overlooked by superficial inspection, leading to discharge the heart as normal. Our data are likely to change the current thinking about MVP as a benign condition and point to the need to draw the attention of forensic pathologists to an entity that has been largely underestimated so far.

**Ventricular arrhythmias in MVP**

In MVP series with prolonged ECG recording, a variable prevalence of ventricular arrhythmias has been reported, reflecting the different MVP definition, the population studied and the complexity of ventricular arrhythmias considered. In particular, the clinical evidence of hemodynamically important regurgitation greatly impacts on the occurrence of ventricular arrhythmias. However, the detection of MVP in survivors of life-threatening arrhythmias suggests that a true association between hemodynamically uncomplicated MVP and arrhythmic SCD may exist. Thus, we decided to focus on "pure" MVP, excluding MVP associated with valve incompetence and LV remodelling, not to defile the message by over-reporting ventricular arrhythmias. Early electrophysiological studies demonstrated that the most common site of origin of VPB is the infero-basal portion of the LV. In the recent study of malignant MVP by Sriram et al, frequent VPBs originated from the outflow tract and PMs. Moreover, electrophysiology mapped the site of origin to the PMs, the LV outflow tract and the mitral annulus, as to suggest
that VPBs arising close to the prolapsing leaflet and adjacent structures are the arrhythmic triggers.

From a pathophysiologic perspective, the mechanism of ventricular arrhythmias in MVP patients with trivial or absent mitral regurgitation remains speculative\textsuperscript{9,38}. MVP-related factors have been first advocated, such as the excessive traction on the PMs by the prolapsing leaflets\textsuperscript{39}; the mechanical stimulation of the endocardium by the elongated chordae, with afterdepolarization-induced triggered activity; the diastolic depolarisation of muscle fibres in redundant leaflets with triggered repetitive automaticity\textsuperscript{40}; and the endocardial friction lesions with extension into the myocardium\textsuperscript{41}. Moreover, the coexistence of extravalvular diseases has been suggested, including autonomic nervous system dysfunction\textsuperscript{42}, conduction system abnormalities\textsuperscript{13}, fibromuscular dysplasia of small coronary arteries\textsuperscript{19} and occult cardiomyopathies\textsuperscript{10,43}.

The myocardial substrate of electrical instability in MVP

Previous pathology studies in MVP patients dying suddenly mostly focused on mitral valve structural alterations, suggesting a role for annular circumference, leaflets length and thickness and presence and extent of endocardial plaques\textsuperscript{8,14-17}. Surprisingly, no investigation did systematically address the LV myocardium to search for the substrate of electrical instability, except for few anecdotic cases\textsuperscript{11,13,14,44,45}. For the first time, we extended the histopathology investigation beyond the valve in all SCD cases and provided convincing evidence of fibrosis in the LV myocardium, which is closely linked to the mitral valve, i.e. the PMs with adjacent free wall and the infero-basal wall. The LV myocardial scarring is qualitatively different from that observed in ischemic heart disease, where it is usually compact and confluent, being instead patchy and interspersed within surviving, hypertrophic cardiomyocytes. Noteworthy, previous
pathology studies addressed the so-called “idiopathic myocardial fibrosis” in SCD victims. By definition this entity is not associated with other structural heart diseases and remains without an explanation. However, the LV fibrosis described in our MVP cases differ in terms of type (i.e. scarring) and location (i.e. LV papillary muscles and basal postero-lateral wall).

Furthermore, we herein demonstrate that CE-CMR can detect LV-LGE in MVP patients with complex ventricular arrhythmias, closely overlapping the histopathologic features observed in SCD victims. At the level of PMs, two LGE sites have been found, i.e. the mid-apical portion and the base/adjacent LV wall. Although PMs LGE has been reported by Han et al in MVP patients with a history of arrhythmias, most of these patients had moderate to severe mitral regurgitation. While confirming these data in purely arrhythmic MVP patients without hemodynamic impairment, we first provide convincing evidence of LGE in the infero-basal LV wall. The arrhythmogenic role of the LV myocardial scarring is supported by the morphology of arrhythmias and by electrophysiological studies in MVP indicating that the most common site of VPB origin is the infero-basal LV wall.

Most of CE-CMR studies for arrhythmic risk stratification are coming from either ischemic heart disease or cardiomyopathies, with the notion the larger the LGE burden the worse the prognosis. Our quantitative data suggest that the volume of LV scarred tissue in MVP is relatively small but still associated with SCD. We should recognize that MVP differs from other non-valvular diseases in terms of LGE distribution (“stretched areas”) and amount. Furthermore, the mechanical stretch by the prolapsing leaflet and elongated chordae could act as a trigger of electrical instability. Further studies with higher number of MVP patients are needed to confirm these preliminary data of LV LGE.

Since the early descriptions, abnormal LV contraction pattern and ECG abnormalities
suggested that MVP has a significant myocardial involvement\textsuperscript{47-51}. The hypothesis that the so-called “MVP syndrome” is a cardiomyopathy, where regional hypercontractility acts as the primum movens of mitral valve geometry disruption, with abnormal tension on the chordae and leaflets and secondary increase in myxomatous tissue and leaflet thickening, has been even advanced\textsuperscript{50,51}. Our pathology and CE-CMR data support the theory that LV abnormalities are rather the consequence of MVP, due to a systolic mechanical stretch of the myocardium closely linked to the valve, i.e. PMs and infero-basal wall, by the prolapsing leaflets and elongated chordae, accounting for a localized hyper-contractility, with myocyte hypertrophy and injury leading eventually to fibrous tissue repair. The increased cardiomyocyte diameter, in the same areas showing replacement-type fibrosis, is in keeping with this theory.

Considering that performance of CE-CMR in all MVP patients would be an expensive proposition, some clinical markers that could target a high-risk subgroup destined for screening by CE-CMR are needed. ECG depolarization abnormalities on infero-lateral leads, complex ventricular arrhythmias (≥ 3 VPB run) with RBBB morphology on 12-lead ECG Holter monitoring and a history of pre-syncope, syncope and aborted SCD seem to represent an indication for CE-CMR.

Finally, we recognize that our data support an association between anatomic substrate and risk, in an entity that is underappreciated as a cause of SCD and also has a low enough incidence that any marker of increased risk might be of significant value to the clinician.

Beta-blockers are commonly used to treat arrhythmias in MVP patients. The fact that 21% of young adult SCD victims and two living patients had aborted SCD despite beta-blocker therapy is disappointing but not surprising\textsuperscript{10}. Prospective multicenter studies are warranted to support the role of CE-CMR and electrovoltage mapping for risk stratification and to assess the
efficacy of antiarrhythmic therapy and targeted catheter ablation in selected cases.

**Limitations of the study**

While acknowledging the small number of MVP patients without complex ventricular arrhythmias, we should recognize that it is difficult to collect “pure” MVP patients without either valve incompetence or ventricular arrhythmias both clinically and at postmortem. Prospective multicenter studies enrolling a higher number of MVP, with and without complex ventricular arrhythmias, are warranted to evaluate the exact prevalence of LGE in the overall MVP population.

Genetic data are not available in our SCD population. Noteworthy, in our series of SCD victims there was macroscopic evidence of myxomatous mitral valve and nearly half (47%) had a previous in vivo diagnosis of MVP, with a cardiological check-up ruling out channelopathies. Moreover, the ECG, which was available for revision in 28%, did not show any evidence of long/short QT or Brugada syndromes. Of the remaining 31 MVP cases, 25 (80%) had first-degree family members referred for cardiological screening, without any evidence of channelopathies, but MVP in 4 cases (16%).

Although we are strong supporters of the relevance of molecular autopsy in the study of SCD\(^1\),\(^2\), we follow the indication by the HRS/EHRA/APHRS expert consensus statement\(^5\). According to these guidelines, an arrhythmia syndrome-focused postmortem genetic testing can be useful for all sudden unexplained death syndrome victims as Class IIa indication; furthermore, evaluation of first-degree blood relatives with resting ECG with high right ventricular leads, exercise stress testing, and echocardiography is recommended as Class I.

**Conclusions**

This study suggests that MVP is a significant cause of SCD in young adults and is the leading
one in women. Arrhythmic MVP patients are mostly female with ventricular arrhythmias of LV origin and frequent repolarization abnormalities on inferior leads. The hallmark of arrhythmic MVP is fibrosis of PMs and infero-basal LV free wall, which well correlates with arrhythmia morphology, pointing to a myocardial stretch by the prolapsing leaflets and elongated chordae. CE-CMR allows the identification of this arrhythmic substrate and is a promising non-invasive tool for risk stratification and SCD prevention.

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Conflict of Interest Disclosures: None.

References:


of the ventricular interstitium in idiopathic myocardial fibrosis and sudden cardiac death. *Heart Rhythm.* 2004;1:141-149.


Table 1. Clinical and pathologic features of 43 patients who died suddenly with MVP due to myxomatous degeneration.

<table>
<thead>
<tr>
<th>Variables</th>
<th>SCD due to MVP 43 patients</th>
<th>Control 15 patients</th>
<th>p</th>
</tr>
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<tbody>
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<td>Age, years median (range)</td>
<td>32 (19-40)</td>
<td>30 (18-40)</td>
<td>0.33</td>
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<td>Female, n (%)</td>
<td>26 (61)</td>
<td>10 (67)</td>
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<td>Athletes, n (%)</td>
<td>4 (9)</td>
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<td>Pectus excavatum, n (%)</td>
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<td>1.0</td>
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<td>Pregnancy, n (%)</td>
<td>2/26 (8)</td>
<td>1/10</td>
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<td>Circumstances of SCD, n (%)</td>
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<td>- on emotion/effort</td>
<td>8 (19)</td>
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<td>- at rest</td>
<td>30 (70)</td>
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<td>12 (28)</td>
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<td>Inverted/biphasic T wave D2, D3, aVF n (%)</td>
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<td>VAs, n (%)</td>
<td>12 (28)</td>
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<td>VAs morphology, n (%)</td>
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<td>- RBBB</td>
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<td>Beta-blocker therapy, n (%)</td>
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<td>Gross features</td>
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<td>Heart weight (g), mean ±SD*</td>
<td>357±53</td>
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<td>LV wall thickness (mm), mean±SD</td>
<td>12.6±1.3</td>
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<td>30 (70)</td>
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<td>Endocardial fibrous plaque, n (%)</td>
<td>25 (58)</td>
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<td>Histology features</td>
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<tr>
<td>LV scar</td>
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<td>- papillary muscles, n (%)</td>
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<td>- infero-basal wall, n (%)</td>
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<td>0</td>
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<td>Fibrous tissue /myocardium (% area)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- papillary muscles, mean ± SD†</td>
<td>30.5±10.7</td>
<td>6.3±1.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>- infero-basal wall, mean ± SD†</td>
<td>33.1±7.6</td>
<td>6.4±1.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiomyocytes diameter (µm), mean±SD†</td>
<td>19.2±6.0</td>
<td>12.8±0.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviations: LV= Left ventricle; MVP= mitral valve prolapse; RBBB= right bundle branch block; SCD= sudden cardiac death; VAs= ventricular arrhythmias; VS= ventricular septum.
Table 2. Clinical, ECG and CMR features of 44 patients with MVP.

<table>
<thead>
<tr>
<th>Variables</th>
<th>MVP with Complex VA</th>
<th>Complex VA &gt;3 VPB run 10 pts</th>
<th>Complex VA =3 VPB run 20 pts</th>
<th>MVP without Complex VA 14 pts</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 3 VPB vs</td>
<td>&gt;3 VPB vs</td>
<td>=3 VPB vs</td>
<td>≥ 3 VPB vs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complex VA</td>
<td>Complex VA</td>
<td>Complex VA</td>
<td>Complex VA</td>
<td></td>
</tr>
<tr>
<td>Age, years median (range)</td>
<td>41 (28-43)</td>
<td>37 (32-43)</td>
<td>44 (36-52)</td>
<td>51 (24-64)</td>
<td>0.44</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>22 (73)</td>
<td>9 (90)</td>
<td>13 (65)</td>
<td>7 (50)</td>
<td>0.18</td>
</tr>
<tr>
<td>Symptoms, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aborted SCD</td>
<td>2 (7)</td>
<td>2 (20)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>palpitations</td>
<td>15 (50)</td>
<td>7 (70)</td>
<td>8 (40)</td>
<td>5 (36)</td>
<td>0.52</td>
</tr>
<tr>
<td>syncope</td>
<td>2 (7)</td>
<td>2 (20)</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>chest pain</td>
<td>2 (7)</td>
<td>0</td>
<td>2 (10)</td>
<td>1 (7)</td>
<td>1.00</td>
</tr>
<tr>
<td>dyspnea</td>
<td>2 (7)</td>
<td>1 (10)</td>
<td>1 (5)</td>
<td>1 (7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Therapy, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>13 (43)</td>
<td>5 (50)</td>
<td>8 (40)</td>
<td>6 (43)</td>
<td>1.00</td>
</tr>
<tr>
<td>Sotalol</td>
<td>3 (10)</td>
<td>1 (10)</td>
<td>2 (10)</td>
<td>0</td>
<td>0.54</td>
</tr>
<tr>
<td>Other antiarrhythmics</td>
<td>1 (3)</td>
<td>1 (10)</td>
<td>0</td>
<td>1 (7)</td>
<td>0.54</td>
</tr>
<tr>
<td>ICD</td>
<td>3 (10)</td>
<td>3 (100)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>12 lead ECG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inverted/biphasic T wave, n (%)</td>
<td>10 (33)</td>
<td>5 (50)</td>
<td>5 (25)</td>
<td>3 (21)</td>
<td>0.5</td>
</tr>
<tr>
<td>D2, D3, aVF</td>
<td>9 (30)</td>
<td>4 (40)</td>
<td>5 (25)</td>
<td>2 (14)</td>
<td>0.46</td>
</tr>
<tr>
<td>D1, aVL</td>
<td>2 (7)</td>
<td>2 (20)</td>
<td>0</td>
<td>1 (7)</td>
<td>1.00</td>
</tr>
<tr>
<td>QTc duration, msec</td>
<td>423 (409-440)</td>
<td>439 (420-446)</td>
<td>420 (409-431)</td>
<td>412 (394-432)</td>
<td>0.19</td>
</tr>
<tr>
<td>ECG-Holter monitoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPB, n (%)</td>
<td>30 (100)</td>
<td>10 (100)</td>
<td>20 (100)</td>
<td>8 (57)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Bigeminal VPB</td>
<td>11 (37)</td>
<td>5 (50)</td>
<td>6 (30)</td>
<td>3 (21)</td>
<td>0.49</td>
</tr>
<tr>
<td>NSVT, n (%)</td>
<td>27 (90)</td>
<td>7 (70)</td>
<td>20 (100)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>SVT, n (%)</td>
<td>1 (3)</td>
<td>1 (10)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>VF, n (%)</td>
<td>2 (7)</td>
<td>2 (20)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>CVAs morphology, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBBB inferior axis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>LBBB superior axis</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (5)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>RBBB inferior axis</td>
<td>13 (43)</td>
<td>7 (70)</td>
<td>5 (25)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>RBBB superior axis</td>
<td>26 (87)</td>
<td>10 (100)</td>
<td>16 (80)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>CMR Morpho-functional Findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EDV, ml/m²</td>
<td>91 (89-103)</td>
<td>91 (91-94)</td>
<td>91 (89-108)</td>
<td>91 (83-91)</td>
<td>0.13</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>64 (60-65)</td>
<td>63 (59-65)</td>
<td>64 (59-65)</td>
<td>66 (64-69)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
| LV mass, gr/m² | 62 (60-63) | 62 (59-74) | 62 (60-63) | 63 (49-63) | 0.48 | 0.55 | 0.57 | 0.75  
| RV EDV, ml/m²  | 77 (71-79) | 77 (71-79) | 77 (75-81) | 77 (76-78) | 0.35 | 0.51 | 0.39 | 0.91  
| RV EF, %       | 64 (61-66) | 65 (62-69) | 64 (62-65) | 64 (64-66) | 0.43 | 0.93 | 0.27 | 0.31  
| Posterior MVP, n (%) | 9 (30) | 5 (50) | 4 (20) | 9 (64) | 0.05 | 0.68 | 0.01 | 0.12  
| Bileaflet MVP, n (%) | 21 (70) | 5 (50) | 16 (80) | 5 (36) | 0.05 | 0.68 | 0.01 | 0.12  
| LV LGE amount (%) | 1.2 (0.8-2.1) | 1.1 (0.9-2.7) | 1.4 (0.7-2.1) | 0.01 | <0.01 | <0.01 | <0.01 | 0.96 |  

**CMR Post-contrast Findings**

| LV LGE | 28 (93) | 10 (100) | 18 (90) | 2 (14) | <0.01 | <0.01 | <0.01 | 0.54  
| papillary muscles | 25 (83) | 10 (100) | 15 (75) | 2 (14) | <0.01 | <0.01 | <0.01 | 0.14  
| infero-basal wall | 22 (73) | 7 (70) | 15 (75) | 1 (7) | <0.01 | <0.01 | <0.01 | 1.00  
| LV LGE amount (%) | 1.2 (0.8-2.1) | 1.1 (0.9-2.7) | 1.4 (0.7-2.1) | 0.01 | <0.01 | <0.01 | <0.01 | 0.96 |  

Abbreviations: CMR = cardiac magnetic resonance; VA = ventricular arrhythmias; EDV = End-Diastolic Volume; EF = Ejection Fraction; ICD = Implantable cardioverter defibrillator; LGE = late gadolinium enhancement; LBBB = left bundle branch block; LV = Left Ventricle; MVP = mitral valve prolapse; NSVT = non-sustained ventricular tachycardia; QTc = QT corrected; RBBB = right bundle branch block; RV = right ventricle; SCD = sudden cardiac death; SVT = sustained ventricular tachycardia; VPB = ventricular premature beats; VF = ventricular fibrillation. Categorical variables are presented as number of patients (%). Continuous values are expressed as median with 25% and 75%-iles.
Figure Legends:

**Figure 1.** SCD in a 36 years old woman with in vivo diagnosis of MVP. A,B) 12-lead basal ECG at the time of emergency department admission for palpitations. Single and coupled VPBs with RBBB morphology are present; note the negative T wave on the inferior leads. At 24 hour Holter-ECG (B) NSVT is also recorded; C) At gross examination, myxomatous degeneration of both leaflets of the mitral valve with elongated chordae is visible; D, E). At histology, severe myxoid thickening of the posterior mitral valve leaflet and myocardial fibrosis of the LV infero-basal wall (D) and PM (E).

**Figure 2.** Histology of three representative SCD cases with MVP. Myocardial scarring is visible at the level of the infero-basal LV free wall, underneath the posterior mitral valve leaflet (A,B,C) and of the PMs plus adjacent free wall (D,E,F). Close-up of the scarring areas showing endo-perimysial and patchy replacement-type fibrosis with interspersed cardiomyocytes (G,H,I).

**Figure 3.** CMR post-contrast sequences findings in MVP patients with complex ventricular arrhythmias and aborted SCD. A,B) A 30 years old woman with MVP and complex ventricular arrhythmias. LGE of the PM is visible on mid-short axis view (A). The 12 lead ECG (B) shows the presence of NSVT with RBBB morphology originating from the posterior PM (superior axis). C,D) A 33 years old woman with MVP and complex ventricular arrhythmias. LGE of the LV infero-basal region, underneath the posterior valve leaflet, with endocardial-midmural extension, is visible on 3-chamber long axis view (C). The 12 lead ECG demonstrates NSVT with RBBB morphology originating from the LV infero-basal wall near the mitral annulus.
A 38 years old man with MVP and aborted SCD. CMR, performed 6 months before cardiac arrest, shows LGE in the infero-basal region of the LV on long-axis view (E). ECG recording of polymorphic SVT degenerating into VF (F).

**Figure 4.** A 34 year old woman with pre-syncopal episodes despite antiarrhythmic drug therapy.

A) Basal ECG shows isolated VPBs with two RBBB morphologies, indicating a LV origin from the PMs and the infero-basal wall close to the mitral anulus. B,C) Electro-physiologic study with programmed stimulation and induction of sustained VT with the same morphology of VPBs originating from the posterior mitral annulus, terminated by electrical cardioversion. D) On CE-CMR, LGE at the level of the LV infero-basal wall is visible.
Arrhythmic Mitral Valve Prolapse and Sudden Cardiac Death
Cristina Basso, Martina Perazzolo Marra, Stefania Rizzo, Manuel De Lazzari, Benedetta Giorgi, Alberto Cipriani, Anna Chiara Frigo, Ilaria Rigato, Federico Migliore, Kalliopi Pilichou, Emanuele Bertaglia, Luisa Cacciavillani, Barbara Bauce, Domenico Corrado, Gaetano Thiene and Sabino Iliceto

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강덕현 교수 서울아산병원 심장내과

초록

배경
승모판 탈출증(mitral valve prolapse, MVP)에서 혈액학적 장애 없이도 심실성 부정맥 및 돌연 심장사(sudden cardiac death, SCD)가 발생할 수 있지만, 승모판 탈출증에서 심실성 부정맥과 SCD의 발병 기전은 논란이 많고, 심실의 전기적 불안정에 대한 구조적 근거는 찾아내기 어렵다.

방법 및 결과
40세 이하의 SCD가 발생한 성인 650명의 심장 병리 registry를 재검토하였고, MVP가 SCD의 유일한 원인이었던 증례들을 재조사하였다. MVP가 동반된 43명의 환자(여성 26명, 연령 범위, 19-40세, 중앙값, 32세)를 찾아 내었는데, 전체 경우 성인 SCD의 7% 및 젊은 여성 SCD의 13%에 해당하였다. 심전도를 얻을 수 있었던 12예 중 10예(83%)에서 T파 역위가 inferior leads에서 관찰되었고, 12예 모두에서 우각하단 심실성 부정맥이 있었 다. 승모판양엽의 탈출증이 70%에서 관찰되었다. 조직학 검사 결과, 좌심실 섬유층이 기저하부벽(basal inferior wall) 부위에서 88%, 우두근 부위에서는 모든 환자에서 발견되었다. 살아 있는 MVP 환자들을 대상으로 임상연구도 시행하였는데, 24시간 홍터 검사에서 심실세동 및 심실성 빈맥 등의 복잡한 심실성 부정맥이 발견된 MVP 환자 30명과 부정맥을 동반하지 않은 MVP 환자(대조군) 14명에서 조영 증강 심장 자기 공명(magnetic resonance)영상 검사를 포함한 연구 프로토콜이 시행되었다. 심장 자기공명영상 검사에서 좌심실의 자연 증강(late enhancement)이 대조군의 14%에서 발견된 반면 부정맥 환자들은 93%에서 발견되었고(P<0.001), SCD 증례들에서의 조직병리학 소견과 검사는 부위에서 자연 증강이 관찰되었다.

결론
MVP는 부정맥으로 인한 SCD에서 과소 평가된 원인이고, 젊은 여성 SCD에서 중요한 원인이다. 승모판 양엽 탈출에 의한 심근 담김을 시사하는 우두근 및 기저하부벽 섬유층은 구조적 특징이고, 심실성 부정맥의 근원과 연관된다. 조영 증강 심장 자기공명 검사는 생체 내에서 이러한 감추어진 기질을 찾아 내어 위험도 측정을 도울 수 있다.