
# UNIVERSITÀ DEGLI STUDI DI MILANO

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Department of Clinical Sciences and Community Health

PhD THESIS

# Multiparametric **SC**ore for prediction of myocardial f**I**brosis in patients with **MIT**ral v**A**lve p**R**olapse: the **SCIMITAR** Trial

MED/11

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# Table of contents

## ABSTRACT

**Background**. A subset of patients with mitral valve prolapse (MVP) —particularly those with Barlow's disease —may develop ventricular arrhythmias (VAs) and sudden cardiac death. Several imaging and clinical features have been proposed as arrhythmic risk factors, yet no validated stratification models exist.

**Methods**. The SCIMITAR study is an ongoing multicentre observational study enrolling adult patients with MVP at transthoracic echocardiography (TTE), independent of mitral regurgitation grade. Both prospective and retrospective cohorts are included. Patients undergo clinical, electrocardiographic, 24hour Holter, TTE, and cardiac magnetic resonance (CMR). The primary aims are to develop a scoring model predictive of fibrosis on CMR, and to identify features associated with significant (≥mild) VAs on 24-hour Holter, namely ≥5% total premature ventricular complexes burden and/or ventricular tachycardias (VTs).

**Results**. To date, 162 patients have been enrolled. Late gadolinium enhancement (LGE) was detected in 39.5% of patients, and significant VAs in 30.2%, while severe VAs (non-sustained VTs with a heart rate >180 bpm or sustained VT) occurred in 3.7%. LGE-positive patients demonstrated a higher prevalence of prior VAs ablation, true mitral annular disjunction (MAD) at TTE (31.3% vs. 15.5%, p=0.017), and more than moderate (non-sustained VTs with a heart rate of 120-179 bpm) VAs (21.9% vs. 10.2%, p=0.041) compared with LGE-negative individuals. Demographic and clinical features showed limited predictive value. No clinically significant difference was documented between patients showing significant VAs compared to those without significant VAs. Conversely, associations were detected between ≥moderate VAs and leaflet thickening, true-MAD at TTE, left ventricular (LV) curling by CMR and LGE, consistently with previously described arrhythmogenic mechanisms.

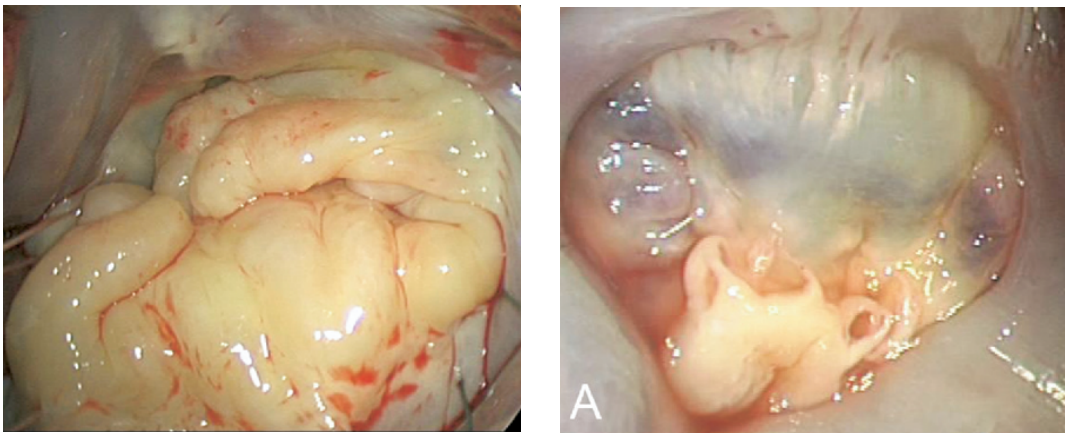
**Conclusions**. Preliminary findings highlight the possible interplay of MAD, LV mechanics, and myocardial fibrosis in the arrhythmogenic profile of MVP. Although severe VAs are infrequent, multimodality imaging and multiparametric clinical approach appear essential for individualized risk stratification.

# 1. INTRODUCTION

## *1.1 Epidemiology and pathophysiology of mitral valve prolapse*

Mitral valve prolapse (MVP) is a common valve disease with a prevalence of 2-3% in the general population. It is characterized by structural changes in the mitral valve (MV) leaflets, due to proteoglycan accumulation and collagen alterations[1,2]. Macroscopically, MVP manifests as redundant valve tissue and is diagnosed by echocardiography as a displacement of one or both leaflets ≥2 mm above the MV annulus (MVA) as observed at end-systole in long-axis views. MVP has two main phenotypic expressions: fibroelastic deficiency (FED) and Barlow's disease (BD)[1-3]. FED is due to an impaired production of connective tissue; it usually affects patients >60 years and is characterized by the involvement of one single segment of the MV, leaflet redundancy and thickening almost exclusively localized to the prolapsing scallop, and frequent chordal rupture[2,3] (Figure 1). BD is likely genetically determined, and characterized by diffuse myxoid deposition, bulky and redundant leaflets[2,3]. It usually affects younger patients and is characterized by multiple segments involvement, often with bileaflet redundancy and thickening, and chordal elongation (Figure 1).

**Figure 1 – Phenotypic expression of mitral valve prolapse**




Represented are the two main phenotypic expressions of MVP, as visualized by the cardiac surgeon. On the left an example of Barlow's disease with thickened and redundant mitral valve leaflets; on the right an example of fibroelastic deficiency with single scallop thickening and prolapse, associated with chordal rupture (from Anyanwu et al.)[2].

## *1.2 Arrhythmic mitral valve prolapse*

The main consequence of MVP is mitral regurgitation (MR), caused by a coaptation defect of the MV leaflets. In the absence of significant MR, MVP is generally considered as a benign condition with a good prognosis[4-6]. Still, a minority of patients with MVP, specifically those with myxomatous degeneration of the MV leaflets (BD), are affected by ventricular arrhythmias (VAs). Indeed, a clinically significant subset of patients (from 0.14% to 1.8% annually) may experience life-threatening

VAs and sudden cardiac death (SCD); however, severe MR accounts for only 20% of SCD observed in MVP patients[1]. At autopsy, MVP prevalence among young patients deceived for SCD is reported to be 4-7%[7].

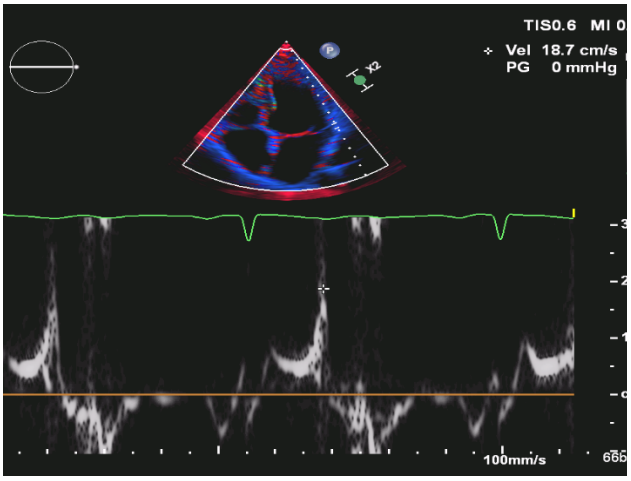
A new clinical entity has been recognized, the arrhythmic mitral valve prolapse (AMVP), which is defined by the documentation of frequent or complex VAs in the absence of another arrhythmic substrate. Significant VAs include ventricular fibrillation, sustained or non-sustained ventricular tachycardia (VT), or ≥5% of ventricular ectopic (VE) beats at 24h-Holter monitoring[7]. In MVP, VAs are likely induced by mechanisms of triggered activity and re-entry, caused by a combination of mechanical stretch, inflammation and consequent myocardial fibrosis, which can be detected by cardiac magnetic resonance (CMR)[1]. Multimodality imaging, as well as clinical, electrocardiographic and Holter parameters are crucial for identifying patients with high arrhythmic risk.

## 2. BACKGROUND OF THE STUDY

Several papers have been published on AMVP, and different demographic, clinical, electrocardiographic characteristics, as well as morphological and structural features of the MV have been hypothesized as potential risk factors for VAs[5-14]:

1. female sex;
2. young age;
3. mid-systolic auscultatory click;
4. history of palpitations, pre-syncope or unexplained syncope;
5. ST segment abnormalities, biphasic or negative T waves in the inferolateral leads;
6. frequent and/or complex VE beats with right-bundle-branch morphology and/or polymorphic VE beats at 24-hour ECG-Holter;
7. bileaflet prolapse;
8. curling of the left ventricle (LV), which is an abnormal systolic movement of the LV inferolateral basal wall that shows an exaggerated inward and downward displacement with minimal or absent anterior movement;
9. Pickelhaube sign, defined as a high-velocity (≥16 cm/s) late-systolic spike in the pulsed-wave tissue Doppler signal of the lateral MVA at transthoracic echocardiography (TTE)[14] (Figure 2);

**Figure 2 - The Pickelhaube sign**

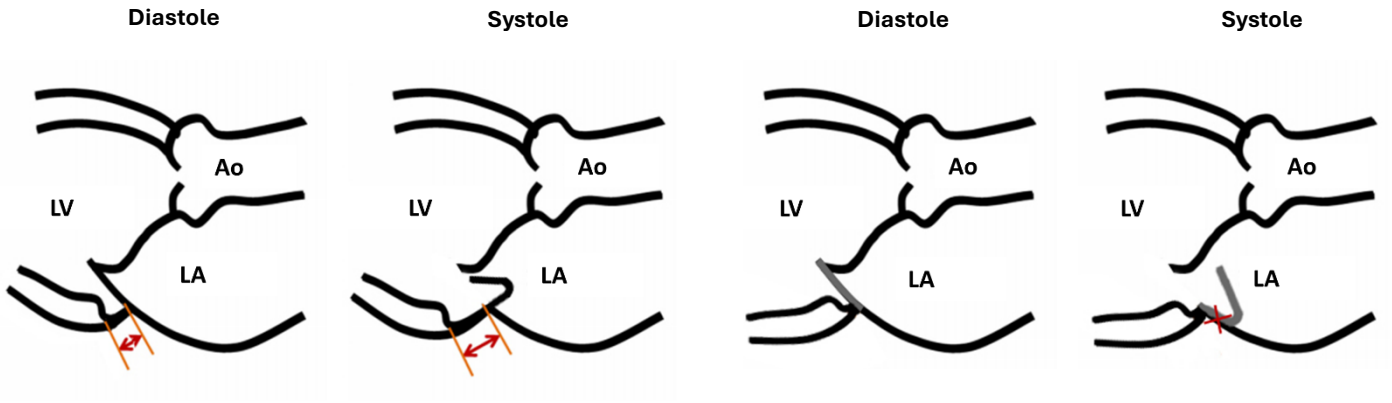



Represented is an example of Pickelhaube sign at tissue Doppler at the level of the lateral mitral valve annulus, with a late-systolic velocity of 18.7 cm/s.

10. mitral annular disjunction (MAD), defined as a separation between the attachment of the posterior MV leaflet to the left atrial wall from the base of the LV myocardium[15-24] (Figure 3);
11. fibrosis (specifically of the LV inferolateral wall and posterior papillary muscle) as detected by CMR[6-8].

Though MAD was observed mainly in patients with BD, it was detected also in patients with FED, forme frustae of MVP, and in structurally normal hearts[20,21]. The hypothesized pro-arrhythmic role of MAD is such that the concept of a “mitral annulus disjunction arrhythmic syndrome” was introduced by Dejgaard and colleagues[22]. Although MAD has traditionally been measured in systole in imaging studies, the concepts of true-MAD and pseudo-MAD have been recently introduced[23]. In true-MAD, the atrial insertion of the posterior leaflet is displaced from the LV myocardium both in systole and diastole (Figure 3, panels on the left); in pseudo-MAD the apparent systolic displacement of the posterior leaflet is represented by the juxtaposition of the prolapsing leaflet to the left atrial wall, whereas no separation is observed in diastole between the posterior mitral annulus and the LV myocardium (Figure 3, panels on the right).

**Figure 3 – True MAD and pseudo-MAD**




Represented is a graphically illustration of true-MAD (panels on the left) and pseudo-MAD (panels on the right).

As CMR has some limitations (limited availability, long time of performance, high costs), it is unknown if and which patients, diagnosed with MVP by TTE, should undergo CMR in routine clinical practice to search for late gadolinium enhancement (LGE) as a surrogate for myocardial fibrosis, which has a known pathophysiological association with VAs.

Additionally, at present, no consensus exists on what the risk factors for VAs are, and how much each risk factor impacts on the overall arrhythmic risk. Therefore, there are no generally accepted risk stratification models for MVP patients.

## 3. METHODS

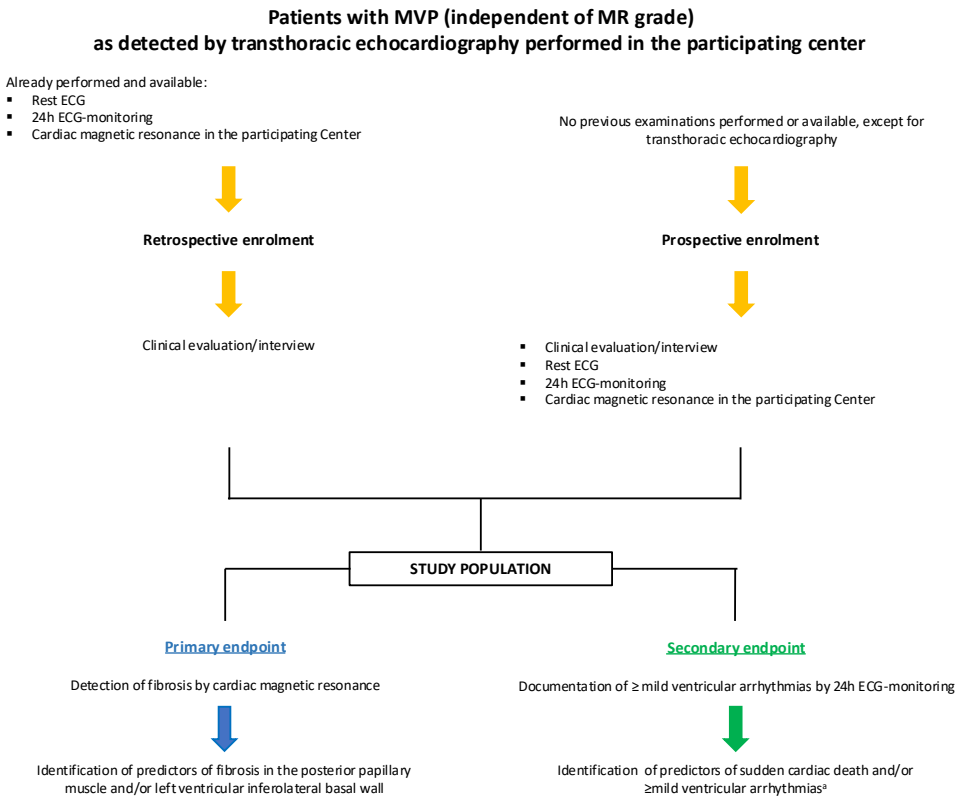
### *3.1 Study population*

Patients with a diagnosis of MVP by TTE, independent of MR grade, either affected by BD or FED, are being enrolled in the present study. Inclusion criteria are: 1) age ≥18 years; 2) TTE diagnosis of MVP, defined as a systolic displacement of one or both MV leaflets ≥2 mm above the plane of the MVA in long-axis views. Exclusion criteria include: 1) coexistence of cardiomyopathies or other ≥moderate valve diseases; 2) scarce acoustic TTE window; 3) usual contraindications for CMR.

### *3.2 Study design and patients' evaluation*

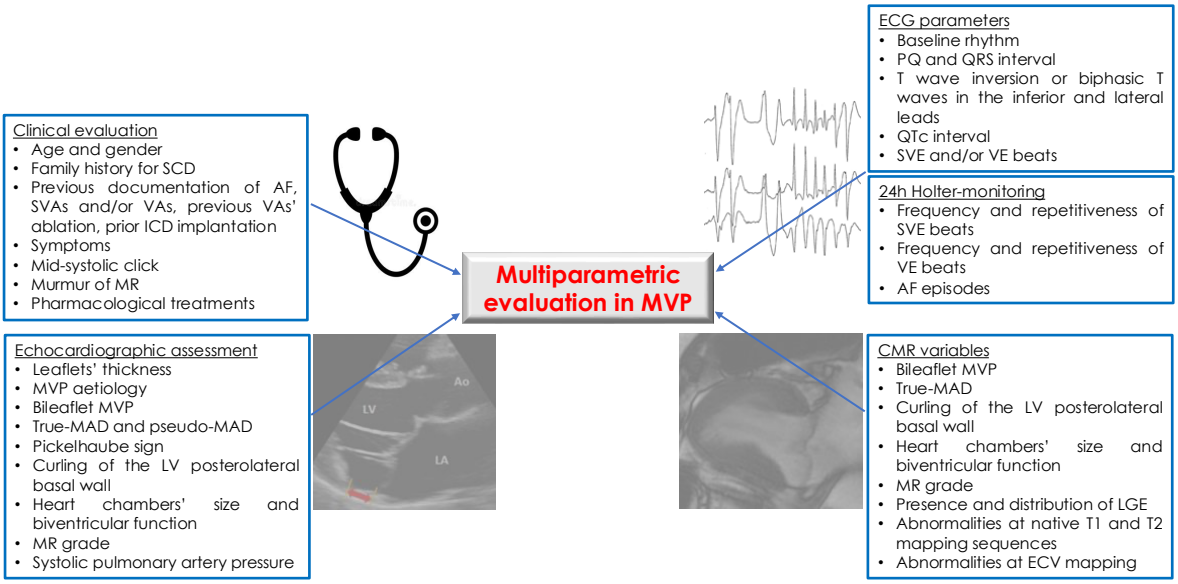
This is an observational multicentre study, promoted by Centro Cardiologico Monzino and started in June 2023. Patients are being enrolled either prospectively or retrospectively (Figure 4). Prospectively enrolled patients undergo a complete multiparametric assessment, as clinically indicated, including clinical evaluation, rest ECG, 24h ECG-monitoring, TTE, and CMR (Figure 5). CMR is performed ≤6 months apart from other examinations. Retrospectively enrolled patients have already performed all the examinations required by the study protocol between 2016 and 2023.

## Figure 4 - Study design




CMR = cardiac magnetic resonance; ECG = electrocardiogram; TTE = transthoracic echocardiography.
[a] As defined in Sabbag et al. EHRA expert consensus statement on arrhythmic mitral valve prolapse and mitral annular disjunction complex in collaboration with the ESC Council on valvular heart disease and the European Association of Cardiovascular Imaging endorsed by the Heart Rhythm Society, by the Asia Pacific Heart Rhythm Society, and by the Latin American Heart Rhythm Society. Europace. 2022

**Figure 5 – Multiparametric assessment of patients**




AF=atrial fibrillation; ECV=extracellular volume; ICD=implantable cardioverter defibrillator; LGE=late gadolinium enhancement; LV=left ventricular; MAD=mitral annular disjunction; MR=mitral regurgitation; MVP=mitral valve prolapse; SCD=sudden cardiac death; SVAs=supraventricular arrhythmias; SVE=supraventricular ectopic; VAs=ventricular arrhythmias; VE=ventricular ectopic.

The aims of the study are the following: 1) to compute a scoring model potentially predictive for the detection of fibrosis by CMR in patients with MVP; 2) to identify features that may predispose to significant VAs in patients with MVP, namely ≥mild VAs at 24h ECG-monitoring.

Clinical evaluation

The following data are being collected:

- demographic variables at the time of enrolment (gender, age);
- family history for SCD;
- previous documentation of atrial fibrillation (AF), supraventricular arrhythmias (SVAs) and/or VAs, previous ICD implantation, previous transcatheter ablation of VAs;
- symptoms (history of unexplained syncope/pre-syncope, palpitations, dyspnoea);
- mid-systolic click;
- murmur of mitral regurgitation;
- pharmacological treatments.

Rest ECG

All ECGs are reviewed for documentation of the following:

- baseline rhythm (sinus rhythm, atrial fibrillation/flutter, junctional rhythm);
- atrioventricular or intraventricular conduction disturbances (PQ and QRS interval);
- T wave inversion or biphasic T waves in the inferior and lateral leads;
- QTc prolongation (QTc interval);
- supraventricular ectopic (SVE) beats;
- VE beats (and their morphology and/or repetitiveness)[7].

24h electrocardiographic monitoring

All arrhythmic events documented by ECG-Holter are being recorded. Specifically:

- frequency of SVE beats (expressed as absolute number and as premature supraventricular complexes burden) and repetitiveness (couplets, triplets, supraventricular tachycardia);
- episodes of AF;
- frequency of VE beats (expressed as absolute number and as premature ventricular complexes burden), morphology (monomorphic or polymorphic), and repetitiveness (couplets, triplets, ventricular tachycardia).

VAs will be classified as suggested in the recently published consensus statement[7]:

- MILD VAs, defined as frequent VE beats (≥5% total premature ventricular complexes burden) or non-sustained (<30 seconds) VT runs with a heart rate <120 bpm
- MODERATE VAs, defined as non-sustained (<30 seconds) VT runs with a heart rate of 120-179 bpm
- SEVERE VAs, defined as non-sustained (<30 seconds) VT runs with a heart rate >180 bpm or sustained (≥30 seconds) VT/VF.

Transthoracic echocardiography

A standard TTE is performed according to current guidelines. Specifically, the following parameters are assessed:

- presence of true-MAD and pseudo-MAD in long-axis views[21,23-24];
- presence of the Pickelhaube sign at tissue Doppler imaging[14];
- presence of curling of the LV posterolateral basal wall[8];
- mitral leaflet thickness, classification of MVP as BD or FED, presence of bileaflet prolapse[2,3];
- left atrial size[25];
- MR grade by integrating qualitative (Color Doppler jet characteristics, pulmonary vein flow pattern) and quantitative criteria (vena contracta width, effective regurgitant orifice area, regurgitant volume, and regurgitant fraction)[26];
- LV diameters, volumes, and ejection fraction[25];

- right ventricular (RV) dimensions, tricuspid annular plane systolic excursion (TAPSE), and fractional area change (FAC)[25];
- systolic pulmonary artery pressure (SPAP) derived from the peak velocity of the tricuspid regurgitation and from the estimated right atrial pressure[27].

Cardiac magnetic resonance

Patients are studied with a 1.5-T scanner, applying the protocol of the Society of Cardiovascular Magnetic Resonance[28]. After acquiring localizer images of the heart, breath-hold steady-state free-procession cine CMR will be performed in standard long- (four-, two-, three-chamber) and short-axis orientations[29]. Late gadolinium enhancement imaging is performed according to each Centre's protocol.

Collected parameters include:

- MR grade, based on the regurgitant volume and regurgitant fraction[30];
- LV mass, and biventricular volumes, stroke volume and ejection fraction;
- presence of curling of the LV posterolateral wall[8];
- assessment of true-MAD and pseudo-MAD using 3 standard LV long-axis cine sequences[22-24];
- presence and distribution of LGE: usually, mid-wall LGE at the papillary muscles or patchy myocardial fibrosis (non-ischemic pattern) at basal LV inferolateral wall[8,22].

Optional parameters that are being collected are:

- presence of abnormalities at native T1 mapping sequences, as detected by modified look-locker inversion (MOLLI) recovery sequences at the LV basal, mid, and apical levels[29,31]; global mean native T1 and segmental analysis are performed on the short-axis images;
- presence of myocardial oedema at T2-weighted fast-spin-echo triple inversion recovery (T2-w TIR) and T2 mapping sequences in standard long- and short-axis orientations[32]; T2 values are obtained from single-shot T2-prepared images acquired at multiple echo times with the same prescription of short-axis T2-w TIR sequences[32];
- presence of abnormalities at extracellular volume (ECV) mapping, generated according to the following formula: myocardial ECV = (1 - haematocrit) × ($\Delta R1_{myocardium}/\Delta R1_{blood}$), where R1 = 1/T1[31]. ECV mapping sequences are acquired at 15 min after gadolinium-based contrast administration, post-contrast MOLLI sequences with the same prescriptions of pre-contrast MOLLI sequences will be acquired[31].

## 3.3 Endpoints

Primary endpoint: detection of left ventricular LGE, as a surrogate for fibrosis, by CMR.

Secondary endpoint: detection of significant VAs, intended as ≥mild VAs at 24h ECG-Holter[7].

### 3.4 Statistical analysis

Continuous variables will be expressed as mean ± standard deviation, or as median [interquartile range], as appropriate. Categorical variables will be presented as absolute numbers (and frequencies). Patients will be classified into two groups, based on the presence of myocardial fibrosis at CMR (LGE+ vs. LGE-) or based on significant VAs' occurrence (VAs+ vs. VAs-). Continuous variables will be compared using the unpaired Student's t test or Mann-Whitney U test, while categorical variables will be compared applying the chi-square test or Fisher's exact test (if the expected cell count was <5), as appropriate.

Baseline parameters potentially predictive for myocardial fibrosis from the univariable analysis (showing statistical significance) will be included in multivariable logistic regression analysis, avoiding the combination of variables showing collinearity and removing covariates with greater than 10% missing data. As fibrosis is reported in 28-37% of patients with MVP undergoing CMR[7], assuming a prevalence of fibrosis of 35%, with 300 patients we can estimate a 95% confidence interval for the area under the roc curve (assumed to be 0.80) of 0.74-0.86. Analogously, parameters showing statistical significance in univariable testing for arrhythmic outcomes will also be included in a multivariable model to identify independent predictors of significant VAs.

Additionally, correlations between VAs (≥mild or ≥moderate) and MAD length, as well as between VAs and the extent of MAD along the MVA (expressed as the numbers of TTE views demonstrating MAD) will be assessed using Spearman's correlation coefficients. To explore the role of mapping parameters as predictors of VAs (≥mild or ≥moderate), and to evaluate their potential prognostic stratification ability, a univariate logistic regression analysis will be performed. Finally, given the very low number of patients with papillary muscle LGE, Fisher's exact test will be applied to assess the potential role of LGE localization at the inferolateral wall or papillary muscle in arrhythmic risk stratification.

A p value ≤0.05 will be required for statistical significance.

## 4. RESULTS

So far, 189 patients have been enrolled in the present study (182 enrolled at IRCCS Centro Cardiologico Monzino and 7 enrolled at IRCCS Ospedale San Raffaele). Patients were excluded for withdrawal of the consent (n=3), for significant CMR artifacts due to VAs (n=1), for inability of the patients to perform or complete CMR for claustrophobia (n=3). Two patients, referred to our Centre for MVP, were excluded because MVP diagnosis was not confirmed at TTE. Five patients were lost before completing all the examinations required by the study. Thirteen prospectively enrolled patients have not been included in these preliminary analyses, as they still have to undergo all the examinations required by the study. Therefore, the present analyses are related to an unselected population of 162 MVP patients, of whom 104 were prospectively enrolled.

Characteristics of the study population are reported in Table 1.

**Table 1 – Characteristics of the study population**

| | **Overall (n=162)** |
|---|---|
| Male (n, %) | 74 (45.7) |
| Age (years) | 53 ± 15 |
| **Medical history** | |
| Family history of SCD (n, %) | 6 (3.7) |
| History of AF (n, %) | 17 (10.5) |
| History of SVAs (n, %) | 29 (17.9) |
| History of VAs (n, %) | 85 (52.5) |
| Previous implantation of ICD (n, %) | 3 (1.9) |
| Previous VAs ablation (n, %) | 8 (4.9) |
| Syncope/presyncope (n, %) | 15 (9.3) |
| Palpitations (n, %) | 84 (51.9) |
| Dyspnoea (n, %) | 30 (18.5) |
| NYHA class (n, %) | |
| I | 133 (82.1) |
| II | 26 (16.0) |
| III | 3 (1.9) |
| **Physical examination** | |
| Systolic click (n, %) | 20 (12.5) |
| Systolic murmur (n, %) | 100 (62.5) |
| **Drugs** | |
| Beta-blockers (n, %) | 71 (43.8) |
| Non-DHP-CCB (n, %) | 0 (0) |
| Amiodarone (n, %) | 2 (1.2) |
| Sotalol (n, %) | 4 (2.5) |
| AAD of class IC (n, %) | 22 (13.6) |
| ACEi (n, %) | 29 (17.9) |
| ARB (n, %) | 11 (6.8) |
| MRA (n, %) | 4 (2.5) |
| Diuretics (n, %) | 14 (8.6) |
| Antiplatelet therapy (n, %) | 19 (11.7) |
| Anticoagulant therapy (n, %) | 11 (6.8) |
| **ECG** | |
| Baseline rhythm (n, %) | |
| Sinus rhythm | 161 (99.4) |
| AF/atrial flutter | 1 (0.6) |
| AV block (n, %) | 11 (6.8) |

| | |
|---|---|
| Intraventricular conduction disturbances (n, %) | 48 (29.6) |
| Long QT (n, %) | 10 (6.2) |
| Inverted/biphasic T waves in the inferolateral leads (n, %) | 45 (27.8) |
| SVE beats (n, %) | 4 (2.5) |
| VE beats (n, %) | 31 (19.1) |
| **ECG Holter** | |
| Baseline rhythm (n, %) | |
| Sinus rhythm | 160 (98.8) |
| AF/atrial flutter | 2 (1.2) |
| SVE beats (n) | 39 [7-250] |
| SVE beats (% of total beats n°) | 0.0 [0.0-0.1] |
| SVE beats ≥5% of total beats (n, %) | 5 (3.1) |
| SVE repetitiveness (n, %) | |
| Couplets | 16 (10.2) |
| Triplets | 4 (2.5) |
| SV tachycardia | 46 (29.3) |
| Atrial fibrillation (n, %) | 7 (4.4) |
| VE beats (n) | 593 [94-2823] |
| VE beats (% of total beats n°) | 0.1 [0.0-3.4] |
| VE beats ≥5% of total beats | 28 (17.3) |
| VE repetitiveness (n, %) | |
| Couplets | 47 (29.0) |
| Triplets | 23 (14.2) |
| NSVT | 32 (19.8) |
| SVT (n, %) | 0 (0) |
| ≥mild VAs (n, %) | 49 (30.2) |
| ≥moderate VAs (n, %) | 24 (14.8) |
| Mild VAs (n, %) | 25 (15.4) |
| Moderate VAs (n, %) | 18 (11.1) |
| Severe VAs (n, %) | 6 (3.7) |
| **TTE** | |
| BSA ($cm^2$) | 1.80 ± 0.20 |
| Aetiology (n, %) | |
| FED | 25 (15.4) |
| Barlow's disease | 137 (84.6) |
| Bileaflet MVP (n, %) | 136 (84.0) |
| AML thickness (mm) | 4.4 ± 1.2 |
| PML thickness (mm) | 4.8 ± 1.3 |
| Chordal rupture (n, %) | 34 (21.0) |
| MR grade (n, %) | |

| | |
|---|---|
| Mild | 57 (35.2) |
| Moderate | 37 (22.8) |
| Moderate-to-severe | 17 (10.5) |
| Severe | 51 (31.5) |
| LAVi (mL/m$^2$) | 42.2 ± 16.9 |
| True-MAD (n, %) | 35 (21.7) |
| Maximal true-MAD distance (mm) | 7 ± 2 |
| N° of views with true-MAD (n, %) | |
| 1 | 24 (68.6) |
| 2 | 7 (20.0) |
| 3 | 4 (11.4) |
| Pseudo-MAD (n, %) | 59 (36.6) |
| Pickelhaube sign (n, %) | 33 (22.1) |
| LV curling (n, %) | 82 (51.3) |
| LV EDDi (mm) | 30.1 ± 4.0 |
| LV ESDi (mm) | 18.2 ± 3.9 |
| LV EDVi (mL/m$^2$) | 69.0 ± 15.6 |
| LV ESVi (mL/m$^2$) | 26.2 ± 7.9 |
| LV EF (%) | 62.0 ± 5.9 |
| RA area (cm$^2$) | 16.6 ± 4.1 |
| RV FAC (%) | 47.0 ± 7.6 |
| TAPSE (mm) | 27 ± 4 |
| TR grade (n, %) | |
| Mild | 152 (96.2) |
| Moderate | 4 (2.5) |
| Moderate-to-severe | 2 (1.3) |
| Severe | 0 (0) |
| SPAP (mmHg) | 29 ± 8 |
| **CMR** | |
| LV EDVi (ml/m$^2$) | 101.0 ± 18.5 |
| LV ESVi (ml/m$^2$) | 41.7 ± 10.7 |
| LV EF (%) | 58.9 ± 5.7 |
| LV mass (g) | 99.8 ± 26.0 |
| LV curling (n, %) | 94 (58.0) |
| Systolic MAD (n, %) | 109 (67.3) |
| True-MAD (n, %) | 85 (52.5) |
| Pseudo-MAD (n, %) | 24 (14.8) |
| Pathological T1 mapping (n, %) | n=136 |
| | 24 (17.6) |
| Pathological T2 mapping (n, %) | n=111 |
| | 7 (6.3) |
| Pathological ECV mapping (n, %) | n=126 |

| | |
|---|---|
| | 15 (11.9) |
| LGE (n, %) | 64 (39.5) |
| LGE localization (n, %) | |
| Inferolateral wall | 49 (76.6) |
| Papillary muscle | 3 (4.7) |
| Interventricular septum | 12 (18.7) |
| MR grade (n, %) | |
| Mild | 82 (50.6) |
| Moderate | 27 (16.7) |
| Moderate-to-severe | 28 (17.3) |
| Severe | 25 (15.4) |
| LAVi (ml/m$^2$) | 48.7 ± 15.9 |
| RV EDVi (ml/m$^2$) | 85.7 ± 16.9 |
| RV ESVi (ml/m$^2$) | 38.3 ± 10.5 |
| RV EF (%) | 55.8 ± 6.2 |

AAD=anti-arrhythmic drugs; ACE=angiotensin converter enzyme; AF=atrial fibrillation; AML=anterior mitral leaflet; ARB=angiotensin-2 receptor blockers; AV=atrioventricular; BSA=body surface area; ECV=extracellular volume; EDD=end-diastolic diameter; EDVi=end-diastolic volume index; EF=ejection fraction; ESD=end-systolic diameter; ESVi=end-systolic volume index; FAC=fraction area change; FED=fibroelastic deficiency; ICD=implantable cardioverter defibrillator; LAVi=left atrial volume index; LGE=late gadolinium enhancement; LV=left ventricular; MAD=mitral annular disjunction; MR=mitral regurgitation; MRA=mineralocorticoid receptor antagonist; MVP=mitral valve prolapse; non-DHP-CCB=non-dihydropyridine calcium-channel blockers; NSVT=non-sustained ventricular tachycardia; NYHA=New York Heart Association; PML=posterior mitral leaflet; RA=right atrium; RV=right ventricular; SCD=sudden cardiac death; SPAP=systolic pulmonary artery pressure; SV=supraventricular; SVAs=supraventricular arrhythmias; SVE= supraventricular ectopic; SVT= sustained ventricular tachycardia; TAPSE=tricuspid annular plane systolic excursion; TR=tricuspid regurgitation; VAs=ventricular arrhythmias; VE=ventricular ectopic.

Most of patients were in NYHA class I, had Barlow's disease and bileaflet prolapse. Patients with non-significant MR (≤moderate) by TTE were more represented that those showing significant regurgitation (moderate-to-severe and severe) (58.0% vs. 42.0%, respectively). True-MAD, curling of the LV inferolateral basal wall, and the Pickelhaube sign at TTE were detected in 21.7%, 51.3%, and 22.1% of patients, respectively. True-MAD at TTE was mainly observed in just one of the 3 long-axis views (68.6% of cases). By CMR, systolic MAD was observed in 67.3% of patients: 78.0% (n=85) true-MAD and 22.0% (n=24) pseudo-MAD. LGE was documented in 64 patients (39.5%), specifically at the level of the papillary muscle (n=3), of the inferior and/or lateral LV wall (n=49), of the interventricular septum (n=12). Forty-nine patients had significant VAs, intended as the documentation of ≥mild VAs at 24h ECG-monitoring. A small proportion of patients (3.7%) had severe VAs. No patient had sustained ventricular tachycardia on ECG Holter, nor had history of resuscitated cardiac arrest.

When classifying patients based on LGE presence by CMR (Table 2), those with LGE (LGE+) showed a significantly lower incidence of SVAs (7.8% vs. 24.5%, p=0.007), a higher prevalence of previous VAs ablation (9.4% vs. 2.0%, p=0.035), and a significantly higher prevalence of true-MAD by TTE (31.3% vs. 15.5%, p=0.017) as compared to those without LGE (LGE-). Although not statistically significant, LGE+ were less frequently affected by AF (4.7% vs. 14.3%, p=0.066) and

prescribed anticoagulant therapy (1.6% vs. 10.2%, p=0.051), whereas the prevalence of male gender (53.1% vs. 40.8%, p=0.124), intraventricular conduction disturbances at rest ECG (47.9% vs. 25.5%, p=0.155) and LV curling at TTE (58.1% vs. 46.9%, p=0.170) was higher in LGE+ vs. LGE-. Finally, while the incidence of significant (≥mild) VAs was not significantly different between LGE+ and LGE- (34.4% vs. 27.6%, p=0.355), LGE+ showed a significantly higher prevalence of moderate VAs (17.2% vs. 7.1%, p=0.047) and ≥moderate VAs (21.9% vs. 10.2%, p=0.041) on 24h ECG-monitoring.

**Table 2 - Characteristics of the study population classifying patients according to LGE detection by cardiac magnetic resonance.**

| | LGE- (n=98) | LGE+ (n=64) | p value |
|---|---|---|---|
| Male (n, %) | 40 (40.8) | 34 (53.1) | NS |
| Age (years) | 51 ± 14 | 55 ± 15 | NS |
| **Medical history** | | | |
| Family history of SCD (n, %) | 4 (4.1) | 2 (3.1) | NS |
| History of AF (n, %) | 14 (14.3) | 3 (4.7) | NS |
| History of SVAs (n, %) | 24 (24.5) | 5 (7.8) | **0.007** |
| History of VAs (n, %) | 51 (52.0) | 34 (53.1) | NS |
| Previous implantation of ICD (n, %) | 0 (0) | 3 (4.7) | NS |
| Previous VAs ablation (n, %) | 2 (2.0) | 6 (9.4) | **0.035** |
| Syncope/presyncope (n, %) | 7 (7.1) | 8 (12.5) | NS |
| Palpitations (n, %) | 54 (55.1) | 30 (46.9) | NS |
| Dyspnoea (n, %) | 17 (17.3) | 13 (20.3) | NS |
| NYHA class (n, %) | | | NS |
| I | 82 (83.7) | 51 (79.7) | |
| II | 16 (16.3) | 10 (15.6) | |
| III | 0 (0) | 3 (4.7) | |
| **Physical examination** | | | |
| Systolic click (n, %) | 11 (11.2) | 9 (14.5) | NS |
| Systolic murmur (n, %) | 60 (61.2) | 40 (64.5) | NS |
| **Drugs** | | | |
| Beta-blockers (n, %) | 42 (42.9) | 29 (45.3) | NS |
| Non-DHP-CCB (n, %) | 0 (0) | 0 (0) | NS |
| Amiodarone (n, %) | 2 (2.0) | 0 (0) | NS |
| Sotalol (n, %) | 1 (1.0) | 3 (4.7) | NS |
| AAD of class IC (n, %) | 15 (15.3) | 7 (10.9) | NS |
| ACEi (n, %) | 18 (18.4) | 11 (17.2) | NS |
| ARB (n, %) | 4 (4.1) | 7 (10.9) | NS |
| MRA (n, %) | 3 (3.1) | 1 (1.6) | NS |

| | | | |
|---|---|---|---|
| Diuretics (n, %) | 9 (9.2) | 5 (7.8) | NS |
| Antiplatelet therapy (n, %) | 8 (8.2) | 11 (17.2) | NS |
| Anticoagulant therapy (n, %) | 10 (10.2) | 1 (1.6) | 0.051 |
| **ECG** | | | |
| Baseline rhythm (n, %) | | | NS |
| Sinus rhythm | 97 (99.0) | 64 (100) | |
| AF/atrial flutter | 1 (1.0) | 0 (0) | |
| AV block (n, %) | 8 (8.2) | 3 (4.7) | NS |
| Intraventricular conduction disturbances (n, %) | 25 (25.5) | 23 (47.9) | NS |
| Long QT (n, %) | 8 (8.2) | 2 (3.1) | NS |
| Inverted/biphasic T waves in the inferolateral leads (n, %) | 31 (31.6) | 14 (21.9) | NS |
| SVE beats (n, %) | 4 (4.1) | 0 (0) | NS |
| VE beats (n, %) | 19 (19.4) | 12 (18.8) | NS |
| **ECG Holter** | | | |
| Baseline rhythm (n, %) | | | NS |
| Sinus rhythm | 96 (98.0) | 64 (100) | |
| AF/atrial flutter | 2 (2.0) | 0 (0) | |
| SVE beats (n) | 64 [10-350] | 30 [6-137] | NS |
| SVE beats (% of total beats n°) | 0.0 [0.0-0.1] | 0.0 [0.0-0.0] | NS |
| SVE beats ≥5% of total beats (n, %) | 4 (4.2) | 2 (3.2) | NS |
| SVE repetitiveness (n, %) | | | NS |
| Couplets | 7 (7.4) | 9 (14.5) | |
| Triplets | 2 (2.1) | 2 (3.2) | |
| SV tachycardia | 30 (31.6) | 16 (25.8) | |
| Atrial fibrillation (n, %) | 5 (5.2) | 2 (3.1) | NS |
| VE beats (n) | 744 [73-2847] | 523 [150-2542] | NS |
| VE beats (% of total beats n°) | 0.3 [0.0-3.4] | 0.1 [0.0-3.0] | NS |
| VE beats ≥5% of total beats | 18 (18.8) | 10 (16.1) | NS |
| VE repetitiveness (n, %) | | | NS |
| Couplets | 28 (28.6) | 19 (29.7) | |
| Triplets | 16 (16.3) | 7 (10.9) | |
| NSVT | 16 (16.3) | 16 (25.0) | |
| SVT (n, %) | 0 (0) | 0 (0) | NS |
| ≥mild VAs (n, %) | 27 (27.6) | 22 (34.4) | NS |
| ≥moderate VAs (n, %) | 10 (10.2) | 14 (21.9) | **0.041** |
| Mild VAs (n, %) | 17 (17.3) | 8 (12.5) | NS |
| Moderate VAs (n, %) | 7 (7.1) | 11 (17.2) | **0.047** |
| Severe VAs (n, %) | 3 (3.1) | 3 (4.7) | NS |
| **TTE** | | | |
| BSA ($cm^2$) | 1.78 ± 0.19 | 1.83 ± 0.22 | NS |

| | | | |
|---|---|---|---|
| Aetiology (n, %) | | | NS |
| FED | 17 (17.3) | 8 (12.5) | |
| Barlow's disease | 81 (82.7) | 56 (87.5) | |
| Bileaflet MVP (n, %) | 81 (82.7) | 55 (85.9) | NS |
| AML thickness (mm) | 4.4 ± 1.2 | 4.4 ± 1.1 | NS |
| PML thickness (mm) | 4.8 ± 1.2 | 4.9 ± 1.3 | NS |
| Chordal rupture (n, %) | 23 (23.5) | 11 (17.2) | NS |
| MR grade (n, %) | | | NS |
| Mild | 31 (31.6) | 26 (40.6) | |
| Moderate | 26 (26.5) | 11 (17.2) | |
| Moderate-to-severe | 11 (11.2) | 6 (9.4) | |
| Severe | 30 (30.6) | 21 (32.8) | |
| LAVi (mL/m$^2$) | 42.2 ± 17.1 | 42.3 ± 16.6 | NS |
| True-MAD (n, %) | 15 (15.5) | 20 (31.3) | **0.017** |
| Pseudo-MAD (n, %) | 39 (39.8) | 20 (31.3) | 0.269 |
| Pickelhaube sign (n, %) | 19 (20.9) | 14 (24.1) | NS |
| LV curling (n, %) | 46 (46.9) | 36 (58.1) | NS |
| LV EDDi (mm) | 30.0 ± 3.7 | 30.2 ± 4.4 | NS |
| LV ESDi (mm) | 18.0 ± 3.8 | 18.6 ± 4.1 | NS |
| LV EDVi (mL/m$^2$) | 68.8 ± 16.0 | 69.2 ± 15.1 | NS |
| LV ESVi (mL/m$^2$) | 26.2 ± 7.9 | 26.2 ± 8.0 | NS |
| LV EF (%) | 61.7 ± 5.9 | 62.5 ± 5.9 | NS |
| RA area (cm$^2$) | 16.4 ± 4.1 | 16.8 ± 4.0 | NS |
| RV FAC (%) | 46.7 ± 7.5 | 47.6 ± 7.8 | NS |
| TAPSE (mm) | 27 ± 4 | 26 ± 4 | NS |
| TR grade (n, %) | | | NS |
| Mild | 91 (95.8) | 61 (96.8) | |
| Moderate | 2 (2.1) | 2 (3.2) | |
| Moderate-to-severe | 2 (2.1) | 0 (0) | |
| Severe | 0 (0) | 0 (0) | |
| SPAP (mmHg) | 30 ± 9 | 29 ± 6 | NS |

AAD=anti-arrhythmic drugs; ACE=angiotensin converter enzyme; AF=atrial fibrillation; AML=anterior mitral leaflet; ARB=angiotensin-2 receptor blockers; AV=atrioventricular; BSA=body surface area; EDDi=end-diastolic diameter index; EDVi=end-diastolic volume index; EF=ejection fraction; ESDi=end-systolic diameter index; ESVi=end-systolic volume index; FAC=fraction area change; FED=fibroelastic deficiency; ICD=implantable cardioverter defibrillator; LAVi=left atrial volume index; LGE=late gadolinium enhancement; LV=left ventricular; MAD=mitral annular disjunction; MR=mitral regurgitation; MRA=mineralocorticoid receptor antagonist; MVP=mitral valve prolapse; non-DHP-CCB=non-dihydropyridine calcium-channel blockers; NS=not significant; NSVT=non-sustained ventricular tachycardia; NYHA=New York Heart Association; PML=posterior mitral leaflet; RA=right atrium; RV=right ventricular; SCD=sudden cardiac death; SPAP=systolic pulmonary artery pressure; SV=supraventricular; SVAs=supraventricular arrhythmias; SVE= supraventricular ectopic; SVT= sustained ventricular tachycardia; TAPSE=tricuspid annular plane systolic excursion; TR=tricuspid regurgitation; VAs=ventricular arrhythmias; VE=ventricular ectopic

When comparing patients based on significant (≥mild) VAs' occurrence, no significant difference was documented between VAs+ and VAs- in terms of demographics, medical history, physical examination, drugs, rest ECG (except for prevalence of VE beats documented at rest ECG: 30.6% vs. 14.2%, p=0.014), cardiac Holter parameters (except for number of VE beats in 24h:

5269[1036-9966] vs. 224[42-964], p<0.001), and CMR variables. Only LV EF by TTE was significantly lower in VA+ vs. VA- (60.2 ± 5.8% vs. 62.8 ± 5.9%, p=0.012), although values remained within the normal range (Table 3).

**Table 3 – Characteristics of the study population according to documentation of significant (≥mild) ventricular arrhythmias.**

| | **<mild VAs (n=113)** | **≥mild VAs (n=49)** | **p value** |
|---|---|---|---|
| Male (n, %) | 53 (46.9) | 21 (42.9) | NS |
| Age (years) | 53 ± 15 | 52 ± 14 | NS |
| **Medical history** | | | |
| Family history of SCD (n, %) | 3 (2.7) | 3 (6.1) | NS |
| History of AF (n, %) | 15 (13.3) | 2 (4.1) | NS |
| History of SVAs (n, %) | 20 (17.7) | 9 (18.4) | NS |
| Previous implantation of ICD (n, %) | 2 (1.8) | 1 (2.0) | NS |
| Previous VAs ablation (n, %) | 4 (3.5) | 4 (8.2) | NS |
| Syncope/presyncope (n, %) | 11 (9.7) | 4 (8.2) | NS |
| Palpitations (n, %) | 55 (48.7) | 29 (59.2) | NS |
| Dyspnoea (n, %) | 22 (19.5) | 8 (16.3) | NS |
| NYHA class (n, %) | | | NS |
| I | 94 (83.2) | 39 (79.6) | |
| II | 18 (15.9) | 8 (16.3) | |
| III | 1 (0.9) | 2 (4.1) | |
| **Physical examination** | | | |
| Systolic click (n, %) | 14 (12.6) | 6 (12.2) | NS |
| Systolic murmur (n, %) | 68 (61.3) | 32 (65.3) | NS |
| **Drugs** | | | |
| Beta-blockers (n, %) | 45 (39.8) | 26 (53.1) | NS |
| Non-DHP-CCB (n, %) | 0 (0) | 0 (0) | NS |
| Amiodarone (n, %) | 2 (1.8) | 0 (0) | NS |
| Sotalol (n, %) | 1 (0.9) | 3 (6.1) | NS |
| AAD of class IC (n, %) | 15 (13.3) | 7 (14.3) | NS |
| ACEi (n, %) | 23 (20.4) | 6 (12.2) | NS |
| ARB (n, %) | 9 (8.0) | 2 (4.1) | NS |
| MRA (n, %) | 4 (3.5) | 0 (0) | NS |
| Diuretics (n, %) | 11 (9.7) | 3 (6.1) | NS |
| Antiplatelet therapy (n, %) | 13 (11.5) | 6 (12.2) | NS |
| Anticoagulant therapy (n, %) | 8 (7.1) | 3 (6.1) | NS |
| **ECG** | | | |

| | | | |
|---|---|---|---|
| Baseline rhythm (n, %) | | | NS |
| Sinus rhythm | 113 (100.0) | 48 (98.0) | |
| AF/atrial flutter | 0 (0) | 1 (2.0) | |
| AV block (n, %) | 9 (8.0) | 2 (4.2) | NS |
| Intraventricular conduction disturbances (n, %) | 40 (35.4) | 12 (24.5) | NS |
| Long QT (n, %) | 7 (6.2) | 3 (6.1) | NS |
| Inverted/biphasic T waves in the inferolateral leads (n, %) | 31 (27.4) | 14 (28.6) | NS |
| SVE beats (n, %) | 2 (1.8) | 2 (4.1) | NS |
| VE beats (n, %) | 16 (14.2) | 15 (30.6) | **0.014** |
| **ECG Holter** | | | |
| Baseline rhythm (n, %) | | | NS |
| Sinus rhythm | 112 (99.1) | 48 (98.0) | |
| AF/atrial flutter | 1 (0.9) | 1 (2.0) | |
| SVE beats (n) | 27 [7-200] | 102 [8-349] | NS |
| SVE beats (% of total beats n°) | 0.0 [0.0-0.1] | 0.0 [0.0-0.1] | NS |
| SVE beats ≥5% of total beats | 5 (4.6) | 0 (0) | NS |
| SVE repetitiveness (n, %) | | | NS |
| Couplets | 14 (13.0) | 2 (4.1) | |
| Triplets | 2 (1.9) | 2 (4.1) | |
| SV tachycardia | 28 (25.9) | 18 (36.7) | |
| Atrial fibrillation (n, %) | 6 (5.4) | 1 (2.0) | NS |
| VE beats (n) | 224 [42-964] | 5269 [1036-9966] | **< 0.001** |
| VE beats (% of total beats n°) | 0.0 [0.0-1.2] | 5.3 [0.7-8.8] | **< 0.001** |
| **TTE** | | | |
| BSA ($cm^2$) | 1.79 ± 0.19 | 1.83 ± 0.24 | NS |
| Aetiology (n, %) | | | NS |
| FED | 20 (17.7) | 5 (10.2) | |
| Barlow's disease | 93 (82.3) | 44 (89.8) | |
| Bileaflet MVP (n, %) | 92 (81.4) | 44 (89.8) | NS |
| AML thickness (mm) | 4.3 ± 1.2 | 4.5 ± 1.2 | NS |
| PML thickness (mm) | 4.8 ± 1.2 | 5.0 ± 1.5 | NS |
| Chordal rupture (n, %) | 27 (23.9) | 7 (14.3) | NS |
| MR grade (n, %) | | | NS |
| Mild | 39 (34.5) | 18 (36.7) | |
| Moderate | 23 (20.4) | 14 (28.6) | |
| Moderate-to-severe | 12 (10.6) | 5 (10.2) | |
| Severe | 39 (34.5) | 12 (24.5) | |
| LAVi ($mL/m^2$) | 41.3 ± 15.9 | 44.4 ± 18.9 | NS |
| True-MAD (n, %) | 22 (19.6) | 13 (26.5) | NS |
| Pseudo-MAD (n, %) | 41 (36.3) | 18 (36.7) | NS |

| | | | |
|---|---|---|---|
| Pickelhaube sign (n, %) | 25 (24.0) | 8 (17.8) | NS |
| LV curling (n, %) | 56 (50.5) | 26 (53.1) | NS |
| LV EDDi (mm) | 30.0 ± 4.0 | 30.3 ± 3.9 | NS |
| LV ESDi (mm) | 18.1 ± 3.8 | 18.6 ± 4.1 | NS |
| LV EDVi (mL/m$^2$) | 68.7 ± 15.7 | 69.4 ± 15.6 | NS |
| LV ESVi (mL/m$^2$) | 25.6 ± 7.9 | 27.5 ± 7.9 | NS |
| LV EF (%) | 62.8 ± 5.9 | 60.2 ± 5.8 | **0.012** |
| RA area (cm$^2$) | 16.6 ± 4.0 | 16.5 ± 4.3 | NS |
| RV FAC (%) | 46.6 ± 8.0 | 48.0 ± 6.8 | NS |
| TAPSE (mm) | 26 ± 4 | 27 ± 4 | NS |
| TR grade (n, %) | | | NS |
| Mild | 107 (96.4) | 45 (95.7) | |
| Moderate | 3 (2.7) | 1 (2.1) | |
| Moderate-to-severe | 1 (0.9) | 1 (2.1) | |
| Severe | 0 (0) | 0 (0) | |
| SPAP (mmHg) | 29 ± 8 | 30 ± 8 | NS |
| **CMR** | | | |
| LV EDVi (mL/m$^2$) | 101.1 ± 18.2 | 100.9 ± 19.4 | NS |
| LV ESVi (mL/m$^2$) | 41.5 ± 10.5 | 42.3 ± 11.5 | NS |
| LV EF (%) | 59.2 ± 5.7 | 58.4 ± 5.6 | NS |
| LV mass (g) | 99.8 ± 25.7 | 99.9 ± 26.8 | NS |
| LV curling (n, %) | 64 (56.6) | 30 (61.2) | NS |
| Systolic MAD (n, %) | 76 (67.3) | 33 (67.3) | NS |
| True-MAD (n, %) | 60 (53.1) | 25 (51.0) | NS |
| Pseudo-MAD (n, %) | 16 (14.2) | 8 (16.3) | NS |
| Pathological T1 mapping (n, %) | n=100 | n=36 | |
| | 21 (21.0) | 3 (8.3) | NS |
| Pathological T2 mapping (n, %) | n=78 | n=33 | |
| | 4 (5.1) | 3 (8.3) | NS |
| Pathological ECV mapping (n, %) | n=93 | n=33 | |
| | 13 (14.0) | 2 (6.1) | NS |
| LGE (n, %) | 42 (37.2) | 22 (44.9) | NS |
| MR grade (n, %) | | | NS |
| Mild | 55 (48.7) | 27 (55.1) | |
| Moderate | 18 (15.9) | 9 (18.4) | |
| Moderate-to-severe | 20 (17.7) | 8 (16.3) | |
| Severe | 20 (17.7) | 5 (10.2) | |
| LAVi (mL/m$^2$) | 47.2 ± 14.6 | 52.4 ± 18.4 | |
| RV EDVi (mL/m$^2$) | 86.9 ± 16.6 | 83.0 ± 17.6 | NS |
| RV ESVi (mL/m$^2$) | 39.1 ± 10.1 | 36.5 ± 11.3 | NS |
| RV FE (%) | 55.5 ± 6.2 | 56.6 ± 6.4 | NS |

AAD=anti-arrhythmic drugs; ACE=angiotensin converter enzyme; AF=atrial fibrillation; AML=anterior mitral leaflet; ARB=angiotensin-2 receptor blockers; AV=atrioventricular; BSA=body surface area; EDDi=end-diastolic diameter index; EDVi=end-diastolic volume index; EF=ejection fraction; ESDi=end-systolic

diameter index; ESVi=end-systolic volume index; FAC=fraction area change; FED=fibroelastic deficiency; ICD=implantable cardioverter defibrillator; LAVi=left atrial volume index; LGE=late gadolinium enhancement; LV=left ventricular; MAD=mitral annular disjunction; MR=mitral regurgitation; MRA=mineralocorticoid receptor antagonist; MVP=mitral valve prolapse; non-DHP-CCB=non-dihydropyridine calcium-channel blockers; NS=not significant; NSVT=non-sustained ventricular tachycardia; NYHA=New York Heart Association; PML=posterior mitral leaflet; RA=right atrium; RV=right ventricular; SCD=sudden cardiac death; SPAP=systolic pulmonary artery pressure; SV=supraventricular; SVAs=supraventricular arrhythmias; SVE= supraventricular ectopic; SVT= sustained ventricular tachycardia; TAPSE=tricuspid annular plane systolic excursion; TR=tricuspid regurgitation; VAs=ventricular arrhythmias; VE=ventricular ectopic

Additional analyses were performed comparing patients showing ≥moderate VAs with those showing <moderate VAs at 24h ECG-monitoring (Table 4). Interestingly, the age difference between the two groups approached statistical significance (47 ± 12 years in ≥moderate VAs vs. 54 ± 15 years in < moderate VAs, p=0.054). History of previous VAs' documentation was significantly more frequent in patients showing ≥moderate VAs (79.2% vs. 47.8%, p=0.005), the posterior MV leaflet was significantly thicker (5.3 ± 1.4 mm vs. 4.7 ± 1.2 mm, p=0.041), and true-MAD prevalence at TTE was significantly higher (37.5% vs. 19.0%, p=0.042); though prevalence of LV curling by TTE was higher, this difference did not reach statistical significance (62.5% vs. 49.3%, p>0.05). As regards CMR parameters, a significantly higher rate of LV curling (79.2% vs. 54.3%, p=0.023) and LGE (58.3% vs. 36.2%, p=0.041), as well as a trend towards higher systolic MAD prevalence (79.2% vs. 65.2%, p>0.05) and true-MAD (62.5% vs. 50.7%, p>0.05) were documented in patients with ≥moderate VAs as compared to those with <moderate VAs.

**Table 4 – Characteristics of the study population according to documentation of ≥moderate ventricular arrhythmias.**

| | **<moderate VAs (n=138)** | **≥moderate VAs (n=24)** | **p value** |
|---|---|---|---|
| Male (n, %) | 64 (46.4) | 10 (41.7) | NS |
| Age (years) | 54 ± 15 | 47 ± 12 | 0.054 |
| **Medical history** | | | |
| Family history of SCD (n, %) | 4 (2.9) | 2 (8.3) | NS |
| History of AF (n, %) | 17 (12.3) | 0 (0) | NS |
| History of SVAs (n, %) | 23 (16.7) | 6 (25.0) | NS |
| History of VAs (n, %) | 66 (47.8) | 19 (79.2) | **0.005** |
| Previous implantation of ICD (n, %) | 2 (1.4) | 1 (4.2) | NS |
| Previous VAs ablation (n, %) | 7 (5.1) | 1 (4.2) | NS |
| Syncope/presyncope (n, %) | 14 (10.1) | 1 (4.2) | NS |
| Palpitations (n, %) | 72 (52.2) | 12 (50.0) | NS |
| Dyspnoea (n, %) | 27 (19.6) | 3 (12.5) | NS |
| NYHA class (n, %) | | | NS |
| I | 113 (81.9) | 20 (83.3) | |
| II | 22 (15.9) | 4 (16.7) | |
| III | 3 (2.2) | 0 (0) | |

| | | | |
|---|---|---|---|
| **Physical examination** | | | |
| Systolic click (n, %) | 16 (11.8) | 4 (16.7) | NS |
| Systolic murmur (n, %) | 87 (64.0) | 13 (54.2) | NS |
| **Drugs** | | | |
| Beta-blockers (n, %) | 60 (43.5) | 11 (45.8) | NS |
| Non-DHP-CCB (n, %) | 0 (0) | 0 (0) | NS |
| Amiodarone (n, %) | 2 (1.4) | 0 (0) | NS |
| Sotalol (n, %) | 3 (2.2) | 1 (4.2) | NS |
| AAD of class IC (n, %) | 21 (15.2) | 1 (4.2) | NS |
| ACEi (n, %) | 28 (20.3) | 1 (4.2) | NS |
| ARB (n, %) | 10 (7.2) | 1 (4.2) | NS |
| MRA (n, %) | 4 (2.9) | 0 (0) | NS |
| Diuretics (n, %) | 13 (9.4) | 1 (4.2) | NS |
| Antiplatelet therapy (n, %) | 17 (12.3) | 2 (8.3) | NS |
| Anticoagulant therapy (n, %) | 11 (8.0) | 0 (0) | NS |
| **ECG** | | | |
| Baseline rhythm (n, %) | | | NS |
| Sinus rhythm | 137 (99.3) | 24 (100) | |
| AF/atrial flutter | 1 (0.7) | 0 (0) | |
| AV block (n, %) | 10 (7.3) | 1 (4.2) | NS |
| Intraventricular conduction disturbances (n, %) | 41 (29.7) | 7 (29.2) | NS |
| Long QT (n, %) | 9 (6.5) | 1 (4.2) | NS |
| Inverted/biphasic T waves in the inferolateral leads (n, %) | 39 (28.3) | 6 (25.0) | NS |
| SVE beats (n, %) | 3 (2.2) | 1 (4.2) | NS |
| VE beats (n, %) | 24 (17.4) | 7 (29.2) | NS |
| **ECG Holter** | | | |
| Baseline rhythm (n, %) | | | NS |
| Sinus rhythm | 136 (98.6) | 24 (100) | |
| AF/atrial flutter | 2 (1.4) | 0 (0) | |
| SVE beats (n°) | 29 [6-236] | 27 [100-367] | NS |
| SVE beats (% of total beats n°) | 0.0 [0.0-0.0] | 0.0 [0.0-0.1] | NS |
| SVE repetitiveness (n, %) | | | NS |
| Couplets | 14 (10.5) | 2 (8.3) | |
| Triplets | 3 (2.3) | 1 (4.2) | |
| SV tachycardia | 36 (27.1) | 10 (41.7) | |
| Atrial fibrillation (n, %) | 7 (5.1) | 0 (0) | NS |
| **TTE** | | | |
| BSA ($cm^2$) | 1.79 ± 0.19 | 1.87 ± 0.25 | NS |
| Aetiology (n, %) | | | NS |
| FED | 24 (17.4) | 1 (4.2) | |

| | | | |
|---|---|---|---|
| Barlow's disease | 114 (82.6) | 23 (95.8) | |
| Bileaflet MVP (n, %) | 114 (82.6) | 22 (91.7) | NS |
| AML thickness (mm) | 4.3 ± 1.2 | 4.6 ± 1.3 | NS |
| PML thickness (mm) | 4.7 ± 1.2 | 5.3 ± 1.4 | **0.041** |
| Chordal rupture (n, %) | 32 (23.2) | 2 (8.3) | NS |
| MR grade (n, %) | | | NS |
| Mild | 46 (33.3) | 11 (45.8) | |
| Moderate | 31 (22.5) | 6 (25.0) | |
| Moderate-to-severe | 14 (10.1) | 3 (12.5) | |
| Severe | 47 (34.1) | 4 (16.7) | |
| LAVi (mL/m$^2$) | 41.7 ± 16.0 | 45.5 ± 21.3 | NS |
| True-MAD (n, %) | 26 (19.0) | 9 (37.5) | **0.042** |
| Pseudo-MAD (n, %) | 51 (37.0) | 8 (33.3) | NS |
| Pickelhaube sign (n, %) | 28 (22.0) | 5 (22.7) | NS |
| LV curling (n, %) | 67 (49.3) | 15 (62.5) | NS |
| LV EDDi (mm/mq) | 30.1 ± 4.0 | 30.4 ± 3.6 | NS |
| LV ESDi (mm/mq) | 18.2 ± 4.0 | 18.6 ± 3.6 | NS |
| LV EDVi (mL/m$^2$) | 68.4 ± 15.4 | 71.9 ± 16.6 | NS |
| LV ESVi (mL/m$^2$) | 25.8 ± 7.9 | 28.5 ± 8.0 | NS |
| LV EF (%) | 62.2 ± 6.0 | 60.8 ± 5.5 | NS |
| RA area (cm$^2$) | 16.5 ± 4.0 | 16.7 ± 4.4 | NS |
| RV FAC (%) | 46.7 ± 7.8 | 48.8 ± 6.5 | NS |
| TAPSE (mm) | 27 ± 4 | 27 ± 4 | NS |
| TR grade (n, %) | | | NS |
| Mild | 128 (95.5) | 24 (100.0) | |
| Moderate | 4 (3.0) | 0 (0) | |
| Moderate-to-severe | 2 (1.5) | 0 (0) | |
| Severe | 0 (0) | 0 (0) | |
| SPAP (mmHg) | 30 ± 8 | 27 ± 5 | NS |
| **CMR** | | | |
| LV EDVi (mL/m$^2$) | 100.8 ± 17.7 | 102.6 ± 23.2 | NS |
| LV ESVi (mL/m$^2$) | 41.5 ± 10.5 | 42.8 ± 12.3 | NS |
| LV EF (%) | 59.0 ± 5.8 | 58.5 ± 5.1 | NS |
| LV mass (g) | 99.4 ± 25.5 | 102.5 ± 28.8 | NS |
| LV curling (n, %) | 75 (54.3) | 19 (79.2) | **0.023** |
| Systolic MAD (n, %) | 90 (65.2) | 19 (79.2) | NS |
| True-MAD (n, %) | 70 (50.7) | 15 (62.5) | NS |
| Psuedo-MAD (n, %) | 20 (14.5) | 4 (16.7) | NS |
| Pathological T1 mapping (n, %) | n=115<br>21 (18.3) | n=21<br>3 (14.3) | NS |
| Pathological T2 mapping (n, %) | n=92<br>5 (5.4) | n=19<br>2 (10.5) | NS |

| | | | |
|---|---|---|---|
| Pathological ECV mapping (n, %) | n=108<br>14 (13.0) | n=18<br>1 (5.6) | <br>NS |
| LGE (n, %) | 50 (36.2) | 14 (58.3) | **0.041** |
| MR grade (n, %) | | | NS |
| Mild | 66 (47.8) | 16 (66.7) | |
| Moderate | 24 (17.4) | 3 (12.5) | |
| Moderate-to-severe | 24 (17.4) | 4 (16.7) | |
| Severe | 24 (17.4) | 1 (4.2) | |
| LAVi (mL/m$^2$) | 48.1 ± 15.5 | 52.6 ± 18.2 | NS |
| RV EDVi (mL/m$^2$) | 86.1 ± 16.0 | 83.7 ± 21.9 | NS |
| RV ESVi (mL/m$^2$) | 38.5 ± 10.0 | 37.1 ± 13.1 | NS |
| RV FE (%) | 55.5 ± 6.2 | 56.6 ± 6.4 | NS |

Assessing correlations between ≥mild or ≥moderate VAs and MAD length or extent by TTE, we found a significant, though weak, correlation only between ≥moderate VAs and numbers of TTE views showing MAD ($\rho$=0.163, p=0.039). Pathological mapping sequences and LGE at the inferolateral LV wall or at the level of the papillary muscle showed no predictive value of arrhythmic events (p>0.05).

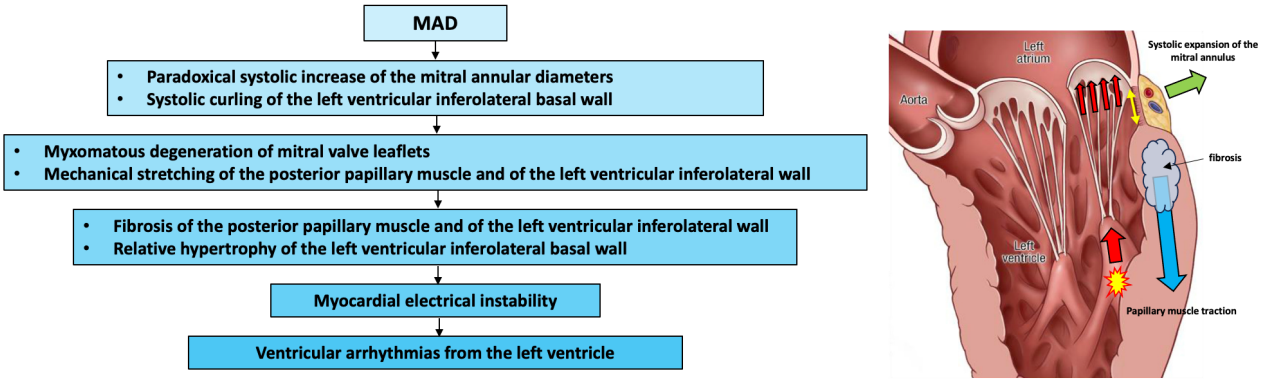
## 5. DISCUSSION

The concept of AMVP has been in the spotlight in the last decade; especially the detection of MAD by TTE and/or CMR, as well as the documentation of LGE by CMR have been the subject of attention.

Preliminary analyses of our study, conducted on a population of unselected MVP patients, demonstrated LGE in 39.5% of patients, in line with the reported prevalence of fibrosis in MVP patients (28-37%)[7]. Statistically significant differences that have emerged so far between patients with and without LGE on CMR, are a lower prevalence of SVAs, a higher prevalence of previous VAs ablation, a higher prevalence of MAD at TTE, and a higher prevalence of ≥moderate VAs at 24h ECG-monitoring in patients with LGE as compared to those without. These data are in agreement with those available in the literature. In 2015 the Padua group published a study on 43 patients with MVP who died of SCD before the age of 40[4]. In all patients, an area of myocardial fibrosis was documented at the level of the posterior papillary muscle and in 88% of cases at the level of the LV inferobasal wall. In the same study, the presence of LGE, and therefore of myocardial fibrosis, at the level of the papillary muscle and the LV inferobasal wall was detected on CMR in 93% of 30 living patients affected by MVP and complex VAs[4]. The same research group analysed 52 patients with BD and complex VAs[8]. In these patients, LGE at CMR correlated with the arrhythmic risk, with the presence of MAD, curling and hypertrophy of the LV lateral basal wall. Finally, a correlation was found between MAD and curling, as well as between MAD and extension of LGE, between MAD and incidence of VE beats and non-sustained VT. Hence the hypothesis that MAD causes paradoxical

systolic expansion of the MVA and curling of the LV inferolateral basal wall. This would cause mechanical stretching of the posterior papillary muscle and LV inferolateral wall, in turn responsible for fibrosis' development. Fibrosis is supposed to cause myocardial electrical instability, and thus VAs[8] (Figure 6).

**Figure 6 - The Padua hypothesis**




Graphical representation of the Padua hypothesis, according to which mitral annular disjunction may be responsible for fibrosis of the posterior papillary muscle and of the left ventricular inferolateral wall, leading to myocardial electrical instability and ventricular arrhythmias.

Based on the preliminary results of our study, we are not able at the moment to compute a scoring model to predict fibrosis in patients with MVP; however, we may hypothesize that CMR may be useful for LGE detection especially in MVP patients showing high-rate (>120 bpm) non-sustained VT or more serious VAs.

The overall prevalence of significant VAs in our population is lower than reported in previous studies (43.2% by Essayagh et al.)[33], which may be due to our limited sample size. This same rationale could justify the observation that the prevalence of severe VAs is not significantly higher in patients with LGE compared to LGE-. However, it should not be overlooked that a significant proportion of MVP patients experience SCD in the absence of LGE on previous CMR and/or myocardial fibrosis at autopsy[34,35].

When comparing patients based on ≥mild VAs' occurrence, no clinically significant difference was documented between VAs+ and VAs-. Interestingly, severe VAs occurred only in 3.7% of the overall population. Indeed, in 2020 the Mayo Clinic group demonstrated that although the incidence of VAs is high in MVP patients, severe forms are relatively uncommon[33]. These seemed to be associated with T wave inversion and ST segment depression in the inferolateral leads, redundancy and thickness of the valve leaflets, presence and length of MAD. Conversely, the presence of MAD was associated with a higher incidence of arrhythmic events and severe VAs[36]. When comparing the survival of patients, matched by age and comorbidity, based on the presence or absence of MAD,

MAD per se proved to be not associated with an increased risk of 10-year mortality. The mere presence of MAD is not a cause for alarm, particularly in asymptomatic patients without documented VAs. What was instead associated with a significant increase in 10-year mortality in patients with MVP was the documentation of severe VAs per se[37].

Though we cannot establish if and which clinical, electrocardiographic, and imaging variables might predict the risk of developing significant VAs at ECG Holter monitoring, as intended per study protocol, our data suggest that typical arrhythmic risk factors (young age, MV leaflets' thickening, true-MAD by TTE and its extension along the MVA, LV curling and LGE) are associated with more serious, and less frequently observed, arrhythmic events. Although the analyses are limited by the small sample size and the low prevalence of pathological T1, T2, and ECV values, these parameters do not appear to be associated with an increased risk of significant VAs, suggesting that arrhythmic risk is more closely associated with the presence of replacement fibrosis (LGE) rather than interstitial fibrosis. The finding that the prevalence of systolic MAD and true-MAD on CMR is not significantly different between patients with ≥moderate VAs and those with <moderate VAs is certainly of interest. Of course, this result may be influenced by the sample size. However, if the absence of a statistically significant difference in systolic MAD and true-MAD prevalence between patients with and without ≥moderate VAs is confirmed at the end of the study, and considering that CMR has greater diagnostic accuracy than TTE for the identification of MAD, the study results could call into question the role of MAD as a potential arrhythmic risk factor in patients with MVP. In this scenario, it could be hypothesized that MAD per se is not the ultimate driver of myocardial fibrosis but rather curling of the basal lateral LV wall. Thus, an alteration in ventricular mechanics, likely associated with the morphological abnormalities of the MV apparatus (leaflet redundancy and prolapse, chordal elongation), would be linked to an increased prevalence of myocardial fibrosis and VAs. In this case, MAD would represent a mere bystander.

These preliminary findings need to be confirmed once the study is concluded and will nonetheless require validation by further studies. However, they offer a valuable perspective for the re-evaluation of the clinical significance of myocardial fibrosis and arrhythmic risk in MVP patients and emphasize the role of multiparametric assessment and multimodality imaging in arrhythmic risk stratification and individualized patient management.

## 6. LIMITATIONS

The current analyses are limited by the fact that the target sample size (n=300) of the study has not yet been achieved. Additionally, the present data largely reflect the experience of a single centre, since the majority of patients enrolled to date have been recruited at our institution. Patient enrolment is ongoing at the second participating Centre and administrative procedures by the Ethics Committee are being finalized to allow a third participating Centre to be included in the study.

## 7. CONCLUSIONS

Once we have reached the expected sample size, we will likely have achieved the statistical power to draw reliable conclusions. The results of the SCIMITAR study, once completed, might help clinicians in identifying MVP patients at the highest arrhythmic risk and therefore deserving a different dedicated clinical management.

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