Prediction of arrhythmic risk in patients with mitral annular disjunction

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Summary

Mitral annular disjunction is a gap between the mitral ring and the ventricular myocardium, and is associated with mitral valve prolapse. A minority of these patients experience life-threatening ventricular arrhythmias, but the incidence of such arrhythmias is largely unknown. Additionally, estimating arrhythmic risk in a clinical setting is challenging and imprecise. In the doctoral thesis *"Prediction of arrhythmic risk in patients with mitral annular disjunction*", Dr. Eivind Westrum Aabel and colleagues assessed the incidence and explored possible risk markers of ventricular arrhythmias in patients with mitral annular disjunction, with the overall aim to improve risk stratification and follow-up of these patients. The three studies of this thesis describe the incidence rate of ventricular arrhythmias and describes possible predictors of increased arrhythmic risk in patients with mitral annular disjunction.

Paper I was the first study to describe the incidence of ventricular arrhythmia using continuous heart rhythm monitoring in 80 patients with mitral annular disjunction, with a high rate of first time ventricular arrhythmia and re-events. Paper 2 assessed 84 patients with mitral annular disjunction using cardiac magnetic resonance imaging. This paper was the first study to describe the novel finding of concomitant right-sided annular disjunction in half of patients with mitral annular disjunction, and the finding that additional tricuspid annular disjunction did not increase arrhythmic risk further. Paper 3 described the prevalence of the high-risk feature T-wave inversions on electrocardiogram in 162 patients with mitral annular disjunction. This paper reports that T-wave inversion was associated with prior ventricular arrhythmia and diffuse myocardial fibrosis, inferring that diffuse myocardial fibrosis might be the underlying substrate for T-wave inversions in these patients.

These observations improve our knowledge of risk stratification and provide clinicians caring for patients with mitral annular disjunction valuable information when evaluating the need for different follow-up strategies. External validation in larger prospective studies are important before fully implementing these observations in clinical practice.

Sammendrag

Mitral annulus disjunksjon er et gap mellom mitralringen og hjertemuskelen i venstre hovedkammer, og er assosiert med mitralklaffprolaps. En liten andel av disse pasientene opplever livstruende hjerterytmeforstyrrelser, men forekomsten av slike arytmier er vesentlig ukjent. I tillegg er arytmirisikoen utfordrende å anslå i klinikken og anslagene er upresise. I sin avhandling *«Prediction of arrhythmic risk in patients with mitral annular disjunction»* har Eivind Westrum Aabel og medarbeidere undersøkt forekomsten av potensielt livstruende arytmier og forsøkt å finne potensielle risikomarkører hos pasienter med mitral annulus disjunksjon, med det overordnede målet om å forbedre risikostratifiseringen og oppfølgingen hos disse pasientene.

Den første studien beskrev forekomsten av ventrikulære arytmier ved bruk av kontinuerlig overvåkning av hjerterytmen hos 80 pasienter med mitral annulus disjunksjon, og viste en høy forekomst av førstegangstilfeller og gjentagende arytmi. Den andre studien undersøkte 84 pasienter med mitral annulus disjunksjon ved bruk av magnetisk resonanstomografi. Studien var den første til å beskrive funnet av samtidig høyresidig annulus disjunksjon hos halvparten av pasientene, og studien fant at tillegg av trikuspidal annulus disjunksjon ikke økte arytmirisikoen ytterligere. Den tredje studien beskrev utbredelsen av høyrisikotrekket T-inversjoner på EKG hos 162 pasienter med mitral annulus disjunksjon. Studien rapporterte at T-inversjoner var assosiert med ventrikulær arytmi og diffuse hjertefibrose, som tyder på at diffuse hjertefibrose kan være det underliggende substratet for T-inversjoner hos disse pasientene.

Observasjonene har forbedret kunnskapen om risikostratifisering og gir klinikere som behandler og følger pasienter med mitral annulus disjunksjon nyttig informasjon ved vurdering av forskjellige oppfølgingsstrategier. Ekstern validering i store prospektive studier er viktig før observasjonene blir fullt implementert i klinisk praksis.

Contents

Acknowledgments

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The last three years have been an epic adventure I will never forget. Throughout this journey, I have met so many great colleagues and scientists that have expanded my view and my knowledge of cardiology. Together we have tackled challenges with victorious results, we have celebrated the small things and we have made new friendships along the way. Fortunately, the journey is not over, but there are many people I am grateful to that have guided me through the, at times, treacherous road.

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Oslo, October 2022

Eivind Westrum Aabel

List of papers

I. **Ventricular Arrhythmias in Arrhythmic Mitral Valve Syndrome – a Prospective Continuous Long-term Cardiac Monitoring Study.**

Eivind W Aabel, Monica Chivulescu, Øyvind H Lie, Einar Hopp, Erik Gjertsen, Margareth Ribe, Thomas M Helle-Valle, Thor Edvardsen, Finn Hegbom, Lars Dejgaard, Kristina H Haugaa.

Europace 2022 Oct 18;euac182. Online ahead of print.

II. **Tricuspid Annulus Disjunction – Novel Findings by Cardiac Magnetic Resonance in Patients with Mitral Annulus Disjunction**

Eivind W Aabel, Monica Chivulescu, Lars A Dejgaard, Margareth Ribe, Erik Gjertsen, Einar Hopp, Tove E Hunt, Øyvind H Lie, Kristina H Haugaa.

J Am Coll Cardiol Img 2021;14(8):1535-1543

III. **Electrical Markers and Arrhythmic Risk Associated with Myocardial Fibrosis in Mitral Valve Prolapse**

Monica Chivulescu, Eivind W Aabel, Erik Gjertsen, Einar Hopp, Esther Scheirlynck, Bernard Cosyns, Erik Lyseggen, Thor Edvardsen, Øyvind H Lie, Lars A Dejgaard, Kristina H Haugaa.

Europace. 2022; Jul 21;24(7):1156-1163

Abbreviations

AMVP = arrhythmic mitral valve prolapse

ECG = electrocardiogram

ECV = extracellular volume

CMR = cardiac magnetic resonance

ICD = implantable cardioverter-defibrillator

ILR = implantable loop recorder

LGE = late gadolinium enhancement

MAD = mitral annular disjunction

MVP = mitral valve prolapse

NSVT = non-sustained ventricular tachycardia

PVC = premature ventricular complexes

VA = ventricular arrhythmia

VT = ventricular tachycardia

TAD = tricuspid annular disjunction

TVP = tricuspid valve prolapse

TWI = t-wave inversions

Introduction

Mitral annular disjunction (MAD) is a separation between the atrial wall-mitral valve junction and the left ventricular attachment[1,2], first described by Bharati et al in 1981 and later studied systematically by Hutchins et al in autopsied heart specimens. MAD has gathered interest in the research community due to its strong association to both syndromic[3,4] and non-syndromic mitral valve prolapse (MVP), which is the most common valve abnormality estimated to be found in 2-3% of the general population[5]. The prevalence of MAD among MVP patients varies across studies depending on the imaging modality and planes used[6], but the pooled prevalence is approximately 30%[7]. MVP carries an excellent prognosis in the vast majority of patients[8,9], and until recently, the determinants for prognosis and symptoms were believed to be mostly defined by the severity of mitral regurgitation and subsequent left ventricular dysfunction. However, the discovery that MVP was frequent among patients with unexplained sudden cardiac death[10] has led to the realisation that a minority of patients with MVP are at risk of potentially life-threatening ventricular arrhythmias (VA). Recently, multiple case reports and few large cohort studies have identified a subpopulation of MVP patients signified by a high risk of VA independent of mitral regurgitation severity[11-13]. The finding of MVP and/or MAD with VA is commonly referred to as arrhythmic mitral valve prolapse (AMVP), and the presence of MAD has shown to be a robust arrhythmic risk marker in several studies[14-16] (Figure 1). Interestingly, MAD is found without concomitant MVP[17] and has been shown to be arrhythmogenic even in the absence of MVP[18]. Thus, the term AMVP also incorporates patients with isolated MAD and VA[19].

Recently, MAD has been shown to be a three-dimensional structure present around the insertion of the posterior mitral valve leaflet[18,20], and even interspersed with normal annular tissue[18]. MAD is best visualised by imaging methods with high spatial resolution[6], such as cardiac magnetic resonance (CMR). Because of the continuity of the annulus fibrosis with the right side of the heart, it is plausible that annular disjunction occurs also in the tricuspid annulus. However, this has not been described previously.

Incidence of ventricular arrhythmias in AMVP patients

The incidence of VA among patients with AMVP is estimated to be 0.2-1.9% annually[11,13,21,22]. However, these estimates are based on studies on sudden cardiac death prevalence, or conducted using arrhythmia monitoring on clinical indication only. These studies are also mostly of retrospective design prone to bias. Thus, the incidence of VA is largely unknown.

Mechanism of ventricular arrhythmias in AMVP patients

The mechanism for arrhythmia development in AMVP patients is theorised to be caused by the excessive stretch and stress exerted on the chorda tendinae and the papillary muscles by the prolapsing leaflet or MAD[23]. This, in turn, leads to myocardial injury[24] and subsequent myocardial fibrosis[25-28], constituting a substrate for re-entry arrhythmias. Furthermore, MAD might exacerbate the stretch and stress when occurring concomitantly with MVP, possibly explaining why MAD is a robust arrhythmic risk marker in patients with arrhythmic MVP[14,29].

The stretching of the papillary muscles and adjacent periannular myocardium can also cause premature ventricular complexes (PVC) through triggered activity. This could explain why the majority of PVCs in these patients originate from the left ventricular papillary muscles and periannular regions on electrophysiological studies[22,30]. These PVCs can in turn act as triggers for VA. However, some patients also have PVCs originating from the right ventricle[10], inferring that there might be other arrhythmic mechanisms than MVP or MAD in these patients. Furthermore, it is plausible that disjunction of the tricuspid annulus is associated with VA in the same way as its left-sided counterpart.

Risk markers of ventricular arrhythmias in AMVP patients

Risk stratification is of the utmost importance in AMVP patients, as to avoid rare but devastating sudden cardiac arrest. The determinants for VA in AMVP are incompletely defined, but the most robust arrhythmic risk markers to date are focal myocardial fibrosis visualised by cardiac magnetic resonance (CMR), by means of late gadolinium enhancement (LGE)[13,26,31] and MAD. However, severe VA occur in patients without LGE, inferring that additional arrhythmic substrates exist[18]. Diffuse myocardial fibrosis could be one of these substrates, since its presence has previously been associated with increased arrhythmic risk in AMVP[28].

Previous descriptions of AMVP high risk features included biphasic or negative T-waves (TWI) in the inferior leads[10]. This ECG finding is associated with VA across different MVP and MAD cohorts, with a prevalence varying between 20% and 78%[10,12]. Yet, the underlying substrate for T-wave inversions in AMVP patients is unknown, and the value of this risk marker is still unclear.

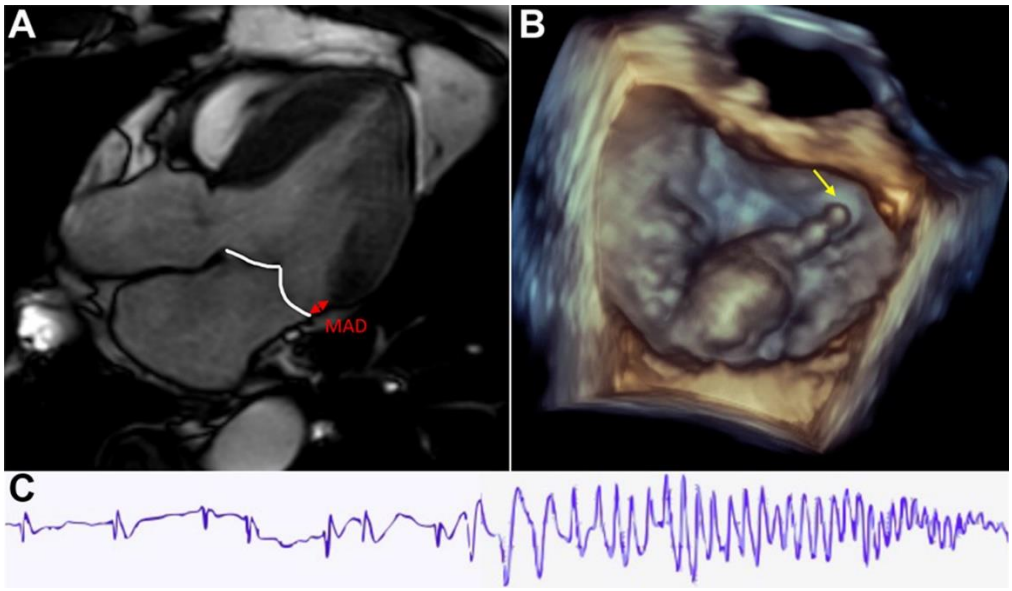


Figure 1. Cardiac imaging and heart rhythm monitoring in a patient with arrhythmic mitral valve prolapse.

(A) Cardiac magnetic resonance in 3-chamber view at end-systole showing prolapse of the posterior mitral leaflet and mitral annular disjunction (red arrowhead). (B) Three-dimensional transesophageal echocardiographic surgical view of the mitral valve showing a prolapsed P2 scallop and chordal rupture with flail (yellow arrow). (C) Polymorphic ventricular tachycardia degenerating into ventricular fibrillation registered by an implantable loop recorder. MAD = mitral annular disjunction. From Chivulescu et al JACC Case Reports 2021, doi: 10.1016/j.jaccas.2021.08.019, with permission.

Aims of the thesis

General aims of the thesis

The overall aim of this thesis was to assess the incidence and explore risk markers of VA in MAD patients, and most importantly, to improve risk stratification and follow-up.

Specific aims

Paper I

We aimed to describe the incidence of VA in patients with MAD. Additionally, we aimed to identify predictors of first-time severe VA, and explore the clinical use of implantable loop recorders (ILR) in the follow-up of these patients. We anticipated that VAs are common when monitored continuously by cardiac devices, and that ILRs are valuable in the follow-up of these patients.

Paper II

We aimed to assess right-sided annular disjunction in patients with MAD, and to relate findings to the extent of left-sided annular disjunction and to VA. We anticipated that the disjunction may not only be found in the mitral annulus, but also extend to the right side of the heart as tricuspid annular disjunction (TAD).

Paper III

We aimed to describe the prevalence of TWI and to explore the association between severe VA and repolarisation abnormalities in patients with MAD. Additionally, we aimed to investigate the morphological substrate of TWI. We anticipated that TWI is common in these patients and is associated with prior VA. We also anticipated that diffuse myocardial fibrosis is associated with TWI, forming the substrate for VAs in these patients.

Objectives of the thesis

Paper I

We performed this study as a single centre, prospective cohort study. The objective was to describe the nature of VA in MAD patients, in regards to:

1) Establish a primary prevention cohort and monitor patients with implantable loop recorders to report the incidence of VA during follow-up.
2) Establish a secondary prevention cohort monitored with ICD to report the incidence of arrhythmic re-events.
3) Describe the use of implantable loop recorders for risk stratification and follow-up, and acknowledge risk factors of subsequent VA.

Paper II

We performed this study as a single centre, ambispective cross-sectional cohort study with the following objectives:

1) To establish a cohort of MAD patients comprehensively assessed by CMR in order to report the existence of right-sided annular disjunction.
2) To explore the association between right-sided annular disjunction and characteristics of the mitral valve apparatus.
3) To explore if biannular disjunction increases risk of VA in MAD patients.

Paper III

We performed this study as a multicentre, ambispective cross-sectional cohort study with the following objectives:

1) To report the prevalence of TWI in a cohort of MAD patients.
2) To report the prognostic value of TWI in predicting VA.
3) To assess both focal and diffuse myocardial fibrosis measured by CMR and relate indices of myocardial fibrosis to TWI and prior VA.

Material

Study population

Study participants were consecutively recruited at two hospitals in Norway (Oslo University Hospital and Drammen Hospital), and at University Hospital Brussels (Universitair Ziekenhuis Brussel, Belgium), from August 2015 to August 2020 (Figure 2). Patients with suspected MAD were invited to a study echocardiogram performed by experienced cardiologists and sonographers at these centres. We excluded participants with obstructive coronary artery disease, non-mitral moderate or severe valvular disease.

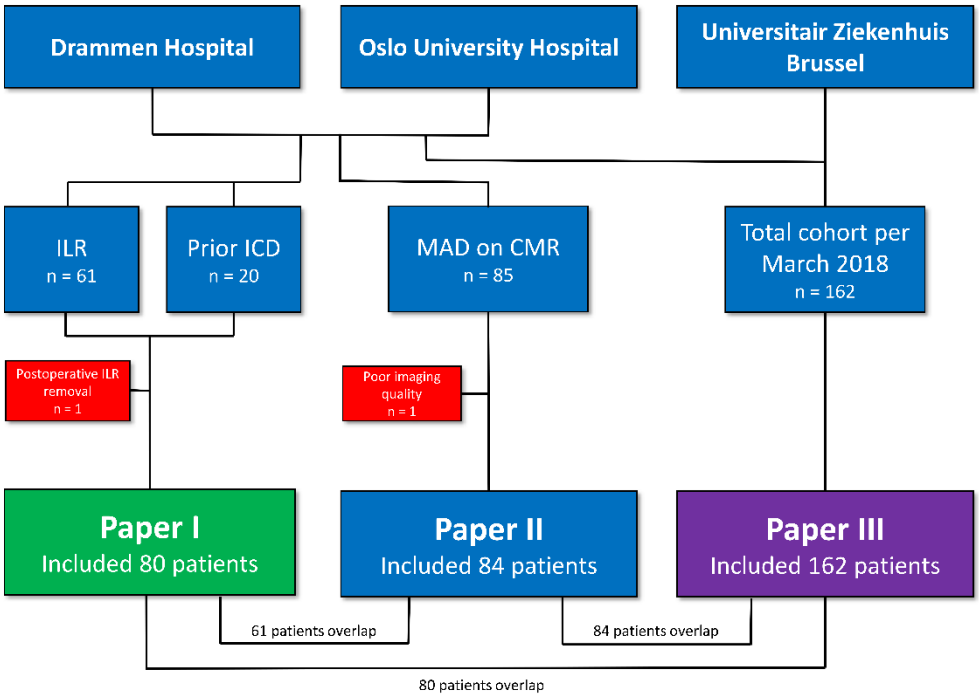


Figure 2. Study recruitment and inclusion.

We recruited study participants from three hospitals. Oslo University Hospital and Drammen Hospital provided patients for Paper I and II, with 80 and 84 patients included, respectively. In Paper III, additional patients were recruited from Universitair Ziekenhuis Brussels, with 162 patients included. The figure shows overlap of patients included in the three studies. CMR = cardiac magnetic resonance, ICD = implantable cardioverter-defibrillator, ILR = implantable loop recorder, MAD = mitral annular disjunction.

Paper I

In Paper I, we included participants from Oslo University Hospital and Drammen Hospital that consented to ILR implantation or had prior ICD, included from August 2015 to August 2020. Eligibility

criteria for ILR implantation were no prior documented severe VA with left ventricular ejection fraction >50%. Additionally, participants needed to have either inferior TWI or one of the following findings on 24-hour Holter monitoring; (i) non-sustained ventricular tachycardia (NSVT), (ii) complex PVCs or (iii) PVC burden >500 per 24-hours.

We defined end of follow-up as last device interrogation or last transmission of ILR data by remote monitoring. For participants that received ICD during follow-up, we ended follow-up at the median duration of ILR monitoring (3.1 years) to avoid bias of longer follow-up in those receiving ICD. Additionally, we censored at time of mitral valve surgery and ablation for VA.

Paper II

We included a subset of participants from Oslo University Hospital and Drammen Hospital with MAD on CMR imaging, included from August 2015 to June 2017. We excluded participants with poor CMR imaging quality of the tricuspid annulus.

Paper III

We included all participants included from Oslo University Hospital, Drammen Hospital and University Hospital Brussels, from August 2015 to March 2018.

Methods

Participants were invited to a comprehensive study evaluation, which included clinical examination, 12-lead ECG, 24-hour Holter monitoring, stress ECG, transthoracic echocardiography and study protocol CMR.

Clinical characteristics

The clinical examination included a medical interview that allowed us to obtain clinical characteristics, and family and medical history. We also specifically asked for symptoms of chest pain, dyspnoea, palpitations, syncope or presyncope. Patients with high likelihood of coronary artery disease were evaluated with coronary angiography prior to inclusion.

Cardiac imaging

Echocardiography

The study echocardiogram was performed on a Vivid E95 scanner (GE Healthcare, Horten, Norway), and data were analysed offline blinded for clinical data (EchoPac v.201, GE Healthcare). We obtained standard parasternal long- and short-axis views, and apical 4-, 2- and 3-chamber views. Left atrial and ventricular volumes, ejection fraction, and mitral and tricuspid regurgitation were measured according to guidelines and regurgitations were graded as mild, moderate or severe[32,33]. The mitral valve was defined as myxomatous if leaflet thickness was ≥5 mm[34]. MVP was defined as ≥2 mm atrial displacement of any part of the mitral leaflets. MAD was defined as ≥1 mm separation from the left atrium-mitral valve leaflet junction to the top of the left ventricular myocardium at end-systole.

In patients with TAD by CMR, we retrospectively reviewed whether TAD was visible by echocardiography using apical 4-chamber and parasternal short axis views.

Cardiac magnetic resonance

The CMR study protocol was performed using a 3.0 T whole-body scanner (Ingenia, Philips Healthcare, Best, the Netherlands) with a phased-array body coil, and analysed offline, blinded for clinical data, with the use of Sectra Workstation IDS7 v.18.1 (Sectra, Linköping, Sweden) at Oslo University Hospital, Rikshospitalet, Norway.

We performed balanced steady-state free precession cine sequences in six left ventricular long axis slices separated by 30 degrees, and in consecutive short axis image planes of 8 mm slice thickness. The protocol included modified Look-Locker inversion recovery sequences in standard long axis and three short axis image planes both prior to (native) and 10 minutes after intravenous injection of 0.20 mmol/kg gadoterate meglutamine contrast agent (Dotarem TM, Guerbet, Villepinte, France).

MAD was assessed on all six left ventricular long axis slices, defined as ≥1 mm separation from the left atrium-mitral valve leaflet junction to the top of the left ventricular myocardium at end-systole. Longitudinal TAD distance was measured in end-systole, from the right atrial wall-tricuspid valve leaflet junction to the top of the right ventricular wall. Circumferential MAD was reported as total degrees. Maximum MAD and TAD distance was defined as the largest longitudinal MAD or TAD measured regardless of location. Posterolateral MAD distance was measured at 120 degrees (3-chamber view), and inferolateral MAD distance was reported as the greatest MAD assessed from 90-240 degrees. We assessed the presence of TAD in the lateral and inferior right ventricular free wall, using standard cine sequences in 4-chamber and right ventricular inflow/outflow views.

Mitral and tricuspid valve prolapse (TVP) were assessed by long axis slices for MVP, and the 4-chamber view and right-ventricular inflow/outflow view for TVP (Figure 3). Prolapse was defined as ≥2 mm superior displacement of any part of the leaflets beyond the respective annulus[32,35].

The presence of LGE was assessed by an expert radiologist using standard techniques on sequential post-contrast short and long axis slices of the left ventricle[36], and reported if present. Native and post-contrast T1 relaxation times were measured on midventricular short axis slices by placing the region of interest in the interventricular septum and the lateral left ventricular wall, and a circular region of interest in the left ventricular blood pool. We calculated myocardial extracellular volume (ECV) as the ratio between myocardial and blood pool T1 relaxivity change multiplied by a factor equal to 1- hematocrit[37]. All T1-mapping CMR studies were performed on the same scanner.

In patients not eligible for our CMR study protocol, we retrospectively analysed previously obtained clinical CMR examinations using Sectra Workstation IDS7 v.18.1 (Sectra, Linköping, Sweden) or Circle (Circle Cardiovascular Imaging, Calgary, Alberta, Canada).

In Paper II, two independent observers (first and second author) assessed intra- and inter-observer reliability for the presence of TAD, longitudinal TAD distance and tricuspid annulus diastolic diameter by reanalysing 20 random CMR studies.

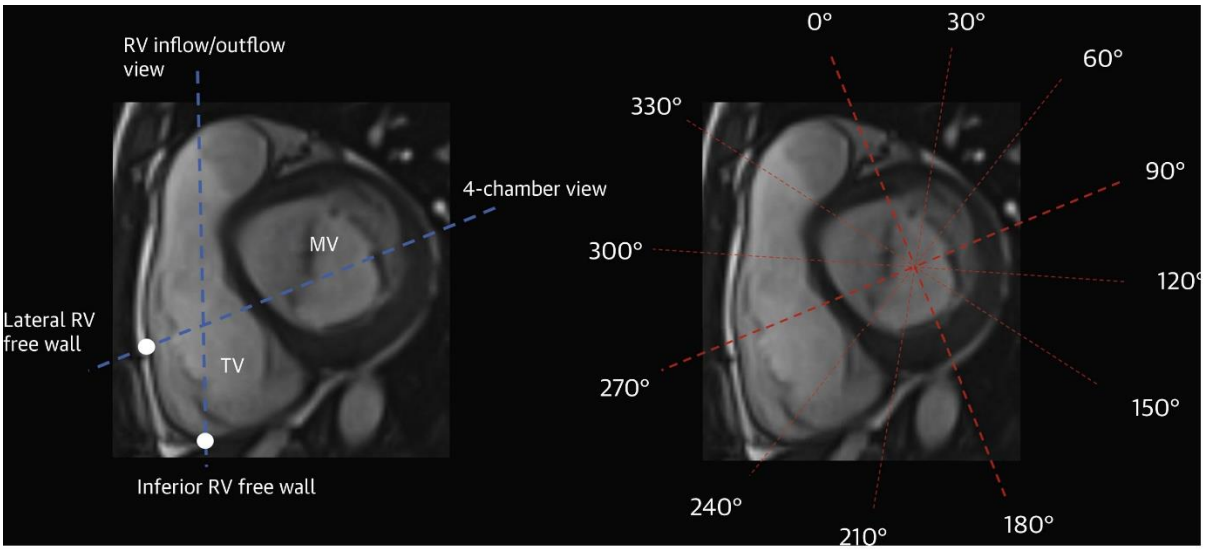


Figure 3. Cardiac magnetic resonance imaging protocols

Cardiac magnetic resonance short axis views of the atrioventricular valve plane displaying the imaging protocol used in this thesis for assessment of TAD (left) and circumferential MAD (right). (Left) CMR short-axis views showing the 4-chamber and right ventricular inflow/outflow views (blue dashed lines) in relation to the tricuspid annulus. The locations assessed for TAD were the lateral and inferior right ventricular free walls (white dots). (Right) CMR short axis views displaying the left ventricular long-axis slices perpendicular to the mitral annulus (red dashed lines) used in the CMR study protocol to assess circumferential degree of MAD. MV = mitral valve, RV = right ventricular, TV = tricuspid valve. From Aabel et al J Am Coll Cardiol Img 2021, doi: 10/1016/j.jcmg.2021.01.028, with permission.

Electrical characteristics

Electrocardiogram

We analysed resting 12-lead ECGs, blinded for clinical data, for the presence and extent of TWI in inferior (II, III and aVF), lateral (I, aVL, V5 and V6) and anterior leads (V3 and V4). We excluded ECGs recorded <5 days after an episode of severe VA and TWI secondary to bundle branch block. TWI was defined as present if the T-wave was inverted ≥0.1 mV and considered pathological when present in ≥2 adjacent leads. Extended TWI was defined as TWI in ≥3 leads. We reported QRS complex duration and QTc duration according to Bazett's formula.

PVC burden was defined as the number of PVCs in 24-hours by Holter monitoring. We evaluated PVC morphology from 12-lead ECG and 12-lead stress ECG and categorised the morphology as left or right bundle branch block morphology with either superior or inferior frontal axis[38].

Ventricular arrhythmias

VA was defined as aborted cardiac arrest, ventricular fibrillation, sustained ventricular tachycardia (VT) or NSVT on resting 12-lead ECG, stress ECG and Holter monitoring. We defined NSVT as ≥3 consecutive ventricular beats with rate ≥100 beats/min and lasting <30 seconds, and sustained VT as ≥3 consecutive ventricular beats with rate ≥100 beats/min lasting ≥30 seconds or requiring cardioversion.

In Paper I, severe VA was defined as either aborted cardiac arrest, ventricular fibrillation, appropriate or aborted ICD therapy, sustained VT or NSVT with symptoms of hemodynamic instability (syncope/presyncope). In Paper II and III, severe VA was defined as either aborted cardiac arrest, ventricular fibrillation or sustained ventricular tachycardia. NSVT burden was defined as the number of NSVTs detected by the cardiac device during follow-up.

In Paper I, we evaluated and reviewed all stored ILR events in the Carelink™ system for V at end-of-follow-up. An expert electrophysiologist re-evaluated and confirmed device electrograms considered VA by the first author.

Implantable cardiac devices

In participants who consented, we implanted a subcutaneous Reveal LINQ (Medtronic, Minneapolis, USA) in the left parasternal area in local anaesthesia. All patients were on remote monitoring by Carelink™ (Medtronic, Minneapolis, USA), with the possibility of daily alerts. Patients were instructed to manually activate ILR recording when experiencing arrhythmic symptoms.

We programmed the ILR to store tachyarrhythmias automatically when persisting for ≥5 consecutive beats and at heart rates 220 minus age beats/minute, while we allowed for adjustment in these parameters in case of frequent recording of false events.

We contacted participants with VA detected by remote monitoring for assessment of symptoms that coincided with the VA. These participants were also scheduled for an assessment at our outpatient clinic for potential ICD implantation. ICD programming were left to the discretion of the treating physicians.

Statistical analyses

Statistical analyses were performed using Stata/SE v16.1 (StataCorp LLC, TX, USA) or SPSS v.26.0 (Chicago, Illinois, USA). Two-sided p values <0.05 were considered to be significant. Continuous data were presented as mean with standard deviation or median with interquartile range (IQR), and compared with Student's t-test, one-way ANOVA or Mann-Whitney U test, respectively. Categorical data were presented as numbers with percentages and compared using chi squared or Fisher exact

tests, as appropriate. PVC burden was transformed using log base 10 when used in regression models to meet model linearity assumptions.

Paper I

Incidence rates of severe VA and NSVT were reported using person-years at-risk. To identify possible risk markers of severe VA, we used univariate and multivariate (separately adjusted for age and sex) cox proportional hazard regression models, reported by hazard ratio (HR) and 95% confidence intervals (CI).

Paper II

We tested whether TAD was associated with VA in a multivariate logistic regression model adjusted for age. Intra- and inter-observer reliability of presence of TAD, longitudinal TAD distance and tricuspid annulus diameters were assessed by means of Cohen κ and Bland-Altman plots, as appropriate.

Paper III

We tested the association between indices of diffuse myocardial fibrosis and electrical and imaging parameters using univariate linear regression and Pearson correlation analysis. Additionally, we calculated odds ratios (OR) and 95% CI for TWI, LGE and VA using univariate and multivariate logistic regression analysis.

Ethical considerations

Every study participant gave written informed consent. The studies complied with the Declaration of Helsinki and was approved by the Regional Committee for Medical Research Ethics in Norway (2015/596/REK nord) and by the Ethical Committee of UZ Brussels in Belgium (2016/407).

Specific ethical considerations

At the time of study planning and recruitment, it was still unclear whether MAD is a normal variation of cardiac anatomy, a strict pathological finding, or something in between. Thus, incidental finding of MAD on cardiac imaging might lead to further medical assessment of healthy individuals and impose potential risk associated with these assessments.

AMVP patients undergoing CMR have already long CMR acquisition times due to a comprehensive protocol including LGE. Further inclusion of T1, ECV and TAD assessment in all AMVP patients undergoing CMR for risk stratification might prolong acquisition and evaluation time considerably, and consequently increase patient discomfort and health care costs, without having any clear clinical benefit.

ILR seemed useful in follow-up of participants in Paper I, and arrhythmias detected by the ILR led to ICD implantation in 1 in 6 participants. However, we have no data on whether using ILR for follow-up improves prognosis or, rather, leads to overambitious implantation of ICD with associated risk, patient discomfort and health care cost.

Summary of results

Paper I

Study population

We included 80 patients with MAD fulfilling ILR eligibility criteria (median age 45 [IQR, 23 to 59], 68% female) (Table 1) and followed them for 3.1 years (IQR, 2.9 to 3.3). None of the patients were lost to follow-up. ILR was implanted in 60 patients that met ILR eligibility criteria, and 20 patients had prior ICD (15 with aborted cardiac arrest, 2 with sustained ventricular tachycardia and 3 with frequent NSVT with syncope/presyncope). During follow-up, 3 patients underwent mitral valve surgery and four patients underwent ablation for VA (three in the ILR group and one in the ICD group).

Table 1. Characteristics of 80 study participants by monitoring device

	All **n = 80**	**ILR-group** **n = 60**	**ICD-group** **n = 20**
Female, n (%)	56 (68)	44 (73)	11 (55)
Age, years [IQR]	45 [23-59]	49 [37-60]	34 [24-44]
Hypertension, n (%)	5 (6)	4 (7)	1 (5)
Atrial fibrillation, n (%)	8 (10)	8 (13)	0 (0)
Relevant family history*, n (%)	4 (5)	4 (7)	0 (0)
Antiarrhythmic medication			
Betablockers, n (%)	49 (61)	31 (52)	18 (90)
Flecainide, n (%)	7 (9)	5 (8)	2 (10)
Amiodarone, n (%)	2 (3)	0 (0)	2 (10)
Verapamil, n (%)	3 (4)	0 (0)	3 (5)
Arrhythmic symptoms	66 (83)	55 (92)	11 (55)
Palpitations, n (%)	58 (73)	49 (82)	9 (45)
Presyncope, n (%)	34 (43)	30 (50)	4 (20)
Syncope, n (%)	13 (16)	9 (15)	4 (20)
T-wave inversions, n (%)	18 (23)	12 (20)	6 (30)
PVCs, n per 24h [IQR]	280 [41-3525]	232 [33-1329]	2758 [277-6527]
Stress ECG performed, n (%)	62 (78)	51 (85)	11 (55)
VA at inclusion, n (%)	36 (45)	16 (27)	20 (100)
Aborted cardiac arrest, n (%)	15 (19)	0 (0)	15 (75)
Sustained VT, n (%)	2 (3)	0 (0)	2 (10)
Non-sustained VT, n (%)	19 (24)	16 (27)	3 (15)

Mitral leaflet thickness, mm	3.4 ± 1.2	3.3 ± 1.2	3.5 ± 1.0
Mitral valve prolapse, n (%)	55 (69)	44 (73)	11 (55)
Bileaflet, n (%)	36 (45)	27 (45)	9 (45)
Myxomatous MVP, n (%)	8 (10)	5 (8)	3 (15)
Mitral regurgitation			
None, n (%)	24 (30)	21 (35)	3 (15)
Mild, n (%)	42 (53)	28 (47)	14 (70)
Moderate, n (%)	12 (15)	9 (15)	3 (15)
Severe, n (%)	2 (3)	2 (3)	0 (0)
Ejection fraction, %	55 ± 6	56 ± 6	54 ± 6
Arrhythmias during follow-up			
Follow-up duration, years [IQR]	3.1 [2.8-3.3]	3.1 [2.9-3.3]	3.2 [2.0-3.9]
Severe VA, n (%)	11 (14)	7 (12)	4 (20)
Severe VA incidence, %/person-years (95% CI)	5 (3-9)	4 (2-9)	8 (3-21)
Non-sustained VT, n (%)	37 (46)	24 (40)	13 (65)
Non-sustained VT burden, n [IQR]	0 [0-4]	0 [0-2]	3 [0-4]

*Values are presented as n (%), median (IQR) or mean ± SD. The p-values were calculated by means of Student t-test, Mann-Whitney U test, chi squared or Fisher exact test as appropriate. *Relevant family history included sudden cardiac death in first-degree relatives (n=2), second-degree relative (n=1) and heart transplantation in first-degree relative (n=1). ICD = implantable cardioverter defibrillator, ILR = implantable loop recorder, IQR = interquartile range, MVP = mitral valve prolapse, MR = mitral regurgitation, PM = pacemaker, PVC = premature ventricular contraction, VA = ventricular arrhythmia, VT = ventricular tachycardia.*

Incidence of ventricular arrhythmias

Severe VA occurred in 7 (12%) of patients in the ILR group and 4 (20%) in the ICD group during follow-up, with an annual incidence rate of 4% per person-year (95% CI 2 to 9) and 8% per person-year (95% CI 3 to 21), respectively. The incidence rate was 2% (95% CI 1 to 6) when only including aborted cardiac arrest, sustained VT and NSVT with syncope as arrhythmic event. Ten (17%) patients in the ILR group received ICD during follow-up due to ILR-detected arrhythmias. The indications for ICD were severe VA (n=7), NSVT despite medical therapy (n=1), and NSVTs with concomitant sinus arrest (n=2). Of note, one patient received ICD during follow-up due to ILR-detected NSVT and

syncope, and later experienced appropriate ICD therapy for ventricular fibrillation (patient ILR #1, Figure 4).

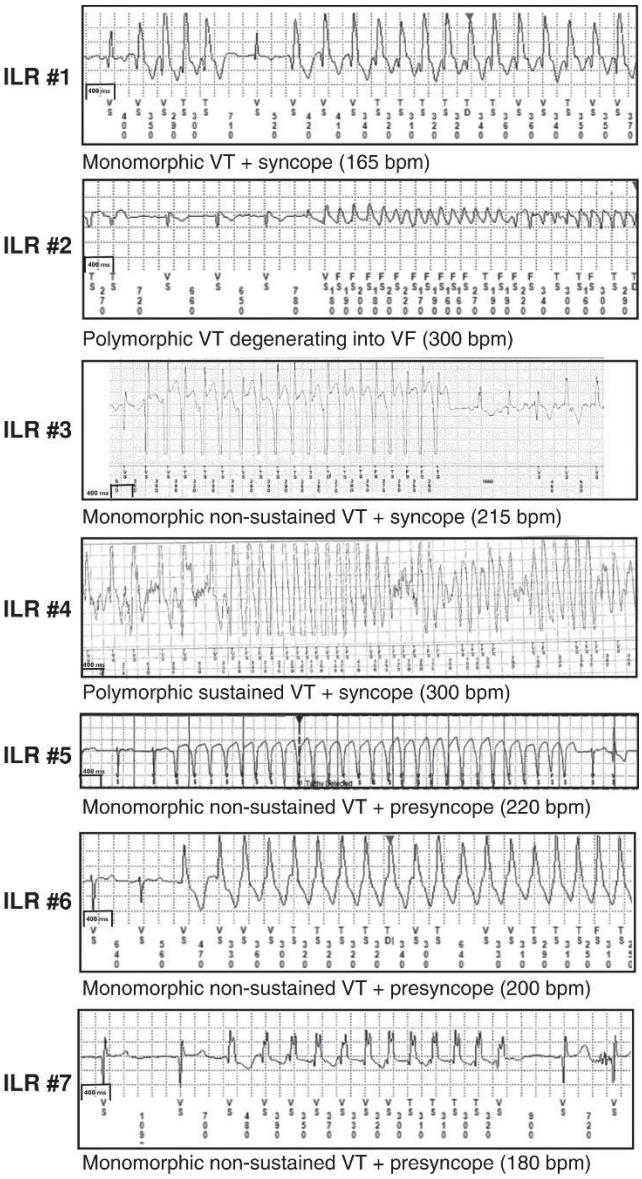


Figure 4. Recordings of the severe ventricular arrhythmias in 7 patients with implantable loop recorder at baseline.

During follow-up, 7 patients had severe ventricular arrhythmias. Patient ILR #1 was implanted with ICD due to frequent non-sustained ventricular tachycardias (VT) NSVTs and syncope, and experienced appropriate ICD therapy for ventricular fibrillation. Patient ILR #2 had polymorphic VT degenerating into VF, which was associated in time with a mitral valve chordal rupture. Patient ILR #3 had monomorphic non-sustained ventricular tachycardia (NSVT) causing syncope. Patient ILR #4 had polymorphic sustained ventricular tachycardia with subsequent traumatic head injury. Patient ILR #5 had monomorphic NSVT with presyncope with sitting and carrying a conversation. Patient ILR #6 had monomorphic ventricular tachycardia with presyncope while standing. Patient ILR #7 had

monomorphic ventricular tachycardia with presyncope. ILR = implantable loop recorder, VT = ventricular tachycardia. From Aabel et al. Europace 2022, doi 10.1093/europace/euac182, with permission.

Among the ILR group, we recorded 102 NSVTs in 24 (40%) patients, with an annual incidence rate of 18% per person-year (95% CI 12 to 27). ILR-detected events constituted 88 recordings, and 14 recordings were due to symptom activation by the patient. NSVT mean cycle length was 309 ± 93 ms (186 ± 28 bpm) and median duration was eight complexes (IQR, 6 to 12) (3 seconds [IQR, 2 to 4]).

Predictors of ventricular arrhythmia in the ILR group

We found that PVC burden, NSVT burden, left ventricular end-diastolic diameter and posterolateral MAD distance by CMR were predictors of first severe VA in univariate analyses (Table 2 and 3). These predictors remained significant when each of the variables were separately adjusted for age and gender in multivariate analyses (Table 3) (all $p<0.05$).

Table 2. Characteristics of 60 mitral annular disjunction patients monitored with implantable loop recorder and dichotomized by severe ventricular arrhythmias during follow-up.

	All	**No severe VA**	**Severe VA**	**p-value**
	n = 60	**n = 53**	**n = 7**	
Follow-up duration, years	3.1 ± 0.5	3.0 ± 0.5	2.9 ± 0.3	0.44
Female, n (%)	44 (73)	38 (72)	6 (86)	0.66
Age, years [IQR]	49 [37-60]	49 [38-60]	46 [27-58]	0.47
Hypertension, n (%)	4 (7)	4 (8)	0 (0)	1.00
Atrial fibrillation, n (%)	8 (13)	8 (15)	0 (0)	0.58
Antiarrhythmic medication				
Betablockers, n (%)	31 (52)	29 (55)	2 (29)	0.25
Flecainide, n (%)	5 (8)	5 (9)	0 (0)	1.00
Verapamil, n (%)	1 (2)	0 (0)	1 (14)	0.12
Arrhythmic symptoms, n (%)	55 (92)	49 (93)	6 (86)	0.48
Palpitations, n (%)	49 (82)	44 (83)	5 (71)	0.60
Presyncope, n (%)	30 (50)	25 (47)	5 (71)	0.42
Syncope, n (%)	9 (15)	7 (13)	2 (29)	0.28
NSVT at inclusion, n (%)	16 (27)	10 (19)	6 (86)	**0.001**
ILR eligibility criterion, ventricular arrhythmia, n (%)	45 (75)	38 (72)	7 (100)	0.18

Electrocardiography				
T-wave inversions, n (%)	12 (20)	11 (21)	1 (14)	1.00
QTc duration, ms	409 ± 36	410 ± 36	405 ± 38	0.77
PVC per 24h, n [IQR]	231 [33-1329]	154 [25-562]	6682 [612-10861]	**0.01**
PVC in bigemini at 24h ECG, n (%)	21 (44)	15 (36)	6 (100)	**0.004**
NSVT at 24h ECG, n (%)	8 (17)	5 (12)	3 (50)	**0.05**
NSVT at stress ECG, n (%)	3 (6)	0 (0)	3 (50)	**0.001**
PVC morphology				
Right bundle branch block, n (%)				
Superior axis, n (%)	28 (48)	22 (43)	6 (86)	**0.05**
Inferior axis, n (%)	12 (21)	10 (20)	2 (29)	0.63
Left bundle branch block, n (%)				
Superior axis, n (%)	0 (0)	0 (0)	0 (0)	NA
Inferior axis, n (%)	11 (19)	10 (20)	1 (14)	1.00
Arrhythmias during follow-up				
NSVT, n (%)	24 (40)	17 (32)	7 (100)	**0.001**
NSVT burden, n [IQR]	0 [0-2]	0 [0-1]	4 [4-7]	**<0.001**
NSVT duration, sec [IQR]	5 [3-7]	5 [2-7]	6 [4-7]	0.28
NSVT highest frequency, bpm	221 ± 31	218 ± 32	229 ± 29	0.45
NSVT shortest cycle length, ms	276 ± 37	280 ± 38	265 ± 32	0.37
Echocardiography				
LV end-diastolic diameter, mm	52 ± 6	51 ± 6	58 ± 6	**0.005**
LV end-diastolic diameter, mm/m2	29 ± 4	28 ± 4	31 ± 3	**0.05**
LV ejection fraction, %	56 ± 6	56 ± 6	52 ± 7	0.09
Mitral valve prolapse, n (%)	47 (78)	41 (77)	6 (86)	1.00
Bileaflet, n (%)	27 (45)	22 (42)	5 (71)	0.27
Mitral regurgitation				0.94
None, n (%)	21 (35)	18 (34)	3 (43)	
Mild, n (%)	28 (47)	25 (47)	3 (43)	
Moderate, n (%)	9 (15)	8 (15)	1 (14)	
Severe, n (%)	2 (3)	2 (4)	0 (0)	
Cardiac magnetic resonance (n = 53)				

Posterolateral MAD distance, mm [IQR]	4 [0-7]	4 [0-6]	9 [8-12]	**0.02**
LGE myocardial wall, n (%)	7 (15)	5 (12)	2 (40)	0.15
LGE papillary muscle, n (%)	11 (23)	9 (21)	2 (40)	0.58
Anterolateral, n (%)	5 (11)	4 (10)	1 (20)	0.45
Posteromedial, n (%)	10 (22)	8 (20)	2 (40)	0.30
LGE, ml [IQR]	0.3 [0-0.5]	0.2 [0-0.4]	0.3 [0-2.0]	0.86

Values are presented as n (%), median (IQR) or mean ± SD. The p-values were calculated by means of Student t-test, one-way ANOVA, Mann-Whitney U test, chi squared or Fisher exact test as appropriate. IQR = interquartile range, LBBB = left bundle branch block, LGE = late gadolinium enhancement, LV = left ventricular, MAD = mitral annular disjunction, NSVT = non-sustained ventricular tachycardia, PVC = premature ventricular complex, RBBB = right bundle branch block, VA = ventricular arrhythmia.

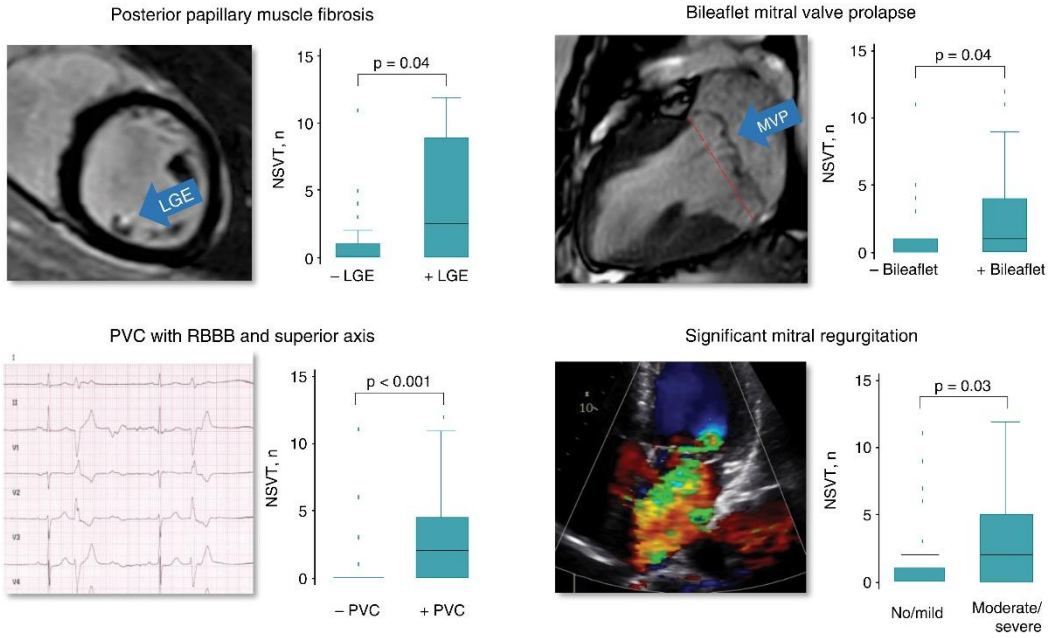
Table 3. Univariate and multivariate cox proportional hazard regression for markers of severe ventricular arrhythmias (n=7) in 60 patients with arrhythmic mitral valve syndrome monitored by implantable loop recorders.

	Univariate HR (95% CI)	**p-value**	**Multivariate HR (95% CI) adjusted for age and sex**	**p-value**
PVC burden per 10-fold increase	1.64 (1.11-2.42)	**0.02**	1.66 (1.11-2.47)	**0.01**
PVCs with RBBB superior axis	6.69 (0.81-55.57)	0.08		
NSVT, per 1-increment	1.22 (1.12-1.42)	**0.01**	1.28 (1.06-1.55)	**0.01**
Posterolateral MAD distance, per 1 mm-increment	1.27 (1.05-1.55)	**0.01**	1.43 (1.05-1.96)	0.02
Left ventricular end-diastolic diameter, per 1 mm-increment	1.20 (1.05-1.37)	**0.01**	1.25 (1.06-1.47)	**0.01**

Univariate cox proportional hazard regression was used for markers of severe ventricular arrhythmias during follow-up, and significant parameters were added to a multivariate regression model to adjust for age and sex. CI = confidence interval, MAD = mitral annular disjunction, NSVT = non-sustained

ventricular tachycardia, OR = odds ratio, PVC = premature ventricular complex, RBBB = right bundle branch block.

Markers of greater NSVT burden during follow-up included bileaflet MVP, LGE in posteromedial papillary muscle, PVCs with right bundle branch block morphology and superior axis, and moderate/severe mitral regurgitation (all p<0.04). Participants without any of these markers had a lower incidence of NSVTs compared to those with 1 or more marker (5% per person-year [95% CI 2 to 15] vs. 29% per person-year [95% CI 19 to 44], p<0.001) (Figure 5).



	NSVT markers		
	0 markers	≥ I markers	p-value
Severe VA incidence rate, %/person-years [95% CI]	0% [0–0]	7% [3–14]	0.04
NSVT incidence rate, %/person-years [95% CI]	5% [2–15]	29% [19–44]	<0.001

Figure 5. Markers of greater non-sustained ventricular tachycardia burden detected by implantable loop recorder in 60 patients with arrhythmic mitral valve syndrome.

Non-sustained ventricular tachycardia (NSVT) occurred in 24 (40%) patients during 3.1 years (interquartile range 2.9-3.3). NSVT burden was greater in patients with posteromedial papillary muscle late gadolinium enhancement (LGE) (blue arrow), bileaflet prolapse (blue arrow), moderate/severe mitral regurgitation or premature ventricular complexes with right bundle branch block and superior axis. Absence of any of these markers was related to low arrhythmic risk. LGE = late gadolinium enhancement, NSVT = non-sustained ventricular tachycardia, PVC = premature ventricular complex, RBBB = right bundle branch block, VA = ventricular arrhythmia. From Aabel et al. Europace 2022, doi 10.1093/europace/euac182, with permission.

Paper II

Study population

We included 84 patients with MAD identifiable with CMR (mean age 48±16 years; 63% female), of which 60 (71%) had performed our CMR study protocol. For the remaining 24 patients, we used standard CMR studies collected retrospectively. VA was documented in 34 (41%) patients (Table 4), of which 12 (14%) had a history of aborted cardiac arrest, 2 (2%) with sustained VT and 20 (24%) with NSVT.

Table 4. Characteristics of mitral annular disjunction patients with or without tricuspid annular disjunction

	Total (n = 84)	**No TAD (n = 42)**	**TAD (n = 42)**	**p value**
General characteristics				
Female, n (%)	53 (63)	29 (69)	24 (57)	0.26
Age, years	48 ± 16	43 ± 15	52 ± 16	**0.02**
Symptoms				
NYHA functional class, n (%)				
I	65 (77)	32 (76)	33 (79)	0.79
II	15 (18)	8 (19)	7 (17)	0.78
III	4 (5)	2 (5)	2 (5)	1.00
Chest pain, n (%)	24 (29)	15 (36)	9 (21)	0.15
Palpitations, n (%)	59 (70)	29 (68)	30 (73)	0.81
Pre-syncope, n (%)	35 (42)	16 (38)	19 (45)	0.51
Syncope, n (%)	13 (16)	6 (14)	7 (17)	0.76
Arrhythmias				
Ventricular arrhythmias, n (%)	34 (41)	22 (52)	12 (29)	**0.03**
Aborted cardiac arrest, n (%)	12 (14)	9 (21)	3 (7)	0.12
Sustained VT, n (%)	2 (2)	0 (0)	2 (5)	0.24
Non-sustained VT, n (%)	20 (24)	13 (31)	7 (17)	0.12
Premature ventricular complexes per 24 h (n = 67), n (IQR)	268 (26 - 2415)	238 (33 – 2087)	394 (19-2570)	0.93

Premature ventricular complexes origin (n = 53)				
Left-sided origin, n (%)	50 (60)	26 (62)	24 (29)	0.65
Superior axis, n (%)	45 (54)	23 (55)	22 (52)	0.82
Inferior axis, n (%)	22 (26)	14 (33)	8 (19)	0.14
Right-sided origin, n (%)	19 (23)	12 (29)	7 (17)	0.19
Superior axis, n (%)	0 (0)	0 (0)	0 (0)	NA
Inferior axis, n (%)	19 (23)	12 (29)	7 (17)	0.19
Cardiac magnetic resonance				
Maximum longitudinal TAD distance, mm		NA	5.0 ± 2.3	NA
Tricuspid valve prolapse, n (%)	35 (42)	14 (33)	21 (50)	0.12
Tricuspid annulus diameter, diastolic, mm/m2	19.8 ± 3.2	20.5 ± 2.9	19.4 ± 3.5	0.12
Tricuspid annulus diameter, systolic, mm/m2	18.1 ± 2.7	18.1 ± 2.6	18.0 ± 2.9	0.99
Circumferential MAD (n = 60), degrees	145 ± 61	115 ± 58	164 ± 57	**0.002**
Maximum longitudinal MAD distance, mm	7.9 ± 3.2	6.4 ± 2.9	9.4 ± 2.9	**<0.001**
Mitral valve prolapse, n (%)	63 (75)	24 (57)	39 (92)	**<0.001**
Anterior leaflet only, n (%)	15 (18)	11 (26)	4 (10)	**0.002**
Posterior leaflet only, n (%)	24 (28)	4 (10)	19 (45)	**0.02**
Bileaflet, n (%)	24 (28)	9 (21)	16 (38)	0.78

Values are mean ± SD, median (IQR) or n (percentage). P values are calculated by Student's T-test or Mann-Whitney U test, and χ^2 or Fisher exact test as appropriate.

MAD = mitral annular disjunction, NYHA = New York Heart Association, TAD = tricuspid annular disjunction. VT = ventricular tachycardia.

Presence and characteristics of tricuspid annular disjunction

Concomitant TAD was found in 42 (50%) patients (Figure 6 and 7), with mean maximum distance of 5.0±2.3 mm. TAD was found in the two locations available for analysis, where 16 patients (38%) had

TAD only in the lateral right ventricular free wall, 7 (17%) only in the inferior right ventricular free wall, and 19 (45%) in both locations.

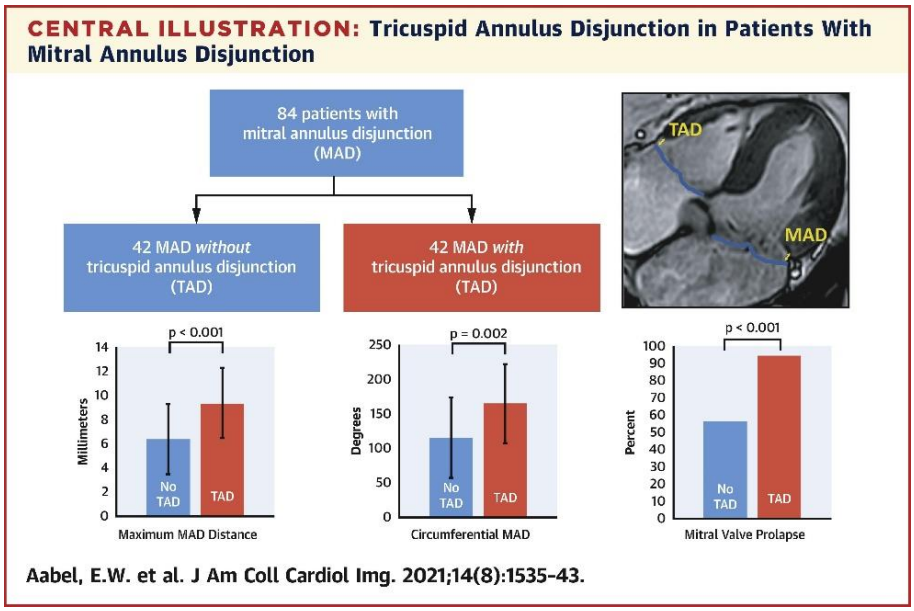


Figure 6. Tricuspid annular disjunction in patients with mitral annular disjunction

We included 84 patients with MAD on cardiac magnetic resonance, of which 50% had concomitant tricuspid annular disjunction (top left). CMR 4-chamber view of a patient with biannular disjunction (top right). Patients with TAD had larger maximum longitudinal MAD distance, greater extent of circumferential MAD, and more frequent mitral valve prolapse. MAD = mitral annular disjunction, TAD = tricuspid annular disjunction. From Aabel et al J Am Coll Cardiol Img 2021, doi: 10/1016/j.jcmg.2021.01.028, with permission.

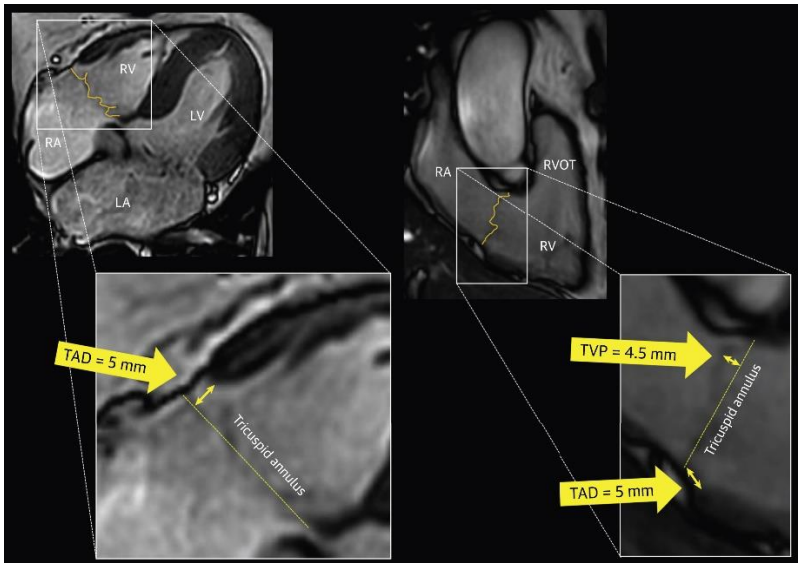


Figure 7. Cardiac magnetic resonance in a patient with biannular disjunction

Cardiac magnetic resonance in a patients with mitral annular disjunction showing concomitant tricuspid annular disjunction in 4-chamber view (left) and right ventricular inflow/outflow view (right). TAD Was present in both the lateral (left) and inferior (right) right ventricular free wall. The lower right panel shows concomitant tricuspid valve prolapse. LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle, RVOT = right ventricular outflow tract, TAD = tricuspid annular disjunction, TVP = tricuspid valve prolapse. From Aabel et al J Am Coll Cardiol Img 2021, doi: 10/1016/j.jcmg.2021.01.028, with permission.

Patients with concomitant TAD were older compared to those with MAD only (52±16 years vs. 43±15, p=0.02). Furthermore, patients with TAD had greater circumferential extent of MAD (164±57 degrees vs. 115±58 degrees, p=0.002) and larger maximum longitudinal MAD distance (9.4±2.9 mm vs. 6.4±2.9 mm, p<0.001) (Table 4). Among the 42 patients with TAD on CMR imaging, retrospective re-evaluation of echocardiography studies revealed TAD in only 2 (5%) patients.

We found reproducibility for longitudinal TAD distance and tricuspid annulus diameter, with no systematic deviation between observers (Figure 8). K-value for the presence of TAD was 1.0 for both TAD locations.

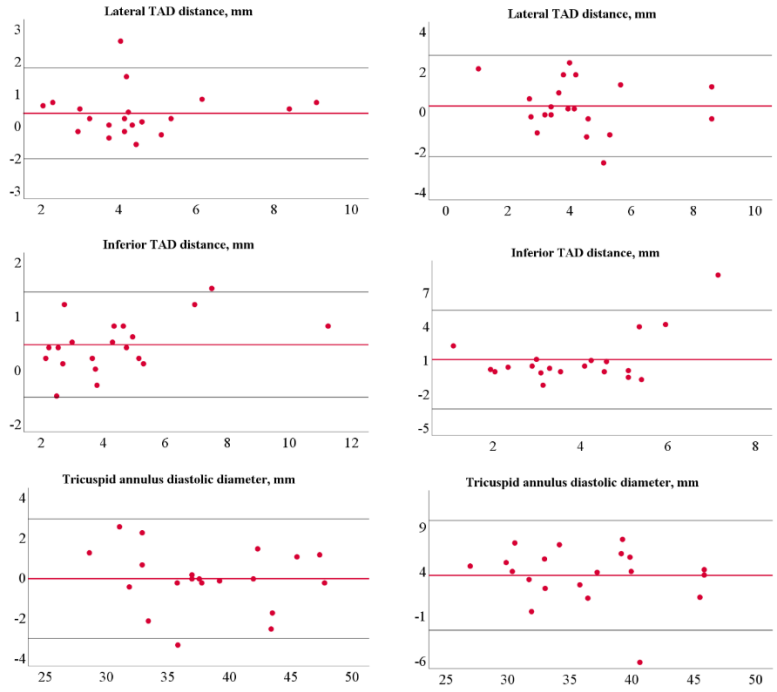


Figure 8. Intra- and interobserver reliability for cardiac magnetic resonance imaging parameters.

Bland-Altman plots of intraobserver (left panel) and interobserver (right panel) reliability for longitudinal TAD distance and tricuspid annulus diastolic diameter, performed by the first two authors

by reanalysing 20 random cardiac magnetic resonance studies. TAD = tricuspid annular disjunction. From Aabel et al. J Am Coll Cardiol Img 2021, doi: 10.1016/j.jcmg.2021.01.028, with permission.

Tricuspid annular disjunction and valvular prolapse

Patients with concomitant TAD had more frequently MVP (39 patients [92%] vs. 24 patients [52%], p<0.001), while we found no association between TAD and TVP (p=0.12). However, TAD located in the lateral right ventricular free wall (n=35) was associated with TVP (20 patients [57%] vs. 15 patients [31%], p=0.02). We found no difference in other imaging parameters between patients with or without concomitant TAD (Table 4).

Tricuspid annular disjunction and ventricular arrhythmias

Patients with TAD had less frequently VA compared to patients with MAD only (12 patients [29%] vs. 22 patients [52%], p=0.03). However, patients with prior VA were younger than patients without VA (age 39±14 years vs. 54±14 years, p<0.001). In multivariate analysis adjusted for age, the association between VA and TAD did not remain significant (OR 0.54, 95% CI 0.20 to 1.45, p=0.22).

Holter monitoring was performed in 67 patients (75%), and PVC burden was similar in patients with TAD (p=0.93). PVC morphology was possible to evaluate in 53 patients (63%), and the majority (49 patients [92%]) had right bundle branch block morphology, whilst 19 (36%) patients had left bundle branch block morphology. All morphologies with left bundle branch block had inferior frontal axis, suggesting an origin near the right ventricular outflow tract.

Paper III

Study population

We included 162 patients (mean age 50±16, 58% female), of which CMR was available in 120 (74%). Of these 120 CMR assessments, 114 (95%) were prospectively performed at inclusion. For the remaining 6 (5%) patients, we used standard CMR studies collected retrospectively. Prior VA was found in 66 (41%) patients, including severe VA in 16 (10%) patients (13 aborted cardiac arrests and 3 sustained VT) (Table 5).

Table 5. Characteristics of 162 patients with MVP dichotomized according to the presence of t-wave inversions in ≥3 ECG leads.

	Total (n=162)	TWI <3 ECG leads (n=142)	TWI ≥3 ECG leads (n=20)	p-value
Clinical characteristics				
Age, years	50 ± 16	50 ± 16	45 ± 15	0.20

Female, n (%)	93 (57)	78 (55)	15 (75)	0.10
Syncope, n (%)	29 (18)	26 (18)	3 (15)	1.00
Palpitations, n (%)	116 (72)	100 (70)	16 (80)	0.60
Arrhythmias				
VA, n (%)	66 (41)	54 (38)	12 (60)	0.06
Severe VA, n (%)	16 (10)	11 (8)	5 (25)	**0.02**
PVC count [a], n	2.34 ± 1.09	2.29 ± 1.08	2.71 ± 1.17	0.16
Electrocardiogram				
QRS duration, ms	95 ± 15	95 ±14	90 ± 8	0.12
QRS fragmentation, n (%)	23 (14)	22 (15)	1 (5)	0.31
QTc, ms	412 ± 37	409 ± 37	429 ± 31	**0.02**
Cardiac magnetic resonance [b]				
Bileaflet MVP, n (%)	43 (27)	34 (24)	9 (45)	**0.02**
Inferolateral MAD distance, mm	7 ± 3	7 ± 3	10 ± 3	**0.005**
LVEDVi, mL/m2	82 ± 24	81 ± 22	89 ± 33	0.26
LVESVi, mL/m2	35 ± 12	34 ± 12	40 ± 17	0.12
LV ejection fraction, %	58 ± 7	58 ± 7	55 ± 7	0.18
LGE, n (%)	54 (33)	46 (32)	8 (40)	0.48
Basal LV wall LGE	34 (21)	30 (21)	4 (20)	1.00
Papillary muscle LGE, n (%)	21 (13)	17 (12)	4 (20)	0.30
Average T1 time, ms	1267 ± 43	1262 ± 43	1290 ± 42	0.09
Septal T1 time, ms	1273 ± 47	1268 ± 46	1298 ± 46	0.08
Lateral T1 time, ms	1257 ± 45	1253 ± 44	1280 ± 42	0.09
Average ECV, %	27 ± 3	26 ± 3	29 ± 4	**0.01**
Septal ECV, %	27 ± 3	26 ± 3	29 ± 4	**0.02**
Lateral ECV, %	27 ± 3	26 ± 3	29 ± 5	**0.03**

Continuous variables are presented as mean (SD) and categorical variables as frequencies (%). P-values are calculated by Student's t-test, chi2, or Fisher's exact test as appropriate. ECG = electrocardiogram, ECV = extracellular volume, LV = left ventricular, LVEDVi = LV end-diastolic volume index, LVESVi = LV end-systolic volume index, LGE = late gadolinium enhancement, MAD = mitral

annular disjunction, MVP = mitral valve prolapse, TWI = t-wave inversion, PVC = premature ventricular complexes, VA = ventricular arrhythmias.

[a] Log base 10 transformation of the PVC count was performed to assure normal distribution.

[b] Cardiac magnetic resonance imaging was available in 120 patients and LGE in 113 patients, T1-mapping sequences were available in 56 patients.

T-wave inversions, ventricular arrhythmias and focal myocardial fibrosis

We found TWI ≥2 leads in 34 (21%) patients, and 20 (12%) had extended TWI (≥3 adjacent leads). Extended TWI was associated with severe VA (p=0.02) and the risk of severe VA increased with the number of leads with TWI (OR 1.91 [95% CI 1.04 to 3.52] per 1 lead-increment, p=0.04). Patients with extended TWI had greater inferolateral MAD distance (p=0.005) (Figure 9).

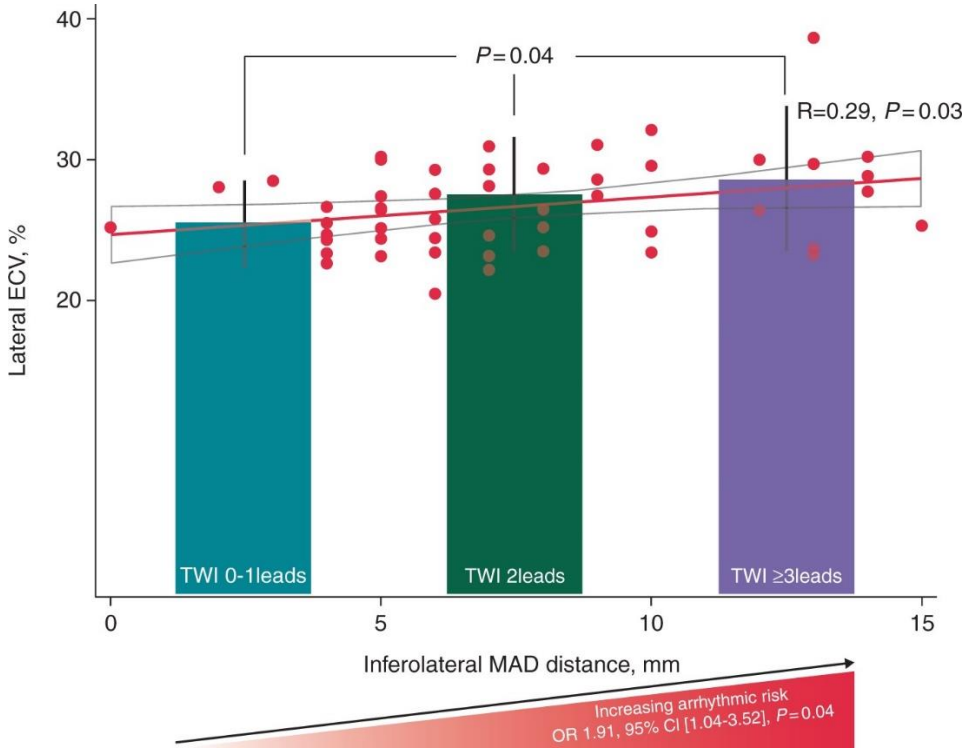


Figure 9. Higher number of ECG leads with TWI indicating higher arrhythmic risk and higher degree of lateral diffuse myocardial fibrosis.

Bar charts show values of lateral ECV by T1-mapping CMR in patients with no TWI or with TWI in 1 ECG lead (left bar), in patients with TWI in 2 ECG leads (middle bar), and in patients with TWI in ≥3 ECG leads. P-value was obtained by one-way ANOVA test with Bonferroni correction. The scatter plot graph shows the correlation between lateral ECV by T1-mapping CMR and inferolateral MAD distance. Inferolateral MAD distance increase with higher lateral ECV values. Correlation coefficient R and P-values were calculated by Pearson correlation test. The risk of severe VA increased with the

number of ECG leads with TWI Odds ratios, 85% CI and P-values for risk of severe VA were calculated by logistic regression analysis. CMR = cardiac magnetic resonance, ECG = electrocardiogram, ECV = extracellular volume, MAD = mitral annular disjunction, TWI = t-wave inversion, VA = ventricular arrhythmias. From Chivulescu et al. Europace 2022, doi: 10/1093/europace/euac017, with permission.

LGE was found in 54 (48%) patients, both in the left ventricular inferolateral wall (n=34) and in the papillary muscles (n=37). Patients with VA had more frequently LGE in the papillary muscles (50% vs 19%, p=0.001). However, LGE was not associated with extended TWI. Additionally, the presence of LGE did not increase with the number of leads with TWI (OR 1.07, 95% CI 0.80 to 1.45, p=0.62).

Diffuse myocardial fibrosis, ventricular arrhythmias and T-wave inversions

Among the prospectively performed CMR studies, 56 (47%) were done with our CMR study protocol allowing for T1 and ECV measurements, both indices of diffuse myocardial fibrosis. Patients with VA had higher lateral T1 relaxation time and higher lateral ECV, even in the group of patients without LGE (Figure 10). Lateral ECV and T1 relaxation time were associated with VA independently of age, sex, LGE, left ventricular end-diastolic volume index and severe mitral regurgitation (lateral ECV OR 1.37 [95% CI 1.02 to 1.84] per 1%-increment, p=0.03; lateral T1 OR 1.04 [95% CI 1.01 to 1.07] per 1 ms-increment, p=0.008).

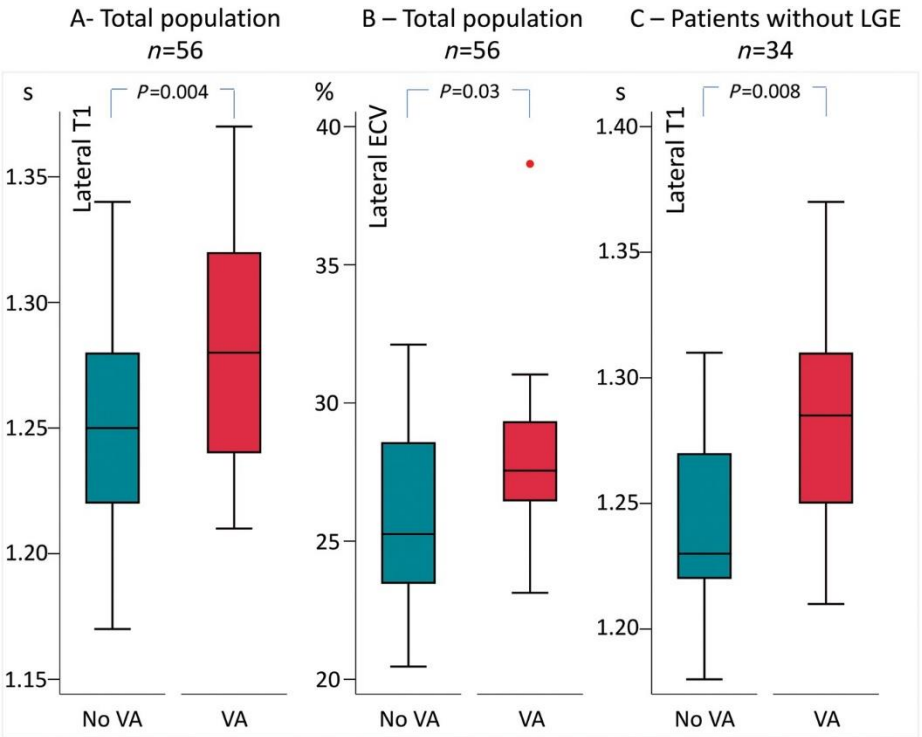


Figure 10. Lateral diffuse fibrosis by T1-mapping cardiac magnetic resonance with and without ventricular arrhythmia

Box plots representing lateral T1 and ECV values in patients with and without ventricular arrhythmia. (A) Lateral T1 in the total study population. (B) Lateral ECV in the total study population. (C) Lateral T1 in patients without late gadolinium enhancement. P-values are calculated by Student's t-test. ECV = extracellular volume, LGE = late gadolinium enhancement, VA = ventricular arrhythmia. From Chivulescu et al. Europace 2022, doi: 10/1093/europace/euac017, with permission.

Lateral ECV values were higher in patients with extended TWI (Table 6), which remained significant when adjusted for age and sex (multivariate OR 1.32 per 1%-increment, 95% CI 1.00 to 1.74, p=0.048). Furthermore, lateral ECV increased with the number of ECG leads displaying TWI (Figure 9). Lateral ECV correlated positively with inferolateral MAD distance (p=0.03) (Figure 9).

Table 6. Linear regression between diffuse fibrosis by T1-mapping cardiac magnetic resonance and clinical, electrical, and imaging parameters.

	Univariate β (95% CI) Lateral T1 (ms)	**p-value**	**Univariate β (95% CI) Lateral ECV (%)**	**p-value**
Clinical characteristics				
Age [a], years	4.95 (-3.43-13.33)	0.24	0.52 (-0.12-1.16)	0.11
Female	0.95 (-24.20-26.10)	0.69	1.66 (-0.15-3.47)	0.07
Syncope	39.96 (-0.88-80.79)	0.06	1.36 (-1.69-4.41)	0.38
Palpitations	14.58 (-11.81-40.96)	0.27	0.96 (-1.01-2.94)	0.33
Arrhythmias				
VA	36.68 (11.37-61.99)	0.005	2.07 (0.16-3.98)	**0.03**
Severe VA	-25.87 (-116.61-64.87)	0.57	-1.29 (-7.88-5.31)	0.70
PVC count [b], n	18.21 (5.51-30.94)	0.006	1.17 (0.16-2.18)	**0.03**
Electrocardiogram				
T-wave inversion	27.94 (1.81-54.07)	0.04	2.31 (0.42-4.19)	**0.02**
QRS duration, ms	0.49 (-0.46-1.44)	0.30	0.01 (-0.07-0.08)	0.89
QRS fragmentation	-16.48 (-54.22-21.27)	0.39	-1.54 (-4.40-1.31)	0.28
QTc, ms	0.44 (0.05-30.94)	0.03	0.06 (0.03-0.08)	**<0.001**
Cardiac magnetic resonance				

Bileaflet MVP	21.17 (-3.98-46.33)	0.10	1.75 (-0.08-3.58)	0.06
Inferolateral MAD distance, mm	4.50 (1.26-7.73)	0.007	0.27 (0.02-0.52)	**0.03**
LVEDVi [c], mL/m2	1.93 (-0.86-4.72)	0.17	0.13 (-0.08-0.33)	0.21
LVESVi [c], mL/m2	4.49 (-1.20-10.19)	0.12	0.32 (-0.09-0.74)	0.13
LV ejection fraction, %	-4.01 (-15.42-7.39)	0.68	-0.45 (-1.28-0.37)	0.28
LGE	12.10 (-13.16-37.36)	0.34	1.10 (-0.75-2.95)	0.24
Basal LV wall LGE	23.64 (-4.80-52.08)	0.10	2.24 (0.18-4.29)	**0.03**
Papillary muscle LGE	20.39 (-21.03-61.81)	0.33	3.30 (0.37-6.23)	**0.03**

P-values were calculated by univariate linear regression analysis. *ECG = electrocardiogram, ECV = extracellular volume, LV = left ventricular, LVEDVi = LV end-diastolic volume index, LVESVi = LV end-systolic volume index, LGE = late gadolinium enhancement, MAD = mitral annular disjunction, MVP = mitral valve prolapse, TWI = t-wave inversion, PVC = premature ventricular complexes, VA = ventricular arrhythmias.* [a] Per 10 year increment. [b] Log base 10 transformation of the PVC count was performed to assure normal distribution. [c] Per 5-units increment.

Discussion

Main findings

The three studies of this thesis describe possible predictors of increased arrhythmic risk in patients with MAD and AMVP. Importantly, these studies provide clinicians caring for AMVP patients with valuable information when evaluating the need for different follow-up strategies. Paper I was the first study to describe the incidence of VA using continuous heart rhythm monitoring in an MAD/AMVP cohort, with a high rate of first time VA and re-events. Paper 2 was the first study to describe the novel finding of concomitant right-sided annular disjunction in half of patients with MAD, and the finding that additional TAD did not increase arrhythmic risk further. Paper 3 described the prevalence of TWI on ECG in a MAD cohort, and that TWI was associated with prior VA, diffuse myocardial fibrosis and greater inferolateral MAD distance.

Incidence of first-time ventricular arrhythmia

We found a high annual incidence of 4% for first time severe VA. Our findings support the current evidence of arrhythmic risk in patients with AMVP. However, the incidence in our study was higher than previously reported in studies using symptom-driven Holter monitoring[12,14], and retrospective assessment of sudden cardiac death registries[21]. This might have been because we used continuous rhythm monitoring in our study, and that we included softer endpoints than in comparable studies. Furthermore, our cohort consisted of participants already considered at arrhythmic risk, further explaining the high incidence rate in our cohort.

We also found a high incidence of re-events among AMVP patients with secondary prevention ICD, showing that life-threatening arrhythmic events in these patients are recurrent and not stand-alone events. The re-event incidence was high despite the majority of participants using beta blockers. This observation is similar to the descriptive study by Hourdain et al[39] on survivors of cardiac arrest with MVP.

We also found a high annual incidence of NSVT of 18%. The majority of NSVTs had short duration and rate less than 200 bpm, possibly explaining why the majority were asymptomatic and automatically detected by the ILR. To our knowledge, this is the first description of asymptomatic VA in a primary prevention cohort, using systematic and continuous cardiac rhythm monitoring not based on clinical indication.

Predictors of first-time ventricular arrhythmia

Greater PVC burden by Holter monitoring and ILR-detected NSVT burden predicted first time severe VA. Recently, Essayagh et al. showed that greater severity of VA on Holter monitoring was associated with excess long-term mortality in MVP patients[12]. However, the study by Essayagh et al. was

performed with symptom-driven Holter monitoring, and in a population of old MVP patients with more comorbidities of competing risk, and high degree of mitral regurgitation[29]. The design of Paper I allowed for objective assessment of arrhythmias during follow-up and in a population more representative for the population at risk[11,13]. Hence, PVC burden and NSVT should be included in risk stratification.

In Paper I, we found that greater left ventricular dimensions were associated with severe VA. Severe mitral regurgitation leads to left ventricular remodelling and left ventricular dilatation, as well as being a risk marker for VA in other studies[40]. However, only a few participants in our study had severe mitral regurgitation, suggesting other mechanisms for our finding. There is some evidence of MVP not being an isolated valvular disorder, but, rather, a cardiomyopathy-like condition[40,41] characterised by greater left ventricular dimensions and fibrosis, independently of mitral regurgitation severity. Possible explanations for this remodelling, other than severe mitral regurgitation, might be frequent PVCs[42], increased load exerted on the left ventricle due to the additional blood volume contained in the prolapsing leaflets[43], or myocardial tissue disorders. The possibility of AMVP being a cardiomyopathy is further suggested by the high prevalence of MVP and MAD in patients with connective tissue disorders[3,4] and the association between MVP and mutations in TGF-β signalling pathways[44]. Furthermore, recent studies and case reports suggest a link between MVP and likely pathogenic variants in different cardiomyopathy genes[45], including TTN and FLNC[46] associated with dilated cardiomyopathy or hypertrophic cardiomyopathy.

We found that posterolateral MAD distance measured by CMR were predictive of subsequent severe VA. For decades, the research community has disputed over whether MAD is an abnormality or a normal anatomical variation[17,47]. MAD in the posterolateral myocardial wall has previously been associated with VA[14-16], also independently of mitral valve prolapse[18]. However, recently, Toh et al. reported that MAD was highly prevalent in structurally normal hearts within the P1 and P3 scallops of the posterior mitral leaflet[17], possibly indicating that MAD in these regions could be a part of normal cardiac anatomy. However, MAD in the posterolateral wall, involving the P2 scallop, was found only in a minority of patients. Our findings adds to the evidence that MAD in the posterolateral wall is predictive for subsequent VA and should be included in clinical risk stratification, while MAD in other locations might not be predictive of VA.

TAD was not predictive of further increased arrhythmic risk in our cohort. The tricuspid apparatus has both structural and functional differences compared to the mitral apparatus[48]. Hence, the tricuspid apparatus and right ventricle might have a lower resistance to traction and, thus, might not be prone to triggered activity or development of fibrosis in the right ventricular wall or the papillary

muscles. This theory is supported by the finding of no fibrosis in the right ventricular free wall in sudden cardiac death victims with MVP[49], although the authors did not investigate patients with TAD specifically. Furthermore, this theory is supported by our finding that PVCs with left bundle branch block morphology, all had inferior axis suggesting an origin near the outflow tracts, and not the right ventricular myocardium.

Extended TWI were predictive of VA in Paper III, with increased risk with increasing number of ECG leads displaying TWI. We also found a prevalence of TWI around 20%, comparable to other studies [10,12,50-52]. Extended TWI was found in 13% of patients, and were associated with more severe mitral valve disease. However, TWI was not predictive of VA in Paper I. This could be explained by differences in design (ambispective vs prospective), or it could be a type II error due to the low sample size and limited outcomes in Paper I compared to Paper II.

Myocardial fibrosis as a risk marker for ventricular arrhythmia

Previous studies have shown that myocardial fibrosis are more common in patients with MVP than other causes of mitral valve disease[28,53]. This association suggests MVP specific pathophysiologic adaptations leading to a profibrotic state[54]. The presence of LGE in AMVP patients has been linked to increased arrhythmic risk in several retrospective[18,24,25] and prospective studies[26,55]. The most common sites of LGE in AMVP is the papillary muscles and adjacent myocardial segments[53]. We did not find an association between LGE and severe VA in Paper I. This could be a type II error due to the low number of endpoints and lack of CMR imaging in some patients. Nevertheless, we found that LGE was predictive of higher ILR-detected NSVT burden, a surrogate marker for severe VA in our study, and adds to the evidence of LGE being a marker for VA.

In Paper III, we showed that MVP patients with prior VA and higher PVC burden had higher indices of diffuse myocardial fibrosis in the lateral left ventricular wall, even among those without LGE. This observation is similar to two other reports with significantly smaller sample sizes than in our study[28,56]. The non-uniform distribution seen in these studies are similar to autopsy findings of deceased SCD victims with AMVP, showing diffuse myocardial fibrosis in the posterolateral left ventricular wall with an endocardial to epicardial gradient[49]. This gradient is similar to histological findings in other conditions known to cause left ventricular remodelling and sudden cardiac death, such as hypertrophic and dilated cardiomyopathy[57,58].

The association between TWI and indices of diffuse myocardial fibrosis in Paper III, could suggest that diffuse myocardial fibrosis is the underlying etiology of TWI in AMVP patients. Interestingly, increased degree of histological diffuse myocardial fibrosis correlates with TWI in SCD victims[59].

The potential causes of diffuse myocardial fibrosis in AMVP are many. Firstly, diffuse myocardial fibrosis can develop due to chronic volume overload as a manifestation of left ventricular remodelling. Indeed, ECV increases with increasing severity of mitral regurgitation[53], irrespective of underlying etiology. Secondly, patients with high PVC burden might get diffuse myocardial fibrosis as a subtle form of left ventricular remodelling. However, this has yet to be proven. Thirdly, it could be related to an underlying cardiomyopathy-like condition. Irrespective of underlying cause, the presence of this type of interstitial fibrosis is an important finding, as it relates to increased rate of referral to mitral valve surgery and cardiovascular death[53]. Diffuse myocardial fibrosis even seems to regress after surgical mitral valve repair[60], suggesting this type of fibrosis to be modifiable.

We were not able to assess myocardial fibrosis in the right ventricular wall, which could have given a better insight into the mechanism of TAD on the myocardium, or lack thereof. Han et al showed in an autopsy study of sudden cardiac death victims with AMVP that the amount of fibrosis in the right ventricular free wall was similar to matched controls[49]. However, the study by Han et al did not specifically assess patients with TAD. A recent case report infers a relationship with arrhythmias from the lateral right ventricle[61], but the role of TAD in possible right ventricular involvement in AMVP patients warrants further systematic research.

Clinical implications and future perspectives

Cardiac magnetic resonance imaging for predicting ventricular arrhythmias

Our finding that MAD in the posterolateral wall was predictive when measured by CMR and not transthoracic echocardiography, increases the clinical value of performing CMR for risk stratification in AMVP patients. This adds to the current knowledge that CMR is the gold standard for assessing annular disjunction, and is also the gold standard non-invasive imaging modality for assessing myocardial fibrosis. Additionally, diffuse myocardial fibrosis measured by CMR T1-mapping could prove useful in risk stratification. However, it is important to note that the majority of both T1 and ECV values in Paper III are within what is generally considered normative ranges. It remains to be explored whether diffuse fibrosis is an early sign of disease and is pathological even within the normative ranges.

Annular disjunction

The results of Paper II adds important knowledge that annular disjunction is in fact a biannular condition. Interestingly, tricuspid valve prolapse is a common concomitant finding in patients with MVP[62-64], and annular disjunction could be the common feature. This should be investigated in future studies. We also need studies on whether TAD is a normal variation of cardiac anatomy or strictly pathological, and studies on the impact of TAD on normal function of the tricuspid apparatus.

Our finding that TAD was more easily detectable on CMR than echocardiography adds to the evidence that CMR is the better imaging modality for assessing annular disjunction[6,16,65]. Still, MAD keeps being evaluated only by echocardiography in large studies[14], possibly due to the superior cost effectiveness and availability of echocardiography.

Arrhythmia monitoring in MAD and MVP patients

Complex PVCs and NSVTs by Holter monitoring predicted arrhythmic risk in Paper I, and the same Holter findings have previously predicted excess mortality in a separate cohort[12]. In light of these observations, Holter monitoring seems valuable for risk prediction, and is generally at low-cost and easily obtained in an outpatient setting.

The results from Paper I infers that ILRs can be used for arrhythmia monitoring when closer monitoring is warranted. ILRs are minimally invasive, have a long follow-up possibility and have a high diagnostic yield[66,67], but their use is limited due to high cost. In case of prior syncope or presyncope, the use of ILR is recommended for arrhythmia monitoring by the ESC guidelines[68] and a recent expert consensus on AMVP[19]. However, because the ILR does not give therapy for life-threatening VAs, an ILR does not replace primary preventive ICD in very high risk AMVP patients. Furthermore, we need studies that investigate the prognostic role of ILR implantation in AMVP patients in order to use this device further.

Antiarrhythmic therapy in AMVP

The re-event incidence was high in Paper 1 despite the majority of ICD patients using beta blockers. This finding is similar to previous studies[12,39] and shows that there is no established medical therapy to suppress VAs and relieve arrhythmic symptoms in these patients. Invasive catheter ablation can suppress VAs, and thus relieve symptoms, in a subset of patients. However, many patients have multifocal ventricular ectopy, often originating from deep in the myocardium or papillary muscles not easily accessible for catheter ablation. Furthermore, recurrence of VAs is common despite initial successful catheter ablation procedures[39]. The only strategy to prevent sudden cardiac death for high-risk patients is to implant an ICD. However, this approach does not provide any symptomatic relief, and there are no randomized controlled trials on the efficacy of primary prophylactic implantation of ICD in these patients. Thus, we need randomized controlled trials that investigate different non-invasive therapies, catheter ablation and primary prophylactic ICD implantation in these patients.

Limitations

Selection bias of study participants

Study participants were recruited from three referral centres (two of them being tertiary centres) leading to a selection bias of symptomatic patients with a reason for referral to these centres in the first place. Furthermore, in-hospital selection bias might have occurred (e.g. recruiting older patients followed for mitral regurgitation or younger patients referred for VA evaluation). Furthermore, we excluded patients with severe VA due to other plausible causes, possibly skewing inclusion of younger VA patients with no comorbidities. All these possible selection biases affect the external validity of our observations, and the results of our study do not translate to the general MVP or MAD population, nor to asymptomatic individuals with incidental finding of MVP or MAD.

Sample size

All three studies included in this thesis have a small sample size and limited number of endpoints, which reduces the statistical robustness and the generalisability of the reported observations.

Definition of mitral annular disjunction

The cut-off value for MAD was chosen to include every patient with a measurable MAD in our cohort. Considering recent reports on some degree of MAD possibly being normal variation of cardiac anatomy[17], our approach could have led to inclusion of patients with MAD within the «normal» spectrum. Additionally, patients were screened by echocardiography, which is not the gold standard for assessing annular disjunction. However, this information was not known at the time of study planning, but, nonetheless, might affect external validity.

Missing cardiac magnetic resonance imaging data

Some patients with severe VA had non-MRI-conditional ICDs or pacemakers prior to inclusion, and, thus, we were not able to perform CMR (including our CMR study protocol). This led to a limited sample size of high-risk patients assessed for TAD and diffuse myocardial fibrosis, which in turn limits the robustness and generalisability of our observations related to these parameters.

Specific limitations

Paper I

No official definition of AMVP existed at the time of study planning, and, thus, we implanted ILR in patients with our own pre-specified criteria. Consequently, a discrepancy between our ILR eligibility criteria and the current official definition[19] of AMVP exists. This discrepancy reduces the external validity of our results, and our observations cannot be generalised to other populations of MAD and MVP patients.

The ILR did not record asymptomatic VA with shorter duration (<5 beats) or slower rate (220-age) than the programmed detection zones. Hence, the overall incidence of VA might be underestimated, especially among the younger study participants. Furthermore, there was a discrepancy between VT heart rate cut-offs due to programming differences between ICD and ILR, as well as between various ICDs. This is a technical limitation difficult to avoid and inherent to cardiac devices.

Lastly, our study was not designed to evaluate the efficacy and safety of using ILRs systematically in follow-up of AMVP patients, nor the efficacy and safety of primary preventive ICD implantation. Thus, it is still unknown whether long-term cardiac monitoring leads to improved prognosis, or, rather, overambitious antiarrhythmic therapy or implantation of ICDs exposing patients to possible complications. To resolve these unanswered issues, we need properly designed randomised clinical trials.

Paper II

This study was not designed for proper evaluation of TAD, nor finding a cut-off for defining TAD. Rather, it was a retrospective description of this novel CMR finding among our cohort included for comprehensive MAD evaluation. Because of this, we lack a normal patient population and, thus, cannot conclude whether TAD is a normal variation of cardiac anatomy or a pathological finding. Secondly, because all patients included in our cohort had MAD, we are still left with the unanswered question whether TAD occurs without concomitant mitral valve pathology. Thirdly, our study was not designed for circumferential detection of TAD, which might have led to underestimation of TAD prevalence in MAD patients.

Paper III

General limitations of this study can be found above. Yet, one additional limitation require further elaboration. We could not deem causality between diffuse myocardial fibrosis and TWI due to the ambispective and observational nature of the study.

Conclusions

General conclusions

The findings of this thesis estimated the incidence of VAs and added valuable information on VA risk stratification and follow-up in patients with MAD. Cardiac rhythm monitoring and CMR imaging were valuable tools in achieving this. All the reported observations were associated with important scientific limitations, and properly monitored prospective studies in separate cohorts are needed to strengthen the confidence in the results.

Specific conclusions

Paper I

The incidence of first-time life-threatening VA in patients with MAD was high. PVC burden, NSVTs detected by ILR, left ventricular diameter and posterolateral MAD distance by CMR were strong predictors of life-threatening events. These parameters may be helpful in the detection of high-risk patients that may warrant closer monitoring or primary prevention ICD, but separate cohorts and randomised controlled trials should validate these findings. Implantable loop recorders seemed valuable in follow-up of MAD patients. Additionally, the incidence of re-events among ICD patients were high, adding to the scientific evidence that first time life-threatening VAs in AMVP patients are not stand-alone events.

Paper II

We provided the first description of right-sided annular disjunction as a common CMR finding in patients with MAD, and enhanced current knowledge that annular disjunction is a 3-dimensional biannular phenomenon. Patients with concomitant TAD were older and had a greater extent of mitral valve pathology. However, presence of TAD was not a marker of VA.

Paper III

We found a prevalence of TWI similar to previous reports. We expanded the current knowledge with the observation that extended TWI was associated with higher risk of severe VA, and the risk of VA increased with increasing number of leads displaying TWI. The extent of TWI was associated with higher degree of diffuse myocardial fibrosis in the lateral left ventricular wall, suggesting this as the underlying substrate for TWI in AMVP patients. Furthermore, diffuse fibrosis indicated higher arrhythmic risk even in the absence of focal fibrosis.

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I

Paper I:

Ventricular Arrhythmias in Arrhythmic Mitral Valve Syndrome – A Prospective Continuous Long-term Cardiac Monitoring Study.

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CLINICAL RESEARCH

Ventricular arrhythmias in arrhythmic mitral valve syndrome—a prospective continuous long-term cardiac monitoring study

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Aims Arrhythmic mitral valve syndrome is linked to life-threatening ventricular arrhythmias. The incidence, morphology and methods for risk stratification are not well known. This prospective study aimed to describe the incidence and the morphology of ventricular arrhythmia and propose risk stratification in patients with arrhythmic mitral valve syndrome.

Methods Arrhythmic mitral valve syndrome patients were monitored for ventricular tachyarrhythmias by implantable loop recorders (ILR) and secondary preventive implantable cardioverter-defibrillators (ICD). Severe ventricular arrhythmias included ventricular fibrillation, appropriate or aborted ICD therapy, sustained ventricular tachycardia and non-sustained ventricular tachycardia with symptoms of hemodynamic instability.

Results During 3.1 years of follow-up, severe ventricular arrhythmia was recorded in seven (12%) of 60 patients implanted with ILR [first event incidence rate 4% per person-year, 95% confidence interval (CI) 2–9] and in four (20%) of 20 patients with ICD (re-event incidence rate 8% per person-year, 95% CI 3–21). In the ILR group, severe ventricular arrhythmia was associated with frequent premature ventricular complexes, more non-sustained ventricular tachycardias, greater left ventricular diameter and greater posterolateral mitral annular disjunction distance (all $P < 0.02$).

Conclusions The yearly incidence of ventricular arrhythmia was high in arrhythmic mitral valve syndrome patients without previous severe arrhythmias using continuous heart rhythm monitoring. The incidence was even higher in patients with secondary preventive ICD. Frequent premature ventricular complexes, non-sustained ventricular tachycardias, greater left ventricular diameter and greater posterolateral mitral annular disjunction distance were predictors of first severe arrhythmic event.

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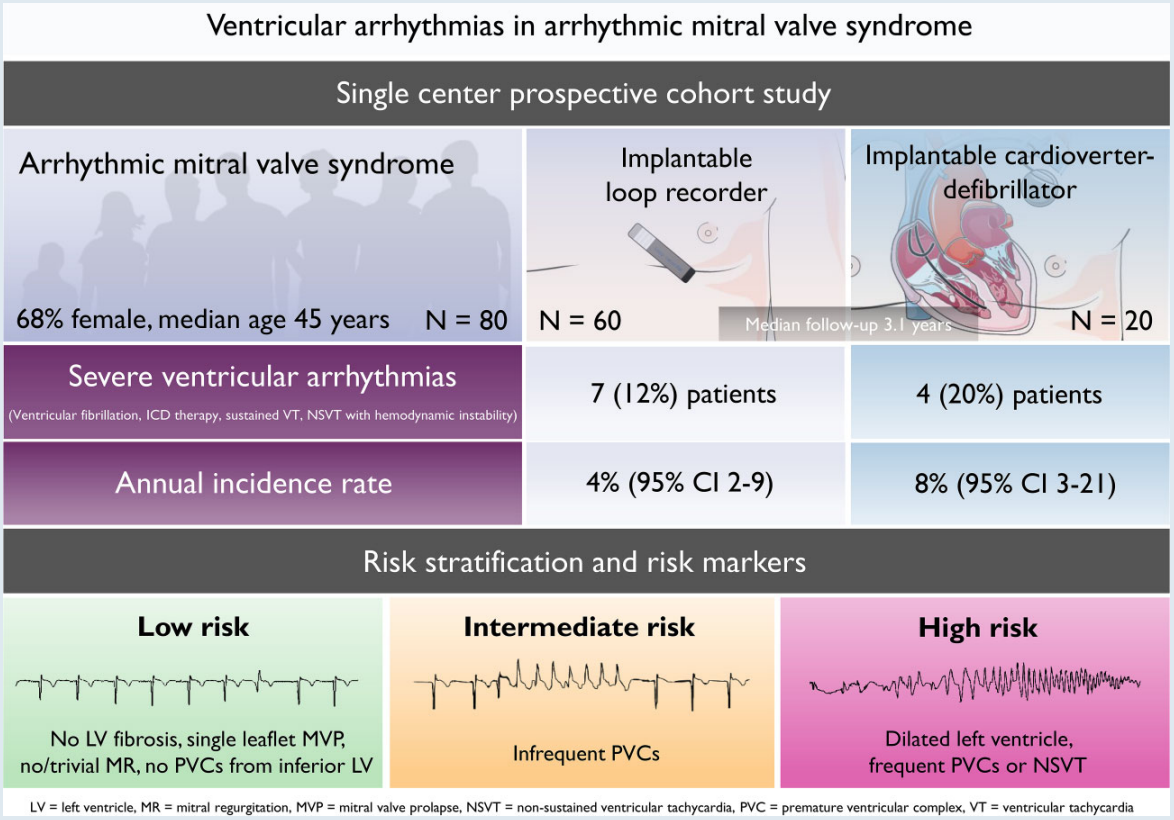
Graphical Abstract



We included 80 patients with arrhythmic mitral valve syndrome followed for 3.1 years; 60 were implanted with a loop recorder (ILR) and 20 had prior implantable cardioverter defibrillator (ICD). Severe ventricular arrhythmia occurred in seven patients (12%) in the ILR-group and four (20%) in the ICD-group. Servier Medical Art. LV = left ventricle, MR = mitral regurgitation, MVP = mitral valve prolapse, NSVT = non-sustained ventricular tachycardia, PVC = premature ventricular complex, VT = ventricular tachycardia.

Keywords Mitral valve prolapse • Ventricular tachycardia • Sudden cardiac death • Implantable loop recorder • Cardiomyopathy • Mitral annular disjunction

What's new?

- Patients with arrhythmic mitral valve syndrome are at risk of severe arrhythmic events, and risk stratification could be used to guide proper treatment.
- Patients without prior severe arrhythmic events had a 4% annual incidence of severe ventricular arrhythmic event.
- The annual incidence of severe arrhythmic re-events was 8% among patients with secondary preventive implantable cardioverter-defibrillator.

Introduction

Mitral valve prolapse (MVP) is a common and generally benign condition.[1] The association between MVP and sudden cardiac death was reported several decades ago, with an incidence of 0.2 to 0.4% per year in the general MVP population.[2] However, there is emerging evidence of an arrhythmic phenotype with an unclear incidence of life-threatening arrhythmias.[2] The definition of this syndrome is not clearly established and different terms have been proposed, including arrhythmic MVP.[3,4] Arrhythmic symptoms are common in these patients, and they frequently have multifocal ventricular arrhythmias arising from the outflow tracts, mitral annulus or left ventricular papillary muscles.[4–7] The most widely recognized risk markers are female gender, younger age, bileaflet MVP, T-wave inversions on ECG, left ventricular myocardial fibrosis and mitral annular disjunction (MAD).[7–11] However, current risk markers associated with life-threatening arrhythmias derive from cross-sectional and retrospective studies and lack prospective validation. The incidence of severe ventricular arrhythmias is unknown and clinical decisions on primary prevention implantable cardioverter defibrillator (ICD) remain challenging.

We aimed to describe the incidence of ventricular arrhythmias in patients with arrhythmic mitral valve syndrome. For this, we extended our previous study[9] by using continuous heart rhythm monitoring. We aimed to provide incidence rates and the morphology of ventricular arrhythmias in patients with and without prior severe ventricular arrhythmia. Additionally, we aimed to explore tools for risk stratification, and strategies for follow-up.

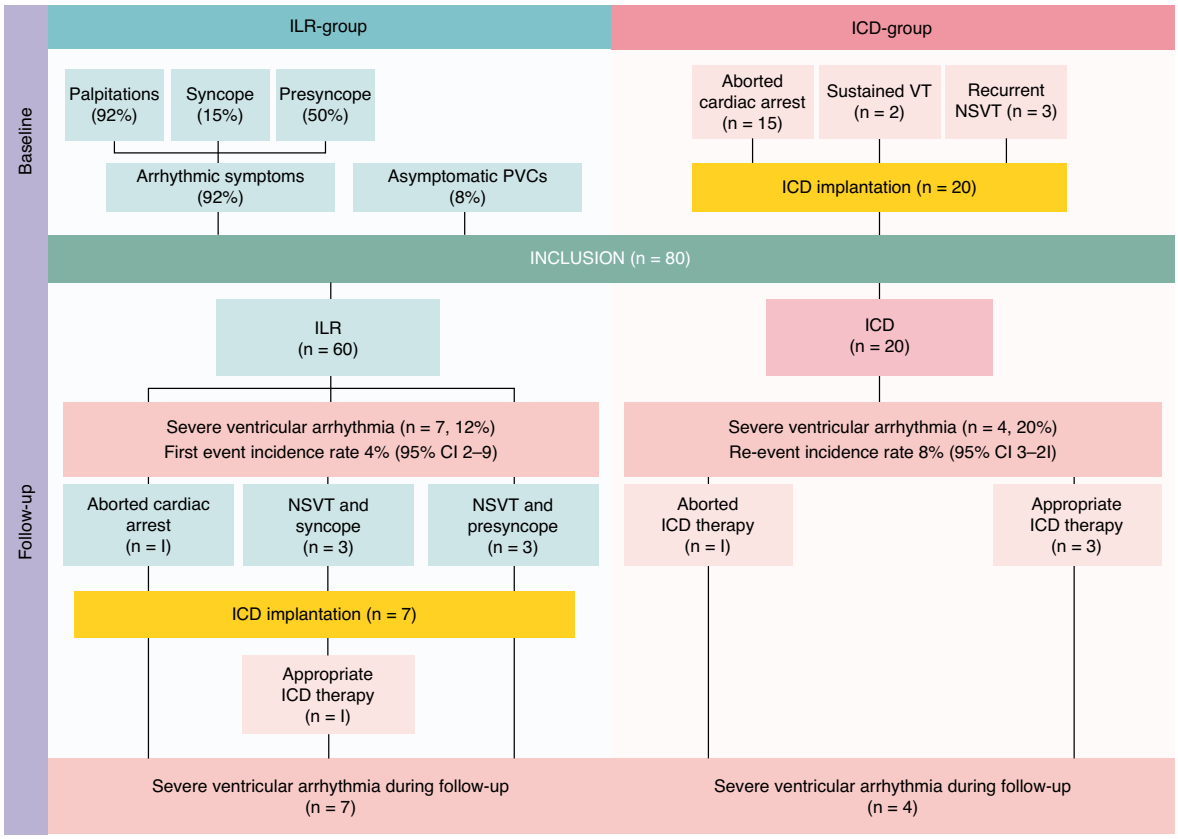


Figure 1 Study flow chart. We included 80 patients with arrhythmic mitral valve syndrome followed for 3.1 years; 60 were ILR and 20 had prior ICD. Severe ventricular arrhythmia occurred in 7 patients (12%) in the ILR-group and 4 (20%) in the ICD-group. One patient with ILR-detected arrhythmia leading to ICD implantation later experienced appropriate ICD shock.

Methods

Study population, study design and recruitment

In this prospective cohort study, we consecutively recruited patients for continuous heart rhythm monitoring following the study procedures from our previously published cohort of MAD patients.[9] In short, we screened patients with possible MAD at two hospitals in Norway, Oslo University Hospital and Drammen Hospital, from August 2015 through August 2020 (see Supplementary material online, *Figure S1*, and Supplementary material online, *Table S1*). If the echocardiographer at these recruiting centers suspected MAD, we invited the patient to a comprehensive study evaluation at Oslo University Hospital, including clinical examination, family history, 12-lead electrocardiogram (ECG), 24 h ECG, stress ECG, transthoracic echocardiography and cardiac magnetic resonance imaging (CMR).

Arrhythmic mitral valve syndrome was defined as MAD and/or MVP with arrhythmic symptoms or documented complex premature ventricular complexes (PVC). Patients with arrhythmic mitral valve syndrome were asked to be part of this prospective follow-up study, if they fulfilled prespecified eligibility criteria. The prespecified eligibility criteria were no prior documented severe ventricular arrhythmia with left ventricular ejection fraction >50% and either inferior T-wave inversions on ECG or one of the following findings on Holter monitoring; non-sustained ventricular tachycardia (NSVT), complex PVCs (multifocal PVCs, or PVCs occurring in bigemini or couplets) or >500 PVCs per 24 h. In those who consented, we implanted a subcutaneous Reveal LINQ (Medtronic, Minneapolis, USA) in the left parasternal area in local anesthesia. Additionally, we included patients with arrhythmic mitral valve syndrome with ICD implanted due to prior severe ventricular arrhythmias. We did not include patients where clinically indicated genetic testing revealed a pathogenic variant, which could explain the phenotype and the arrhythmic event.

End of follow-up was defined as last device interrogation or last transmission of ILR data by remote monitoring. The study complied with the Declaration of Helsinki and was approved by the Regional Committee for Medical Research Ethics (2015/596/REK nord). All study participants gave written informed consent.

Follow-up by implantable cardiac device

We programmed the ILR to automatically store tachyarrhythmias that persisted for at least five consecutive beats and at heart rates 220 minus patient's age beats/min. We adjusted ILR programming in case of frequent recordings of false events. All patients were on remote monitoring [Carelink™ (Medtronic, Minneapolis, USA)], with possibility for daily alerts if needed. Patients were instructed to activate electrogram recordings manually when experiencing symptoms. We contacted patients with ventricular arrhythmias detected by remote monitoring for assessment of symptoms during the detected arrhythmia, and we evaluated them for ICD implantation. ICD programming was left to the discretion of the treating physicians.

For patients receiving ICD during follow-up, we ended follow-up after the median duration of ILR monitoring (3.1 years) to avoid bias of longer follow-

Table 1 Characteristics of 80 study participants by monitoring device

	All ($n = 80$)	ILR-group ($n = 60$)	ICD-group ($n = 20$)
Female, *n* (%)	56 (68)	44 (73)	11 (55)
Age, years (IQR)	45 (23–59)	49 (37–60)	34 (24–44)
Hypertension, *n* (%)	5 (6)	4 (7)	1 (5)
Atrial fibrillation, *n* (%)	8 (10)	8 (13)	0 (0)
Relevant family history[a], *n* (%)	4 (5)	4 (7)	0 (0)
Antiarrhythmic medication			
Betablockers, *n* (%)	49 (61)	31 (52)	18 (90)
Flecainide, *n* (%)	7 (9)	5 (8)	2 (10)
Amiodarone, *n* (%)	2 (3)	0 (0)	2 (10)
Verapamil, *n* (%)	3 (4)	0 (0)	3 (5)
Arrhythmic symptoms, *n* (%)	66 (83)	55 (92)	11 (55)
Palpitations, *n* (%)	58 (73)	49 (82)	9 (45)
Presyncope, *n* (%)	34 (43)	30 (50)	4 (20)
Syncope, *n* (%)	13 (16)	9 (15)	4 (20)
T-wave inversions, *n* (%)	18 (23)	12 (20)	6 (30)
PVCs, *n* per 24 h (IQR)	280 (41–3525)	232 (33–1329)	2758 (277–6527)
Stress ECG performed, *n* (%)	62 (78)	51 (85)	11 (55)
VA at inclusion, *n* (%)	36 (45)	16 (27)	20 (100)
Aborted cardiac arrest, *n* (%)	15 (19)	0 (0)	15 (75)
Sustained VT, *n* (%)	2 (3)	0 (0)	2 (10)
Non-sustained VT, *n* (%)	19 (24)	16 (27)	3 (15)
Mitral leaflet thickness, mm	3.4 ± 1.2	3.3 ± 1.2	3.5 ± 1.0
Mitral valve prolapse, *n* (%)	58 (73)	47 (78)	12 (60)
Bileaflet MVP, *n* (%)	36 (45)	27 (45)	9 (45)
Myxomatous MVP, *n* (%)	8 (10)	5 (8)	3 (15)
Mitral regurgitation			
None, *n* (%)	24 (30)	21 (35)	3 (15)
Mild, *n* (%)	42 (53)	28 (47)	14 (70)
Moderate, *n* (%)	12 (15)	9 (15)	3 (15)
Severe, *n* (%)	2 (3)	2 (3)	0 (0)
Mitral annular disjunction, *n* (%)	80 (100)	60 (100)	20 (100)
Ejection fraction, %	55 ± 6	56 ± 6	54 ± 6
Arrhythmias during follow-up			
Follow-up duration, years (IQR)	3.1 (2.8–3.3)	3.1 (2.9–3.3)	3.2 (2.0–3.9)
Severe VA, *n* (%)	11 (14)	7 (12)	4 (20)
Severe VA incidence, %/person-years (95% CI)	5 (3–9)	4 (2–9)	8 (3–21)
Non-sustained VT, *n* (%)	37 (46)	24 (40)	13 (65)
Non-sustained VT burden, *n* (IQR)	0 (0–4)	0 (0–2)	3 (0–4)

Values are presented as *n* (%), median (IQR) or mean ± SD. The *P*-values were calculated by means of Student *t*-test, one-way ANOVA, Mann–Whitney U test, chi squared or Fisher exact test as appropriate.

[a]Relevant family history included sudden cardiac death in first-degree relatives ($n = 2$), second-degree relative ($n = 1$) and heart transplantation in first degree relative ($n = 1$). ICD = implantable cardioverter defibrillator, ILR = implantable loop recorder, IQR = interquartile range, MVP = mitral valve prolapse, MR = mitral regurgitation, PM = pacemaker, PVC = premature ventricular contraction, VA = ventricular arrhythmia, VT = ventricular tachycardia.

up in those receiving ICD. We also censored patients undergoing mitral valve surgery or ablation for ventricular arrhythmia at time of the procedure.

Ventricular arrhythmias

We defined NSVT as ≥ 3 consecutive ventricular beats with heart rate > 100 beats/min lasting < 30 s documented by ECG, stress ECG or 24 h ECG at inclusion, or by an implanted cardiac device during follow-up (as per device programming). We defined NSVT burden as the number of NSVTs detected by the cardiac device during follow-up. Severe ventricular arrhythmia was defined as either aborted cardiac arrest, ventricular fibrillation, appropriate or aborted ICD-therapy, sustained ventricular tachycardia (VT) (>100 beats/min lasting >30 s) or NSVT with symptoms of hemodynamic instability (syncope/presyncope).

Table 2 Severe ventricular arrhythmias during follow-up in 60 patients with arrhythmic mitral valve syndrome monitored by implantable loop recorders

	All *n*(= 60)	No severe VA (*n* = 53)	Severe VA (*n* = 7)	*P*-value
Follow-up duration, years	3.1 ± 0.5	3.0 ± 0.5	2.9 ± 0.3	0.44
Female, *n* (%)	44 (73)	38 (72)	6 (86)	0.66
Age, years (IQR)	49 (37–60)	49 (38–60)	46 (27–58)	0.47
Hypertension, *n* (%)	4 (7)	4 (8)	0 (0)	1.00
Atrial fibrillation, *n* (%)	8 (13)	8 (15)	0 (0)	0.58
Antiarrhythmic medication				
Betablockers, *n* (%)	31 (52)	29 (55)	2 (29)	0.25
Flecainide, *n* (%)	5 (8)	5 (9)	0 (0)	1.00
Verapamil, *n* (%)	1 (2)	0 (0)	1 (14)	0.12
Arrhythmic symptoms, *n* (%)	55 (92)	49 (93)	6 (86)	0.48
Palpitations, *n* (%)	49 (82)	44 (83)	5 (71)	0.60
Presyncope, *n* (%)	30 (50)	25 (47)	5 (71)	0.42
Syncope, *n* (%)	9 (15)	7 (13)	2 (29)	0.28
NSVT at inclusion, *n* (%)	16 (27)	10 (19)	6 (86)	0.001
ILR eligibility criterion, ventricular arrhythmia, *n* (%)	45 (75)	38 (72)	7 (100)	0.18
Electrocardiography				
T-wave inversions, *n* (%)	12 (20)	11 (21)	1 (14)	1.00
QTc duration, ms	409 ± 36	410 ± 36	405 ± 38	0.77
PVC per 24 h, *n* (IQR)	231 (33–1329)	154 (25–562)	6682 (612–10 861)	0.01
PVC in bigemini at 24 h ECG, *n* (%)	21 (44)	15 (36)	6 (100)	0.004
NSVT at 24 h ECG, *n* (%)	8 (17)	5 (12)	3 (50)	0.05
NSVT at stress ECG, *n* (%)	3 (6)	0 (0)	3 (50)	0.001
PVC morphology				
Right bundle branch block, *n* (%)				
Superior axis, *n* (%)	28 (48)	22 (43)	6 (86)	0.05
Inferior axis, *n* (%)	12 (21)	10 (20)	2 (29)	0.63
Left bundle branch block, *n* (%)				
Superior axis, *n* (%)	0 (0)	0 (0)	0 (0)	NA
Inferior axis, *n* (%)	11 (19)	10 (20)	1 (14)	1.00
Arrhythmias during follow-up				
NSVT, *n* (%)	24 (40)	17 (32)	7 (100)	0.001
NSVT burden, *n* (IQR)	0 (0–2)	0 (0–1)	4 (4–7)	<0.001
NSVT duration, sec (IQR)	5 (3–7)	5 (2–7)	6 (4–7)	0.28
NSVT highest frequency, bpm	221 ± 31	218 ± 32	229 ± 29	0.45
NSVT shortest cycle length, ms	276 ± 37	280 ± 38	265 ± 32	0.37
Echocardiography				
LV end-diastolic diameter, mm	52 ± 6	51 ± 6	58 ± 6	0.005
LV end-diastolic diameter, mm/m2	29 ± 4	28 ± 4	31 ± 3	0.05
LV ejection fraction, %	56 ± 6	56 ± 6	52 ± 7	0.09
Mitral annular disjunction, *n* (%)	60 (100)	53 (100)	7 (100)	NA
Mitral valve prolapse, *n* (%)	47 (78)	41 (77)	6 (86)	1.00
Bileaflet, *n* (%)	27 (45)	22 (42)	5 (71)	0.27
Mitral regurgitation				0.94
None, *n* (%)	21 (35)	18 (34)	3 (43)	
Mild, *n* (%)	28 (47)	25 (47)	3 (43)	
Moderate, *n* (%)	9 (15)	8 (15)	1 (14)	

Continued

Table 2 *Continued*

	All *n*(= 60)	No severe VA (*n* = 53)	Severe VA (*n* = 7)	*P*-value
Severe, *n* (%)	2 (3)	2 (4)	0 (0)	
Cardiac magnetic resonance (*n* = 53)				
Posterolateral MAD distance, mm (IQR)	4 (0–7)	4 (0–6)	9 (8–12)	0.02
LGE myocardial wall, *n* (%)	7 (15)	5 (12)	2 (40)	0.15
LGE papillary muscle, *n* (%)	11 (23)	9 (21)	2 (40)	0.58
Anterolateral, *n* (%)	5 (11)	4 (10)	1 (20)	0.45
Posteromedial, *n* (%)	10 (22)	8 (20)	2 (40)	0.30
LGE, ml (IQR)	0.3 (0–0.5)	0.2 (0–0.4)	0.3 (0–2.0)	0.86

Values are presented as *n* (%), median (IQR) or mean ± SD. The *P*-values were calculated by means of Student *t*-test, one-way ANOVA, Mann–Whitney U test, chi squared or Fisher exact test as appropriate. IQR = interquartile range, LBBB = left bundle branch block, LGE = late gadolinium enhancement, LV = left ventricular, MAD = mitral annular disjunction, NSVT = non-sustained ventricular tachycardia, PVC = premature ventricular complex, RBBB = right bundle branch block, VA = ventricular arrhythmia.

At end of follow-up, we evaluated and reviewed all stored ILR events in the Carelink™ system for ventricular arrhythmias. An expert electrophysiologist re-evaluated and confirmed electrograms considered ventricular arrhythmias and we determined arrhythmia morphology (polymorphic or monomorphic), cycle length and mode of onset. PVC morphology from ECG and stress ECG was categorized in left or right bundle branch block morphology with superior or inferior frontal axis.[12] T-wave inversion was defined as present if seen in ≥ 2 adjacent ECG leads.

Echocardiography and cardiac magnetic resonance

Cardiac volumes and functions were measured according to guidelines.[13,14] Imaging data were analyzed offline [echocardiographic data by EchoPAC v203 (GE Healthcare, Horten, Norway) and CMR data by Sectra Workstation IDS7 v18.1 (Sectra AB, Linköping, Sweden)]. We defined MVP as superior displacement ≥2 mm of any part of the mitral leaflet beyond the mitral annulus on echocardiography using parasternal long-axis view.[13] The mitral valve was defined as myxomatous if leaflet thickness was ≥5 mm. We defined MAD as ≥1 mm disjunction measured in end-systole, from the left atrial wall-valve leaflet junction to the top of the left ventricular wall.[9,15,16] MAD was measured in all locations available for analysis by both echocardiography and CMR, including circumferential extent by CMR.

The CMR study protocol was performed using a 3-T whole-body scanner (Ingenia, Philips Healthcare, Best, the Netherlands). Posterolateral MAD distance was measured on three-chamber view (120 degrees).[9,16] Late gadolinium enhancement (LGE) was reported if present.[9]

Statistical analysis

We presented continuous data as mean with standard deviation or median with interquartile range (IQR), and categorical data as numbers with percentages and compared data with independent Student's *t*-test, one-way analysis of variance (ANOVA), Mann–Whitney U test, chi squared or Fisher exact tests, as appropriate. Univariate cox proportional hazard regression models identified markers of severe ventricular arrhythmias. Significant ($P < 0.05$) variables from the univariate analyses were included in multivariate regression models and were adjusted for age and sex. We tested the multivariate regression models for proportional hazard assumptions to avoid overfitting. We used log base 10 transformation of the PVC burden to meet model linearity assumptions. We reported incidence rates of ventricular arrhythmias using person-years at-risk. We used single threshold regression analysis to explore a cutoff of PVC burden from where the odds of severe ventricular arrhythmia increased the most (Stata/SE v16.1, StataCorp LLC, TX, USA). Two-sided *P* values < 0.05 were considered significant.

Results

Study population for continuous heart rhythm monitoring at baseline

We included 80 patients with arrhythmic mitral valve syndrome (*Figure 1*, *Table 1*) (see Supplementary material online, *Figure S1*). We implanted ILR in 60 (75%) patients meeting ILR eligibility criteria (*Table 2*; see Supplementary material online, *Table S1*). Another 75 patients were screened and either did not meet ILR eligibility criteria or did not consent (see Supplementary material online, *Table S1*). Furthermore, we included 20 (25%) patients with prior ICD due to previous severe ventricular arrhythmia [aborted cardiac arrest (*n* = 15), sustained VT (*n* = 2), and frequent NSVT with syncope/presyncope (*n* = 3)]. CMR was performed in 69 (86%) patients.

Incidence of severe ventricular arrhythmias during follow-up

We followed patients for 3.1 years (IQR, 2.9–3.3), and follow-up was completed in January 2021. None of the patients was lost to follow-up. During follow-up, three patients underwent mitral valve surgery and four patients underwent ablation for ventricular arrhythmia (three in the ILR group and one in the ICD group).

In the ILR group, first severe ventricular arrhythmia occurred in seven (12%) patients (*Figure 1*, left panel), giving an incidence rate of first severe ventricular arrhythmia of 4% per person-year (95% CI 2–9), and 2% per person-year (95% CI 1–6) when including only aborted cardiac arrest, sustained VT and NSVT with syncope as outcome. One patient with ILR-detected NSVT and syncope received ICD and experienced a subsequent appropriate ICD shock for ventricular fibrillation (ILR #1; see Supplementary material online, *Figure S2*).

In the ICD group, severe ventricular arrhythmias occurred in four (20%) patients during follow-up (*Figure 1*, right panel, and see Supplementary material online, *Figure S3*) (two monomorphic and two polymorphic), giving a re-event incidence rate of 8% per person-year (95% CI 3–21).

Ventricular arrhythmias in the implantable loop recorder group

Non-sustained ventricular tachycardias during follow-up

In the ILR-group, NSVT occurred in 24 (40%) unique patients, with an incidence rate of 18% per person-year (95% CI 12–27), of which 11 (45%) did not have NSVT at baseline. We recorded 102 NSVTs in

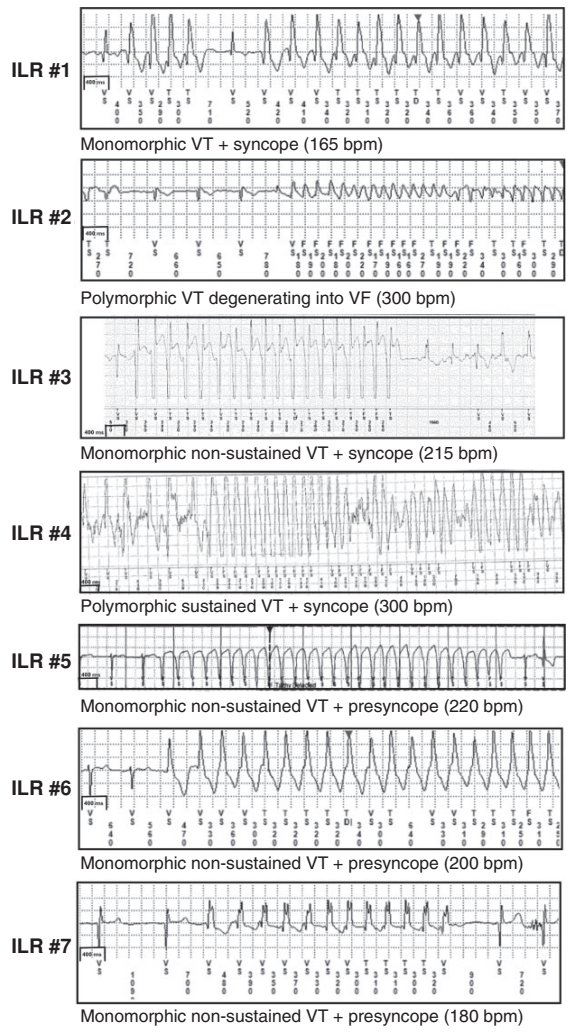


Figure 2 Recordings of the severe ventricular arrhythmias in seven patients with implantable loop recorder at baseline. During follow-up, seven patients had severe ventricular arrhythmias. Patient ILR #1 was implanted with ICD due to frequent NSVTs and syncope at wakeful rest, and experienced appropriate ICD therapy for ventricular fibrillation during mild activity. Patient ILR #2 had polymorphic VT degenerating into VF, which was associated in time with a mitral valve chordal rupture. Patient ILR #3 had monomorphic NSVT causing syncope while standing. Patient ILR #4 had polymorphic sustained VT during exercise with subsequent traumatic head injury. Patient ILR #5 had monomorphic NSVT with presyncope while sitting and carrying a conversation. Patient ILR #6 had monomorphic VT with presyncope while standing. Patient ILR #7 had monomorphic VT with presyncope during wakeful rest.

the 24 patients (ranging from one to 15 episodes in one unique patient), and 88 were due to ILR tachycardia detection and 14 were below the detection zone and, thus, recorded due to symptom activation by the patient. NSVT mean cycle length was 309 ± 93 ms (186 ± 28 bpm) and median duration was eight complexes (IQR, 6–12) [3 s (IQR, 2–4)]. The NSVTs were monomorphic and the arrhythmia initiating PVC coupling intervals varied among the recorded NSVTs [median 530 ms (IQR, 390–650)] and varied within the same patient [maximal variability 310 ms (IQR, 190–480)].

The ILR-detected ventricular arrhythmias led to ICD implantation in ten (17%) of the 60 ILR patients (*Figure 2*; see Supplementary material online, *Figure S2*; see Supplementary material online, *Table S2*). The indications for ICD in these ten patients included severe ventricular arrhythmia ($n = 7$) (*Figure 2*), frequent NSVT despite medical therapy ($n = 1$), and sinus arrest in two patients who received two-chamber ICD due to concomitant recurrent NSVTs (see Supplementary material online, *Figure S4*).

Predictors of occurrence of first severe ventricular arrhythmia in patients monitored by implantable loop recorder

In the ILR group, PVC burden, NSVT burden, left ventricular end-diastolic diameter, and posterolateral MAD distance by CMR were predictors of first severe ventricular arrhythmia in univariate analyses and remained significant when adjusted for age and gender in multivariate analyses (*Table 3*) (all $P < 0.05$).

The odds of severe ventricular arrhythmia increased the most at PVC burden >3525 per 24 h by single threshold regression analysis. Incidence rate for first severe ventricular arrhythmia was 2% (95% CI 0–7) vs. 18% (95% CI 7–49) per person-years in patients with PVC burden below and above 3525 per 24 h, respectively ($P = 0.007$).

LGE, female sex, bileaflet MVP or T-wave inversions were not associated with severe ventricular arrhythmias. There was no difference in occurrence of severe arrhythmias in those fulfilling ILR-eligibility criteria due to ventricular arrhythmias compared to those fulfilling ECG criteria (*Table 2*).

Markers of non-sustained ventricular tachycardia burden

In the ILR-group, markers for greater NSVT burden during follow-up included bileaflet prolapse ($P = 0.04$), LGE in the posteromedial papillary muscles ($P = 0.04$), PVCs with right bundle branch block morphology and superior axis ($P < 0.001$), and moderate/severe mitral regurgitation ($P = 0.03$) (*Figure 3*). Importantly, patients without any of these four markers had no severe ventricular arrhythmias, and had a lower incidence of NSVTs compared to those with ≥1 marker (5% per person-year [95% CI 2 to 15] vs. 29% per person-year [95% CI 19 to 44], $P < 0.001$) (*Figure 3*). We observed no sex differences in the burden of NSVTs ($P = 0.44$), nor differences between patients with and without MVP ($P = 0.78$).

Discussion

The incidence of severe ventricular arrhythmias was high in patients with arrhythmic mitral valve syndrome monitored by ILR or ICD, with a yearly incidence of 4% and 8%, respectively (*Figure 1*). Greater left ventricular dimensions, frequent PVCs, greater ILR-detected NSVT burden during follow-up and greater posterolateral MAD distance identified high-risk patients in the ILR group. The ILR-detected arrhythmias led to ICD implantation in ten of 60 patients. These findings suggest a high diagnostic yield using ILR in patients with arrhythmic mitral valve syndrome.

Incidence, morphology and initiation of ventricular arrhythmias

First severe ventricular arrhythmia occurred in 12% of patients with arrhythmic mitral valve syndrome with no previous severe ventricular arrhythmia, and re-events occurred in 20% of patients with prior severe

Table 3 Univariate and multivariate cox proportional hazard regression for markers of severe ventricular arrhythmias ($n = 7$) in 60 patients with arrhythmic mitral valve syndrome monitored by implantable loop recorders

	Univariate HR (95% CI)	*P*-value	Multivariate HR (95% CI) adjusted for age and sex	*P*-value
PVC burden per 10-fold increase	1.64 (1.11–2.42)	0.02	1.66 (1.11–2.47)	0.01
PVCs with RBBB superior axis	6.69 (0.81–55.57)	0.08		
NSVT, per 1-increment	1.22 (1.12–1.42)	0.01	1.28 (1.06–1.55)	0.01
Posterolateral MAD distance, per 1 mm-increment	1.27 (1.05–1.55)	0.01	1.43 (1.05–1.96)	0.02
Left ventricular end-diastolic diameter, per 1 mm-increment	1.20 (1.05–1.37)	0.01	1.25 (1.06–1.47)	0.01

Univariate Cox proportional hazard regression was used for markers of severe ventricular arrhythmias during follow-up, and significant parameters were added to separate multivariate regression models to adjust for age and sex. CI = confidence interval, MAD = mitral annular disjunction, NSVT = non-sustained ventricular tachycardia, HR = hazard ratio, PVC = premature ventricular complex, RBBB = right bundle branch block.

ventricular arrhythmia during three years of follow-up. The high rates support the emerging awareness of arrhythmic risk in these patients.

In patients without previous severe ventricular arrhythmia (ILR group), the yearly incidence for first severe arrhythmic event was 4% per person-year. Our incidence was higher than previously reported,[2,17] possibly due to the continuous monitoring used in our study and by our ILR eligibility criteria, which included patients with NSVT, complex PVCs or PVC burden >0.5%.

We included NSVT with presyncope as a severe ventricular arrhythmia, further leading to an increased arrhythmic incidence rate. ESC guidelines state that syncope and presyncope should be evaluated similarly, as they carry the same prognosis.[18] Additionally, patients experiencing NSVTs with presyncope should be evaluated for ICD, and we therefore considered this an important clinical event worthy of prediction. When excluding NSVT with presyncope, the yearly incidence rate was still high at 2%.

Findings by the ILR contributed in decisions on ICD implantation in every sixth ILR monitored patient and the ILR detected arrhythmias that explained clinical symptoms such as syncope/presyncope.

The incidence of NSVTs was high and these NSVTs were monomorphic, mostly of short duration. There were no signs of short-coupled arrhythmic mechanisms. The initiating mechanism should be further investigated.

We also demonstrated an even higher risk of arrhythmic re-events with yearly incidence of 8% in patients with prior ICD, in line with a previous report on MVP patients who survived cardiac arrest by Hourdain *et al.*[6] Both in our study and in the study by Hourdain *et al.*, re-events occurred despite use of antiarrhythmic medication, showing the current lack of efficient non-invasive treatment options.

Risk prediction in patients with arrhythmic mitral valve syndrome

Greater PVC burden and ILR-detected NSVT burden predicted first severe ventricular arrhythmia. A previous study related NSVTs or frequent PVCs on Holter monitoring in patients with MVP to excess long-term mortality.[3] Thus, occurrence of NSVTs should be included as an important risk marker for ICD evaluations (*Figure 4*). Furthermore, having PVCs originating from the inferior left ventricle or papillary muscles was associated with higher NSVT burden in line with previous data,[5] indicating a potential benefit of 12-lead Holter monitoring in these patients.

Neither focal myocardial fibrosis by LGE nor T wave inversions were markers of severe ventricular arrhythmia in our study, contrary to previous studies.[3,8,19] The non-association seen in our study was probably due to our smaller sample size, making our study prone to type II errors. LGE was a marker for ILR-detected NSVT, supporting focal myocardial fibrosis as a substrate for ventricular arrhythmias (*Figure 3*). Importantly, severe arrhythmias occurred also in patients without LGE, emphasizing the need of multiple risk markers. Furthermore, we included T-wave inversion as an ILR eligibility criterion, possibly reducing the predictive power for this parameter within the cohort. Thus, in light of recent studies showing predictive value of LGE and T wave inversions, we believe that these markers should be included in risk stratification.

A greater MAD distance by CMR was associated with severe ventricular arrhythmias, which is in line with other non-prospective studies showing an association with greater MAD distance and complex ventricular arrhythmias.[4,5,7,15] The mechanisms behind the potential association between arrhythmias and greater MAD distance and greater left ventricular diameter need to be explored.

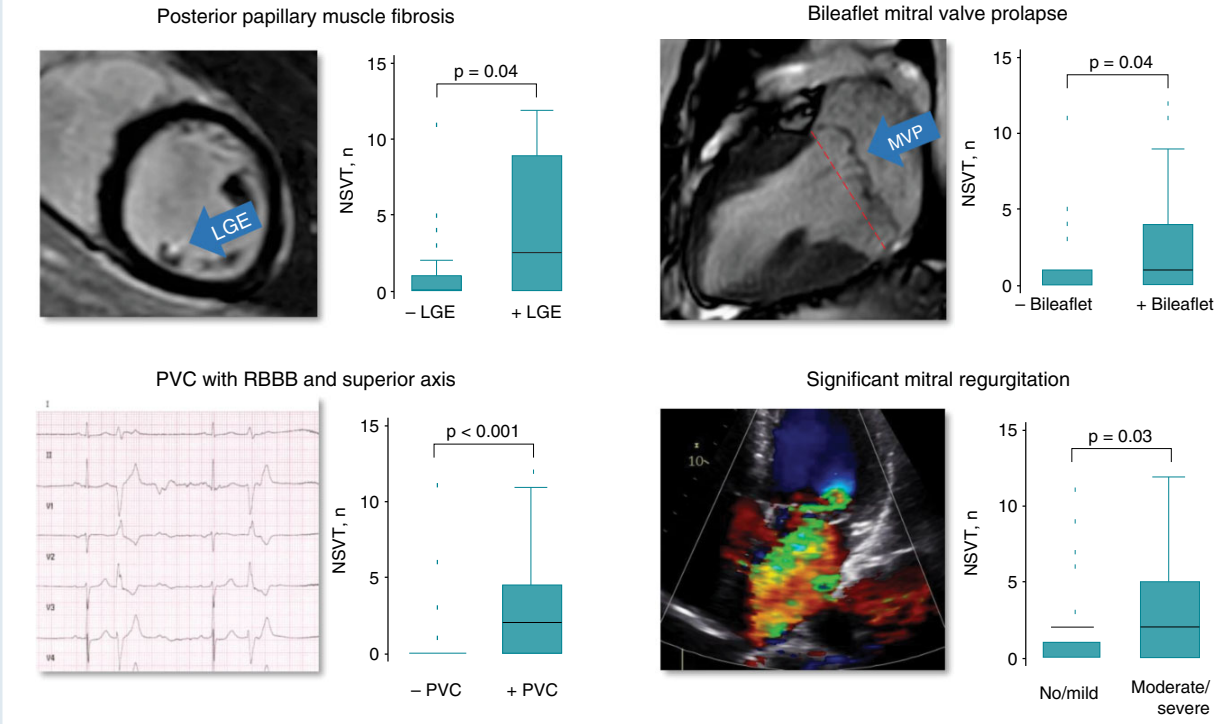
NSVT during stress ECG indicated a value of stress ECG in risk stratification, but was limited by low number of patients.

Use of implantable loop recorder

ILR-detected NSVTs were predictive of severe arrhythmias in our study. Our results suggest that ILR is a useful tool to monitor patients with arrhythmic mitral valve syndrome who do not fulfill indication for primary preventive ICD. During the three years of follow-up, ILR-detected arrhythmias led to ICD implantation in ten patients of which one proved lifesaving with appropriate shock for ventricular fibrillation. Thus, long-term monitoring using ILR led to clinically relevant changes in management and follow-up and we suggest that patients with likely high diagnostic yield should be monitored using ILR (*Figure 4*). However, the prognostic effect of ICD implantation based on ILR-detected arrhythmias remains unknown.

Low risk patients

A low PVC burden showed a reasonable ability to detect patients at lower arrhythmic risk. However, NSVTs occurred also in patients with infrequent PVCs, suggesting that a low PVC count was not sufficient to define a low risk patient. Patients without any of the four NSVT risk markers (LGE, bileaflet MVP, moderate/severe mitral regurgitation and left-sided origin of PVCs) reassuringly seemed at low arrhythmic risk with only 5% yearly incidence of NSVT and with no severe arrhythmic events (*Figures 3* and *4*). These four markers have been associated with unfavorable outcome in MVP patients in other studies,[3,19] and the lack of all of these parameters could reassure low arrhythmic risk.



	NSVT markers		
	0 markers	≥ I markers	p-value
Severe VA incidence rate, %/person-years [95% CI]	0% [0–0]	7% [3–14]	0.04
NSVT incidence rate, %/person-years [95% CI]	5% [2–15]	29% [19–44]	<0.001

Figure 3 Markers of greater NSVT burden detected by implantable loop recorder in 60 patients with arrhythmic mitral valve syndrome. NSVT occurred in 24 (40%) patients during 3.2 years (interquartile range 3.0–3.5). NSVT burden was greater in patients with posteromedial papillary muscle LGE, bileaflet prolapse, moderate/severe mitral regurgitation or premature ventricular complexes with right bundle branch block and superior axis. Absence of any of these markers was related to low arrhythmic risk. RBBB = right bundle branch block, VA = ventricular arrhythmia.

Definition and suggested follow-up in arrhythmic mitral valve syndrome

We propose that the diagnosis of arrhythmic mitral valve syndrome should be defined as MVP and/or MAD in presence of documented PVCs or severe arrhythmic events not explained by other etiologies. These patients should undergo a careful risk stratification. Holter monitoring is important for PVC quantification and for detection of NSVT, as frequent PVCs and NSVTs related to increased arrhythmic risk. Longer and repeated Holter monitoring may reduce errors due to arrhythmia day-to-day variations, and 12-lead Holter monitoring may increase precision by analyses of arrhythmia origin.

Additionally, CMR carries prognostic information with the presence of MAD, posterolateral MAD distance and focal myocardial fibrosis by LGE. Patients without LGE, bileaflet MVP, significant mitral regurgitation and without PVCs originating from the inferior left ventricle may be considered at low arrhythmic risk (*Figure 4*). In contrast, frequent PVCs, occurrence of NSVT, greater posterolateral MAD or dilated left ventricle indicate high arrhythmic risk, and we propose that these patients may be considered for either long-term monitoring with ILR or primary preventive ICD. NSVTs causing symptoms of presyncope/syncope would indicate highest risk and possibly favor primary preventive ICD as also suggested by guidelines[20] (*Figure 4*). We lack data and clinical trials on selection of patients with arrhythmic mitral valve syndrome for primary preventive ICD implantation, and management of these patients vary between centers and countries. The results from our study suggest that high- or intermediate-risk patients might be further risk stratified using ILR (*Figure 4*). Importantly, long-term cardiac monitoring does not replace primary prophylactic ICD implantation in very high-risk patients.

Study limitations

Inherent to the study design using implantable devices, we had a small sample size and provided a limited number of severe ventricular arrhythmias affecting the statistical robustness for exploring risk markers. Larger and independent cohorts of arrhythmic mitral valve syndrome patients should validate our findings.

Our cohort consisted of a selected and symptomatic group of patients that had a clinical indication for referral to a cardiologist, and

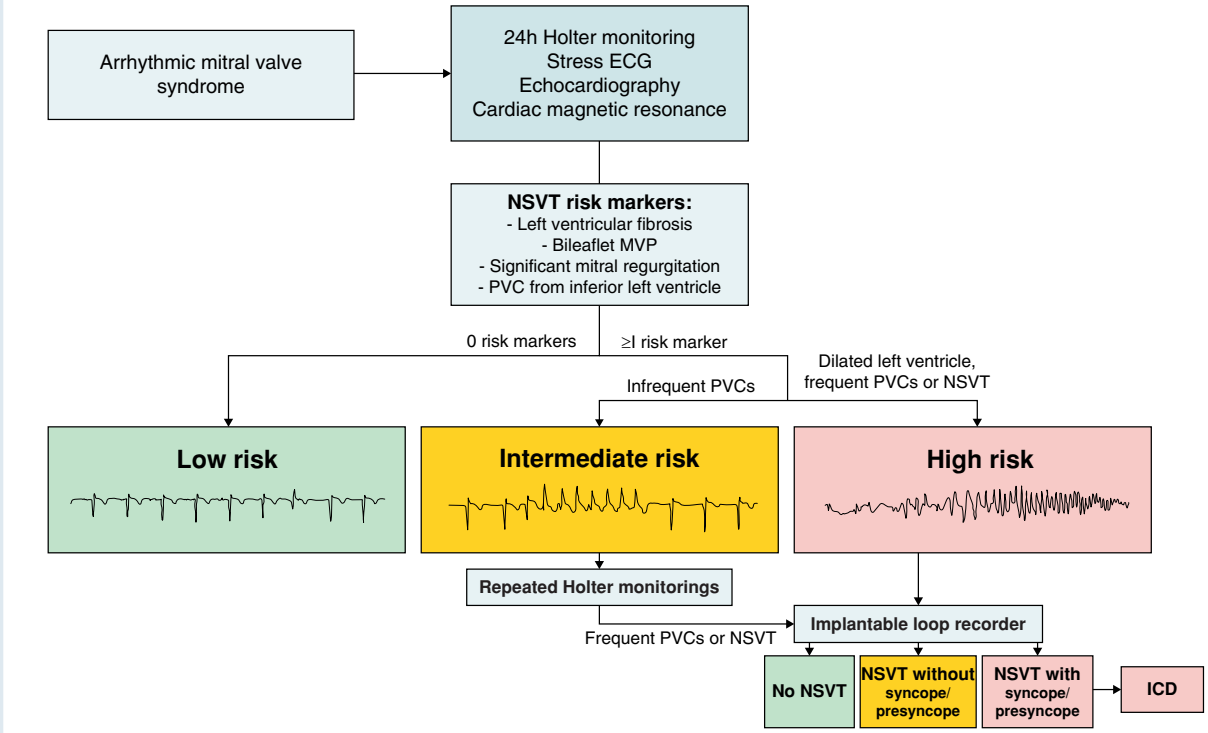


Figure 4 Suggested follow-up in patients with arrhythmic mitral valve syndrome. Patients with arrhythmic mitral valve syndrome should undergo 24 h Holter monitoring, stress ECG, echocardiography and cardiac magnetic resonance for risk stratification. Patients without any of the NSVT risk markers reassuringly seemed at low arrhythmic risk. The presence of NSVT risk markers and dilated left ventricle, frequent PVCs or NSVT could help guide selection of patients for prolonged arrhythmia monitoring by implantable loop recorder.

consequently, the results of our study do not translate to the general MVP population nor to asymptomatic individuals with incidental finding of MVP/MAD. This selective inclusion also affects the external validity of our results. The incidence of ventricular arrhythmias in the general MVP cohort is expected to be considerably lower, as shown in a recent paper by Essayagh *et al.*[17]

The MAD cut-off was arbitrary chosen to define presence of MAD, and confirmed by CMR.

The cardiac devices did not record asymptomatic ventricular arrhythmias with rate or duration below the programmed detection zones, and the overall incidence of ventricular arrhythmias might be underestimated. The discrepancy between VT heart rate cutoffs due to programming differences between ICD and ILR, as well as between various ICDs, is a technical limitation difficult to avoid and inherent to cardiac devices. The single electrogram recordings made it impossible to distinguish arrhythmias originating outside of the mitral valve apparatus in outcome analyses.

We did not use 12-lead Holter monitoring in our study, and the origin of PVCs seen on Holter monitoring could not be determined. Future studies should include 12-lead Holter monitoring with longer duration.

The eligibility criteria used in our study were not meant for clinically selecting patients for ILR monitoring, and should not be used as such in the lack of validation. Additionally, our study was not designed to evaluate the clinical value of systematic ILR implantation in patients with arrhythmic mitral valve syndrome, nor the effect of primary preventive ICD implantation. Whether long-term cardiac monitoring leads to improved prognosis in these patients is still unknown.

The assessment of MVP in presence of MAD is not clearly defined. Future guidelines should address this challenge. We did not assess leaflet redundancy nor curling, which have been associated with ventricular arrhythmias in previous studies.[3]

Conclusion

This is the first prospective follow-up study with extensive continuous cardiac rhythm monitoring in patients with arrhythmic mitral valve syndrome. Using ILR and ICD as monitors, yearly incidence rate of first severe ventricular arrhythmia was 4%, and was 8% for re-events in a selected arrhythmic population. Frequent PVCs, more NSVTs during follow-up, as well as greater left ventricular diameter and greater posterolateral MAD distance, predicted first severe ventricular arrhythmia.

Supplementary material

Supplementary material is available at *Europace* online.

Acknowledgements

In memoriam, we thank our friend and colleague Lars Ove Gammelsrud. He will be sorely missed, but not forgotten.

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Conflict of interest: None declared.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Paper II:

Tricuspid Annulus Disjunction – Novel Findings by Cardiac Magnetic Resonance in Patients with Mitral Annulus Disjunction

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II

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ORIGINAL RESEARCH

Tricuspid Annulus Disjunction

Novel Findings by Cardiac Magnetic Resonance in Patients With Mitral Annulus Disjunction

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ABSTRACT

OBJECTIVES This study aimed to assess whether patients with MAD also have disjunction of the tricuspid annulus.

BACKGROUND Mitral annulus disjunction (MAD) is an abnormal atrial displacement of the mitral annulus. Whether the disjunction extends to the right side of the heart is not known.

METHODS In a cohort of patients with MAD, we assessed the presence of tricuspid annulus disjunction (TAD) with the use of cardiac magnetic resonance. We explored the associations between TAD and MAD characteristics and the relationship to ventricular arrhythmias (nonsustained/sustained ventricular tachycardias and aborted cardiac arrest).

RESULTS We included 84 patients (mean age: 48 ± 16 years; 63% female). We observed TAD in 42 (50%). Patients with TAD were older (age 52 ± 16 years vs. 43 ± 15 years; $p = 0.02$), had greater circumferential extent of MAD (164 ± 57° vs. 115 ± 58°; $p = 0.002$), greater maximum longitudinal MAD distance (9.4 ± 2.9 mm vs. 6.2 ± 2.8 mm; $p < 0.001$), and more frequent mitral valve prolapse (n = 39 [92%] vs. n = 24 [57%]; $p < 0.001$). Ventricular arrhythmias had occurred in 34 patients (41%), who were younger (age 39 ± 14 years vs. 54 ± 14 years; $p < 0.001$) and had lower prevalence of TAD (n = 22 [29%] vs. n = 12 [52%]; $p = 0.03$). TAD was not associated with ventricular arrhythmias when adjusted for age (odds ratio adjusted for age: 0.54; 95% confidence interval: 0.20 to 1.45; $p = 0.22$).

CONCLUSIONS We report for the first time the existence of right-sided annulus disjunction as a common finding in patients with MAD. TAD was associated with more severe left-sided annulus disjunction and mitral valve prolapse, but not with ventricular arrhythmias. (J Am Coll Cardiol Img 2021;14:1535–43) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Arrhythmic mitral valve prolapse (MVP) syndrome is an emerging disease of the mitral valve apparatus characterized by mitral valve prolapse and mitral annulus disjunction (MAD) (1). MAD is an abnormal atrial displacement of the hinge points of the mitral valve away from the ventricular myocardium (2). Mitral disease with bileaflet MVP and MAD are of clinical importance because recent studies have indicated an association between these structures and ventricular arrhythmias (3–6). These patients often present with frequent premature ventricular complexes originating from the mitral annulus, outflow tracts, or left ventricular papillary muscles (6–9). In a recent study, we demonstrated

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

ECG = electrocardiogram

MAD = mitral annulus disjunction

MVP = mitral valve prolapsed

TAD = tricuspid annulus disjunction

MAD as a 3-dimensional circumferential continuum, interspersed with regions of apparently normal mitral annulus (6). However, whether annulus disjunction extends to other parts of the annulus fibrosus and involves the right side of the heart is not known.

We hypothesized that the disjunction may not only be circumferential in the mitral annulus, but also extend to the right side of the heart as tricuspid annulus disjunction (TAD). We aimed to assess right-sided annulus disease in patients with MAD and to relate findings to the extent of left-sided disease and to ventricular arrhythmias.

METHODS

STUDY POPULATION. Patients with MAD were recruited from 2 centers (Oslo University Hospital and Drammen Hospital) following the study protocol previously reported (6). In the present study, we included a subset of patients from the previous cohort with identifiable MAD on cardiac magnetic resonance (CMR) imaging. In short, patients with suspected MAD and no known cardiopulmonary comorbidity were referred for a comprehensive evaluation with clinical examination, electrocardiography (ECG), 24-h ECG, stress ECG, echocardiography, and CMR. Severity of dyspnea was classified according to the New York Heart Association (10). We evaluated patients with symptoms consistent with coronary artery disease with coronary angiography before study inclusion. The study complied with the Declaration of Helsinki and was approved by the Regional Committee for Medical Research Ethics (2015/596/REK nord). Every study participant gave written informed consent.

CARDIAC MAGNETIC RESONANCE. The CMR study protocol was performed using a 3.0-T whole-body scanner (Ingenia, Philips Healthcare, Best, the Netherlands) with a phased-array body coil, and images were analyzed with the use of a Sectra Workstation IDS7 v.18.1 (Sectra, Linköping, Sweden). We measured longitudinal MAD distance in end-systole, from the left atrial wall-mitral valve leaflet junction to the top of the left ventricular wall (6). Maximum MAD distance was defined as the largest longitudinal MAD measured regardless of location. With the study protocol, we obtained circumferential MAD along the mitral annulus as previously described (6). In short, circumferential MAD was assessed by the presence of MAD on 6 left ventricular long-axis cine sequences, each separated by 30° (**Figure 1**). We assessed the presence of TAD in the lateral and inferior right ventricular free wall (**Figure 1**), using standard cine sequences in 4-chamber and right ventricular inflow/outflow views. Longitudinal TAD distance was measured in end-systole, from the right atrial wall-tricuspid valve leaflet junction to the top of the right ventricular wall (**Figure 2**). We defined TAD as present if this distance was ≥1.0 mm. Maximum TAD distance was defined as the largest longitudinal TAD measured regardless of location. We measured the tricuspid annulus diameter at the point of attachment of the tricuspid leaflets to the atrioventricular junction in 4-chamber views in end-systole and in diastole at the time of maximal tricuspid opening. Both measurements were indexed for body surface area. Mitral and tricuspid valve prolapse were assessed by the 6 left ventricular long-axis views and by the 4-chamber and the right ventricular inflow/outflow views, respectively. Prolapse was defined as superior displacement ≥2 mm of any part of the leaflets beyond the respective annulus, according to the American Society of Echocardiography guidelines regarding MVP (11,12). We analyzed earlier standard CMR examinations in patients not eligible for the CMR study protocol.

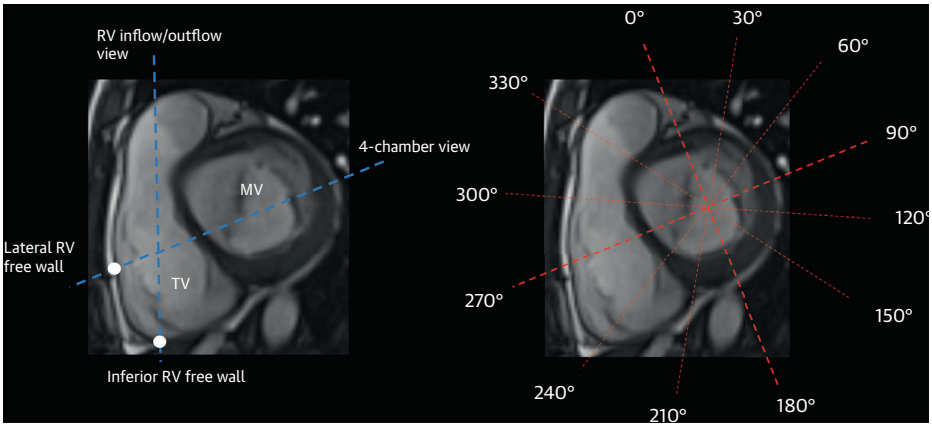
Two independent observers (E.W.A. and M.C.) assessed intra- and interobserver reliability for the presence of TAD, longitudinal TAD distance, and tricuspid annulus diastolic diameter by reanalyzing 20 random CMR studies (Supplemental Figure 1).

ECHOCARDIOGRAPHY. Left ventricular and atrial volumes and ejection fraction were measured according to guidelines (Vivid E95 scanner, GE Healthcare, Horten, Norway). Data were analyzed off-line (EchoPac v.201, GE Healthcare). Mitral and tricuspid regurgitation were quantified according to international guidelines (12,13). The mitral valve was defined as myxomatous if leaflet thickness was ≥5 mm (14). In patients with TAD by CMR, we reviewed whether TAD was visible with the use of echocardiography by means of the apical 4-chamber view and parasternal short-axis view.

ARRHYTHMIAS. A history of aborted cardiac arrest was defined as arrhythmic outcome. In addition, we defined sustained (>100 beats/min lasting >30 s) and nonsustained (≥3 consecutive ventricular beats <30 s with heart rate >100 beats/min) ventricular tachycardia recorded by means of ECG, stress ECG, or Holter monitoring at inclusion as arrhythmic outcome.

We evaluated premature ventricular complex morphology from 12-lead ECG and 12-lead stress ECG and categorized the morphology as left or right bundle branch block morphology with either superior or inferior frontal axis (15).

FIGURE 1 Cardiac Magnetic Resonance Imaging Protocols



Cardiac magnetic resonance (CMR) short-axis views of the atrioventricular valve plane displaying the imaging protocols used for assessment of tricuspid annulus disjunction (TAD) **(left)** and circumferential mitral annulus disjunction (MAD) **(right)**. **(Left)** CMR short-axis views showing the 4-chamber and right ventricular (RV) inflow/outflow views **(blue dashed lines)** in relation to the tricuspid annulus. The locations assessed for TAD were the lateral and inferior right ventricular free wall **(white dots)**. **(Right)** CMR short-axis views displaying the left ventricular long-axis slices perpendicular to the mitral annulus **(red dashed lines)** used in the CMR study protocol to assess circumferential degree of MAD. MV = mitral valve; TV = tricuspid valve.

STATISTICAL ANALYSIS. Continuous data were presented as mean ± SD or median (interquartile range), and categorical numbers with (percentages), as appropriate. Continuous variables were compared by means of the independent Student *t*-test or Mann-Whitney *U*-test, and categorical data by means of chi-square test or Fisher exact tests, as appropriate. We used logistic regression to adjust for age when we tested presence of TAD as a marker of ventricular arrhythmias. Intra- and interobserver reliability was assessed by means of Cohen κ and Bland-Altman plots, as appropriate (SPSS v.26.0, Chicago, Illinois). Two-sided p values <0.05 were considered to be significant.

RESULTS

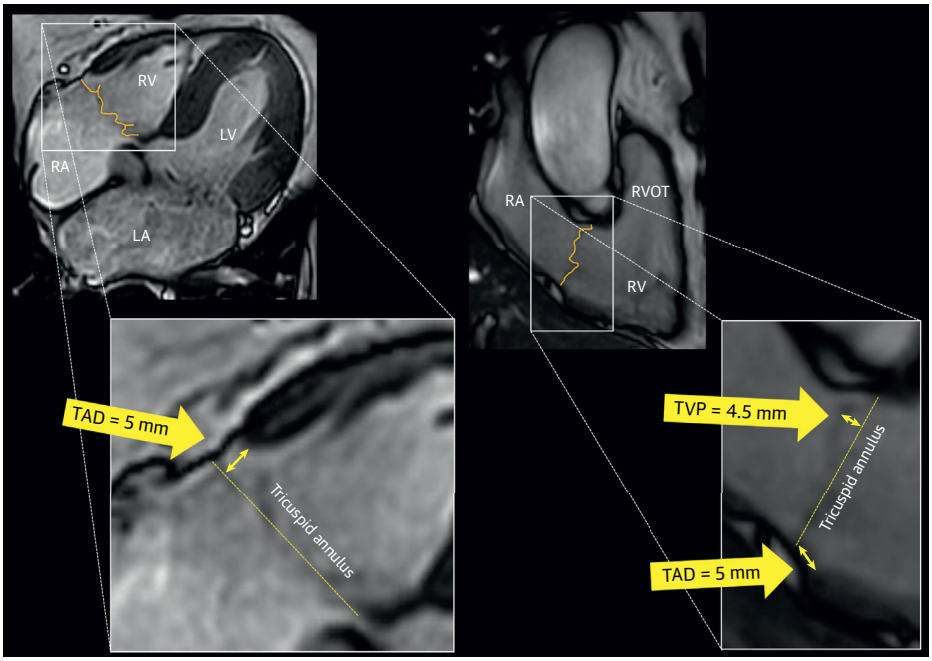
STUDY POPULATION. We included 84 patients with MAD according to CMR (mean age: 48 ± 16 years; 63% female) from our previously published cohort of 129 patients with MAD (6) (**Figure 3**). Among these 84 patients, 60 (71%) had CMR study protocol recordings enabling circumferential MAD assessments (**Figure 3**), and we used standard CMR studies in the remaining 24 patients. Cardiac symptoms were frequent, with 59 patients (70%) reporting palpitations, 35 (42%) pre-syncope, and 13 (15%) having experienced syncope. Twenty-four patients (29%) reported chest pain, and we evaluated 9 of them with the use of coronary angiography. None of the patients had significant stenosis. Arrhythmic outcome was documented in 34 patients (41%) (**Table 1**).

PRESENCE AND CHARACTERISTICS OF TAD ACCORDING TO CMR. TAD was present in 42 (50%) of the 84 patients with MAD (**Central Illustration**). Patients with concomitant TAD were older than those with MAD only (**Table 1**). We observed TAD in both locations available for analysis; 16 patients (38%) had TAD only in the lateral right ventricular free wall, 7 (17%) only in the inferior right ventricular free wall, and 19 (45%) in both locations. Maximum TAD distance according to CMR was 5.0 ± 2.3 mm (**Table 1**). Patients with TAD had greater circumferential extent of MAD ($p = 0.002$), and larger maximum longitudinal MAD distance ($p < 0.001$) (**Table 1**). TAD was evident by echocardiography in only 2 (5%) of the 42 patients with TAD according to CMR (**Figure 4**).

Intra- and interobserver reliability for the detection of TAD and for measurements of TAD distance and tricuspid annulus diameter are presented in Supplemental Figure 1.

TAD AND RELATIONSHIP WITH VALVULAR PROLAPSE. Patients with TAD had a higher prevalence of MVP ($p < 0.001$), whereas there was no clear association between TAD and tricuspid valve prolapse (**Table 1**). However, patients with TAD located in the lateral

FIGURE 2 Cardiac Magnetic Resonance in a Patient With Biannular Disjunction



Cardiac magnetic resonance in a patient with mitral annulus disjunction showing concomitant tricuspid annulus disjunction in 4-chamber view **(left)** and right ventricular inflow/outflow view **(right)**. TAD was present in both the lateral **(left)** and inferior **(right)** right ventricular free wall. The **lower right panel** shows concomitant tricuspid valve prolapse. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; RVOT = right ventricular outflow tract; TAD = tricuspid annulus disjunction; TVP = tricuspid valve prolapse.

right ventricular free wall (n = 35) had more frequent tricuspid valve prolapse (20 patients [57%] vs. 15 patients [31%]; p = 0.02). TAD was more prevalent in patients with isolated posterior mitral leaflet prolapse (p = 0.02) and less prevalent in patients with isolated anterior mitral leaflet prolapse (p = 0.002) (Table 1). There was no difference in tricuspid annulus diameter in patients with or without TAD (Table 1). With the use of echocardiography, there was a similar prevalence and severity of both mitral and tricuspid regurgitation in patients with or without TAD, and left ventricular size and function were similar in the 2 groups (Supplemental Table 1).

TRICUSPID ANNULUS DISJUNCTION AND ARRHYTHMIAS. The 34 patients with arrhythmic outcome included 12 (14%) with a history of aborted cardiac arrest, 2 (2%) with sustained ventricular tachycardia, and 20 (24%) with nonsustained ventricular tachycardia (Table 1). Patients with ventricular arrhythmias were younger than those without (age 39 ± 14 years vs. 54 ± 14 years; p < 0.001). Patients with TAD had lower prevalence of ventricular arrhythmias at inclusion compared with those with MAD only (p = 0.03) (Table 1). However, this association did not remain significant when adjusted for age (odds ratio adjusted for age: 0.54; 95% confidence interval: 0.20 to 1.45; p = 0.22) (Table 1). There was no association between severity of tricuspid regurgitation and occurrence of ventricular arrhythmias (29 patients [41%] with ventricular arrhythmia and no/mild tricuspid regurgitation vs. 4 patients [57%] with ventricular arrhythmia and moderate/severe tricuspid regurgitation; p = 0.44). Maximum longitudinal MAD distance was not associated with ventricular arrhythmias (7.9 ± 3.3 mm vs. 7.8 ± 3.1 mm; p = 0.81).

Of the 84 patients included, 63 (75%) had 24-h monitoring ECG available. Premature ventricular complexes were recorded in 67 patients, and the number of complexes did not differ between those with and without TAD (p = 0.93) (Table 1). We were able to evaluate the morphology of premature ventricular complexes in 53 patients (63%). The majority (n = 49 [92%]) had right bundle branch block morphology, suggesting left-sided origin, and 19 (36%) also had complexes with left bundle branch

block morphology, suggesting right-sided origin (Table 1). All premature ventricular complexes of left bundle branch block morphology had inferior frontal axis, suggesting an origin near the right ventricular outflow tract. There was no association between premature ventricular complexes with right-sided origin and the presence of TAD (Table 1).

DISCUSSION

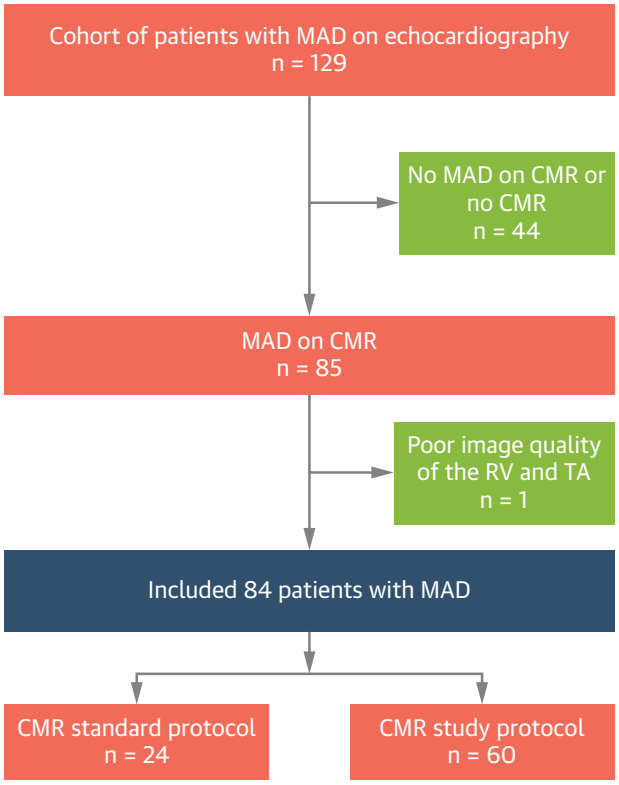
This is the first description of right-sided annulus disjunction as a common finding in patients with MAD. We found TAD in one-half of patients with MAD. This finding suggests that the disjunction affects the entire annulus fibrosus. Furthermore, patients with additional TAD were more likely to have MVP, larger MAD distance, and greater extent of circumferential MAD, suggesting that presence of TAD is an expression of more severe annulus disease (Central Illustration).

TAD AND AGE. Patients with concomitant TAD were older and had more extensive MAD than patients with only left-sided disjunction. These findings may infer that annulus disjunction expands with age or that TAD develops more slowly because of the lower hemodynamic stress exerted on the tricuspid annulus compared with the mitral annulus. Whether disjunction evolves over time with longer and higher annular hemodynamic stress, either by accumulation with increasing age or by the different hemodynamics of the 2 ventricles, should be explored in longitudinal follow-up studies.

TAD AND VALVULAR PROLAPSE. TAD was associated with tricuspid valve prolapse when present in the lateral right ventricular free wall, indicating a link between annulus disease and valvular prolapse. In addition, TAD was associated with isolated prolapse of the posterior mitral leaflet, suggesting that annulus disjunction around the posterior leaflet hinge point extends to the right side of the heart. This hypothesis is supported by the observation that TAD was less prevalent in patients with isolated anterior mitral leaflet prolapse.

Since the first description of MAD, there has been a close connection between left-side annulus disjunction and MVP (2,16,17), and patients with MAD-associated MVP are older than patients with isolated MAD (6). These observations suggest an interaction between MAD and MVP, and that MVP may be more likely to occur in the presence of annular ring disease. A similar mechanism may explain development of right-sided disease. Early studies show an association between MVP and tricuspid valve prolapse (18–20). The present study adds the speculation that annulus fibrosus disease may be the common mechanism leading to both left- and right-sided valvular prolapse.

FIGURE 3 Study Flow Chart



Patients with mitral annulus disjunction (MAD) were recruited from our previous cohort (6), which included 129 patients with MAD according to echocardiography. We performed cardiac magnetic resonance (CMR) in 87 patients, of which 85 patients had MAD according to CMR. We excluded 1 patient because of imaging artifacts of the right ventricle (RV). In the study, we included 84 patients with MAD, of which 60 patients were evaluated with a CMR study protocol to assess circumferential degree of MAD. We analyzed earlier standard CMRs in patients not eligible for the CMR study protocol. TA = tricuspid annulus.

TAD AND ARRHYTHMIAS. TAD was associated with a greater MAD distance measured in multiple imaging planes, but was not associated with ventricular arrhythmias. This may seem contradictory in light of previous studies showing an association between a greater MAD distance in a single imaging plane and ventricular arrhythmias (3–6). Several factors could explain this observation. First, it is possible that some patients with biannular disjunction died of ventricular arrhythmia at a young age or had implanted cardiac devices, which made them ineligible for the present study. Patients with biannular disjunction were older than those with MAD only, suggesting that a selection

TABLE 1 Characteristics of Mitral Annulus Disjunction Patients With or Without Tricuspid Annulus Disjunction

	Total (N = 84)	No TAD (n = 42)	TAD (n = 42)	p Value
General characteristics				
Female	53 (63)	29 (69)	24 (57)	0.26
Age, yrs	48 ± 16	43 ± 15	52 ± 16	0.02
Symptoms				
NYHA functional class				
I	65 (77)	32 (76)	33 (79)	0.79
II	15 (18)	8 (19)	7 (17)	0.78
III	4 (5)	2 (5)	2 (5)	1.00
Chest pain	24 (29)	15 (36)	9 (21)	0.15
Palpitations	59 (70)	29 (68)	30 (73)	0.81
Presyncope	35 (42)	16 (38)	19 (45)	0.51
Syncope	13 (16)	6 (14)	7 (17)	0.76
Arrhythmias				
Ventricular arrhythmias	34 (41)	22 (52)	12 (29)	0.03
Aborted cardiac arrest	12 (14)	9 (21)	3 (7)	0.12
Sustained VT	2 (2)	0 (0)	2 (5)	0.24
Nonsustained VT	20 (24)	13 (31)	7 (17)	0.12
Premature ventricular complexes per 24 h (n = 67)	268 (26–2,415)	238 (33–2,087)	394 (19–2,570)	0.93
Premature ventricular complexes origin (n = 53)				
Left-sided origin	50 (60)	26 (62)	24 (29)	0.65
Superior axis	45 (54)	23 (55)	22 (52)	0.82
Inferior axis	22 (26)	14 (33)	8 (19)	0.14
Right-sided origin	19 (23)	12 (29)	7 (17)	0.19
Superior axis	0 (0)	0 (0)	0 (0)	NA
Inferior axis	19 (23)	12 (29)	7 (17)	0.19
Cardiac magnetic resonance				
Maximum longitudinal TAD distance, mm		NA	5.0 ± 2.3	NA
Tricuspid valve prolapse	35 (42)	14 (33)	21 (50)	0.12
Tricuspid annulus diameter, diastolic, mm/m^2	19.8 ± 3.2	20.5 ± 2.9	19.4 ± 3.5	0.12
Tricuspid annulus diameter, systolic, mm/m^2	18.1 ± 2.7	18.1 ± 2.6	18.0 ± 2.9	0.99
Circumferential MAD, ° (n = 60)	145 ± 61	115 ± 58	164 ± 57	0.002
Maximum longitudinal MAD distance, mm	7.9 ± 3.2	6.4 ± 2.9	9.4 ± 2.9	<0.001
Mitral valve prolapse	63 (75)	24 (57)	39 (92)	<0.001
Anterior leaflet only	15 (18)	11 (26)	4 (10)	0.002
Posterior leaflet only	24 (28)	4 (10)	19 (45)	0.02
Bileaflet	24 (28)	9 (21)	16 (38)	0.78

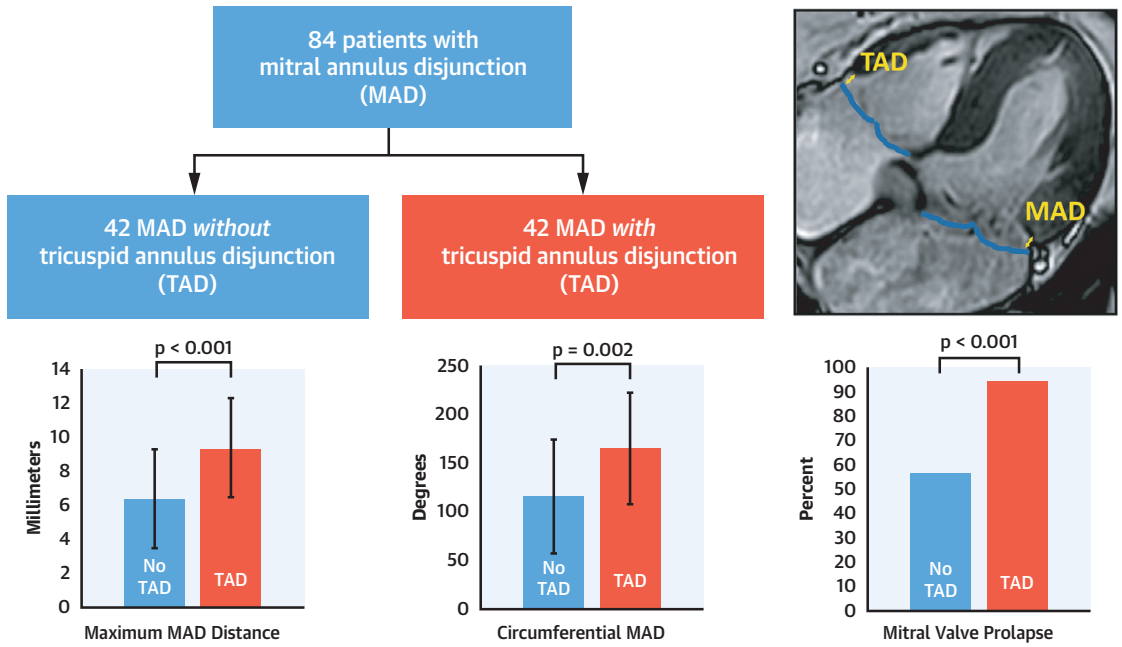
Values are n (%), mean ± SD, or median (interquartile range). The p values were calculated by means of Student *t*-test, or Mann-Whitney *U* test, chi-square test, or Fisher exact test as appropriate.

MAD = mitral annulus disjunction; NYHA = New York Heart Association; TAD = tricuspid annulus disjunction; VT = ventricular tachycardia.

bias may have influenced our data by the survival of patients with a less arrhythmogenic phenotype. Second, ventricular arrhythmias most commonly originate from the left ventricle in this patient population (7–9), supporting the hypothesis that the underlying arrhythmia mechanisms, including traction from the chordae tendinae or micro re-entry due to myocardial fibrosis in the papillary muscles or left ventricular wall, are more prominent in the left side of the heart. Furthermore, the tricuspid apparatus has structural and functional differences compared with the mitral annulus and is more mobile (21). These observations could infer that the right side of the heart may have a lower resistance to traction by prolapsing leaflets, and that the thinner right ventricular and right atrial walls may have implications toward a lower arrhythmic risk than on the left side. The lack of premature ventricular complexes (PVCs) from the right ventricular free wall in the present study may support this hypothesis. Finally, the observation may be a play of chance or an interplay between imperfect markers of ventricular arrhythmias. Importantly, having additional TAD did not exclude risk of ventricular arrhythmias, as 5 patients with biannular disjunction experienced aborted cardiac arrest or sustained ventricular tachycardia.

Several studies have indicated that the presence of MVP and MAD could lead to focal fibrosis of the left ventricular wall or the papillary muscles, acting as a

CENTRAL ILLUSTRATION **Tricuspid Annulus Disjunction in Patients With Mitral Annulus Disjunction**



Aabel, E.W. et al. J Am Coll Cardiol Img. 2021;14(8):1535–43.

We included 84 patients with mitral annulus disjunction (MAD) on cardiac magnetic resonance (CMR), of which 50% had concomitant tricuspid annulus disjunction (TAD) **(top left)**. **(Top right)** CMR 4-chamber view of a patient with biannular disjunction. Patients with TAD had larger maximum longitudinal MAD distance, greater extent of circumferential MAD, and more frequent mitral valve prolapse.

substrate for ventricular arrhythmias (5-7). Patients with an overt left-side annulus disjunction with or without MVP often show ventricular arrhythmias originating from the left ventricle (7,8). Interestingly, in the first study associating bileaflet MVP to a risk of sudden cardiac death, patients also showed PVCs originating from the right ventricle (9). Our study supports this finding, with approximately one-fourth of patients showing right-sided origin of PVCs. The presence of TAD was not associated with right-sided PVCs, suggesting other mechanisms for right-sided electric instability.

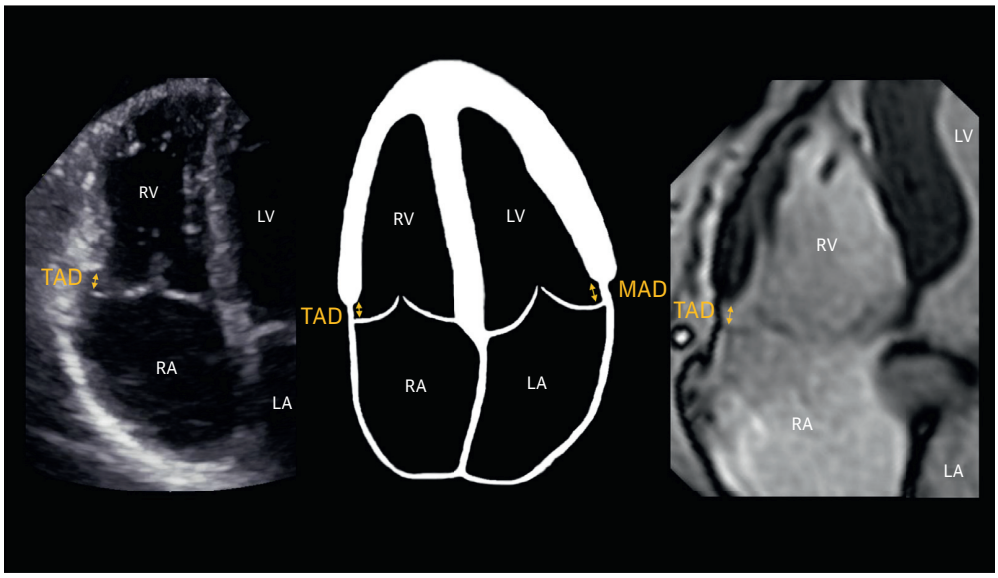
CLINICAL AND SCIENTIFIC IMPLICATIONS. One-half of patients with MAD had concomitant TAD. TAD was a marker of more extensive mitral and tricuspid valve disease. Thus, the clinical identification of TAD could indicate a more severe disease of the annulus fibrosus. However, to explore the possible impact of TAD on the tricuspid valve apparatus, we need optimally designed studies using ideal views for evaluating right-sided structures. The present study supports previous studies indicating CMR as a better modality to detect annulus disjunction (22,23).

TAD was not associated with ventricular arrhythmias in this study, suggesting no clear additional arrhythmic risk with the right side affected. However, this study was limited by relatively few arrhythmic events, and further research into this novel marker is warranted.

STUDY LIMITATIONS. This study had a retrospective cross-sectional design of descriptive nature with inherent limitations, and it was not powered nor designed for TAD evaluation. Another major limitation was the lack of a normal patient population, as well as patients with MVP without MAD. All patients included in this study had MAD, and whether TAD exists without concomitant left-sided disease is not known. Studies on the prevalence and clinical implication of both right- and left-sided annulus disjunction in the general population are warranted, as well as of the development of disjunction over time.

A dedicated CMR study protocol was not performed in all participants, but in the vast majority. Our CMR protocols were not designed for optimal detection of TAD, quantification of mitral regurgitation, nor optimal assessment of single or multiple

FIGURE 4 Tricuspid Annulus Disjunction Observed by Means of Cardiac Magnetic Resonance and Transthoracic Echocardiography in Patients With Mitral Annulus Disjunction



Schematic representation of TAD and MAD in 4-chamber view **(center; orange arrows)**, as seen by means of transthoracic echocardiography **(left)** and cardiac magnetic resonance (CMR) **(right)**. **(Left)** Transthoracic echocardiography RV-focused apical view in a patient with MAD showing concomitant TAD **(orange arrows)**. **(Right)** CMR 4-chamber view from a patient with MAD showing concomitant TAD **(orange arrows)**. LA = left atrium; LV = left ventricle; MAD = mitral annulus disjunction; RA = right atrium; RV = right ventricle; TAD = tricuspid annulus disjunction.

leaflet tricuspid valve prolapse or annular area. Future studies should use multimodality imaging, including additional 3-dimensional transthoracic and transesophageal echocardiography, to comprehensively evaluate mitral and tricuspid valves and annuli and clinically relevant cutoff values for defining TAD.

The number of patients with ventricular arrhythmias was relatively small, which might have affected the robustness of the statistical analysis. A few patients with history of aborted cardiac arrest with implanted cardiac devices were excluded because of missing CMR examinations, which may have biased the association between TAD and severe arrhythmias. All patients in our study were symptomatic or had a clinical indication for referral to a cardiologist, providing a selection bias and overestimation of symptom prevalence.

CONCLUSIONS

This is the first description of right-sided annulus disjunction, TAD, as a common finding in patients with MAD. Patients with concomitant TAD were older and had a greater extent of left-sided annulus disjunction and mitral valve prolapse. We showed, with the use of CMR imaging, that annulus disjunction is a 3-dimensional biannular disease that may involve both the tricuspid and the mitral annuli. Presence of concomitant TAD was not a marker of ventricular arrhythmias in our study.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Annulus disjunction is a 3-dimensional biannular disease that commonly involves both the tricuspid and the mitral annuli.

COMPETENCY IN PATIENT CARE: Tricuspid annulus disjunction is common in patients with mitral annulus disjunction and is associated with greater extent of mitral annulus disease, but is not an individual risk marker of ventricular arrhythmias.

TRANSLATIONAL OUTLOOK: Patients with concomitant tricuspid annulus disjunction were older than those with left-sided disease only. Whether disjunction evolves over time should be explored in longitudinal follow-up studies.

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KEY WORDS cardiac magnetic resonance, mitral annulus disjunction, mitral valve prolapse, tricuspid annulus disjunction, ventricular arrhythmia

APPENDIX For a supplemental figure and table, please see the online version of this paper.

Paper III:

Electrical Markers and Arrhythmic Risk Associated with Myocardial Fibrosis in Mitral Valve Prolapse

Monica Chivulescu, Eivind W Aabel, Erik Gjertsen, Einar Hopp, Esther Scheirlynck, Bernard Cosyns, Erik Lyseggen, Thor Edvardsen, Øyvind H Lie, Lars Dejgaard, Kristina H Haugaa

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III

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CLINICAL RESEARCH
Clinical electrophysiology

Electrical markers and arrhythmic risk associated with myocardial fibrosis in mitral valve prolapse

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Aims We aimed to characterize the substrate of T-wave inversion (TWI) using cardiac magnetic resonance (CMR) and the association between diffuse fibrosis and ventricular arrhythmias (VA) in patients with mitral valve prolapse (MVP).

Methods and results TWI was defined as negative T-wave ≥0.1 mV in ≥2 adjacent ECG leads. Diffuse myocardial fibrosis was assessed by T1 relaxation time and extracellular volume (ECV) fraction by T1-mapping CMR. We included 162 patients with MVP (58% females, age 50 ± 16 years), of which 16 (10%) patients had severe VA (aborted cardiac arrest or sustained ventricular tachycardia). TWI was found in 34 (21%) patients. Risk of severe VA increased with increasing number of ECG leads displaying TWI [OR 1.91, 95% CI (1.04–3.52), $P = 0.04$]. The number of ECG leads displaying TWI increased with increasing lateral ECV (26 ± 3% for TWI 0-1leads, 28 ± 4% for TWI 2leads, 29 ± 5% for TWI ≥3leads, $P = 0.04$). Patients with VA (sustained and non-sustained ventricular tachycardia) had increased lateral T1 ($P = 0.004$), also in the absence of late gadolinium enhancement (LGE) ($P = 0.008$).

Conclusions Greater number of ECG leads with TWI reflected a higher arrhythmic risk and higher degree of lateral diffuse fibrosis by CMR. Lateral diffuse fibrosis was associated with VA, also in the absence of LGE. These results suggest that TWI may reflect diffuse myocardial fibrosis associated with VA in patients with MVP. T1-mapping CMR may help risk stratification for VA.

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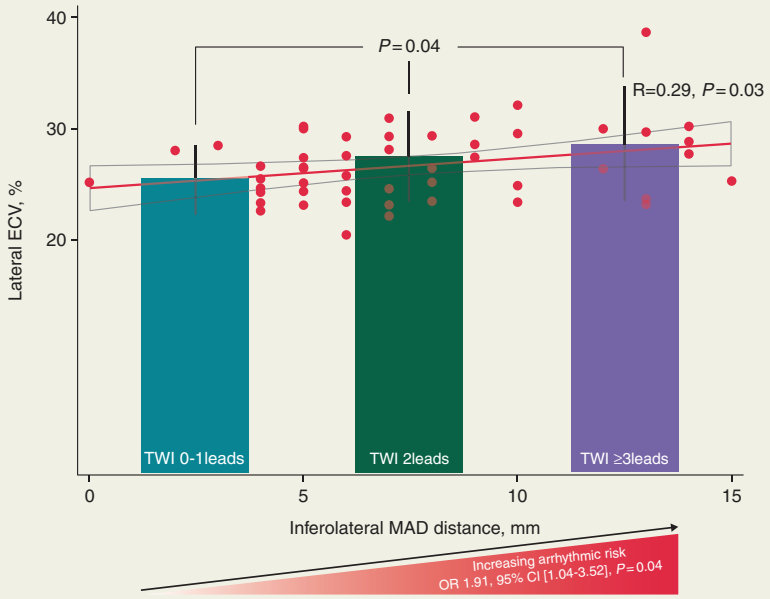
Graphical Abstract



Higher number of ECG leads with TWI indicating higher arrhythmic risk and higher degree of lateral diffuse myocardial fibrosis Bar charts show values of lateral ECV by T1-mapping CMR in patients with no TWI or with TWI in 1 lead (left bar), in patients with TWI in 2 ECG leads (middle bar) and in patients with TWI in ≥3 ECG leads. *P* value was obtained by one-way ANOVA test with Bonferroni correction. The scatter plot graph shows the correlation between lateral ECV by T1-mapping CMR and inferolateral MAD distance. Inferolateral MAD distance increased with higher lateral ECV values. Correlation coefficient *R* and *P* values were calculated by Pearson correlation test. The risk of severe VA increased with the number of ECG leads with TWI. Odds ratios, 95% CI and *P* value for risk of severe VA were calculated by logistic regression analysis. CMR = cardiac magnetic resonance, ECG = electrocardiographic, ECV = extracellular volume, MAD = mitral annulus disjunction, TWI = T-wave inversion VA = ventricular arrhythmias.

Keywords Electrocardiography • Mitral valve prolapse • Ventricular arrhythmias • Diffuse myocardial fibrosis • T1-mapping cardiac magnetic resonance

What's new?

- T-wave inversion on ECG reflects lateral diffuse myocardial fibrosis by T1-mapping cardiac magnetic resonance potentially predisposing to ventricular arrhythmias in patients with mitral valve prolapse.
- Assessment of diffuse myocardial fibrosis by T1-mapping cardiac magnetic resonance can be used for arrhythmic risk stratification in patients with mitral valve prolapse.

Introduction

Sudden cardiac death is a rare but devastating complication in patients with mitral valve prolapse (MVP). Given the high prevalence of MVP in the general population,[1] identifying patients at risk of arrhythmic death is of uttermost importance.

Several factors have been associated with an adverse outcome in patients with MVP including bileaflet MVP,[2] myocardial fibrosis in the inferolateral left ventricular wall or papillary muscles detected by late gadolinium enhancement (LGE) at cardiac magnetic resonance (CMR)[3] and mitral annulus disjunction (MAD), known as atrial displacement of mitral annulus from the ventricular myocardium at end-systole.[4] However, risk stratification remains challenging and robust tools for prediction of severe VA are lacking in patients with MVP.

Previous studies suggested electrocardiographic (ECG) repolarization abnormalities as a characteristic of arrhythmic MVP phenotype with frequent T-wave inversion (TWI) in high-risk patients with MVP.[2,3] However, the underlying morphological substrate of repolarization abnormalities in patients with MVP is not known.

Focal myocardial fibrosis reflected by LGE is the underlying substrate for re-entry arrhythmias thus predisposing to severe VA in MVP patients.[4,5] However, severe VA occurs in patients without LGE suggesting the existence of additional arrhythmic substrates.[4] Diffuse myocardial fibrosis reflected by a shortened post-contrast T1 time at T1-mapping CMR is associated with complex premature ventricular

contractions (PVCs) in patients with MVP.[6] Furthermore, diffuse fibrosis is present in chronic mitral regurgitation due to MVP and related to clinical events.[7] However, whether diffuse fibrosis is a risk marker for VA beyond the presence of LGE in patients with MVP is unknown.

We aimed to describe the prevalence of TWI and to explore the association between severe VA and repolarization abnormalities in a cohort of patients with MVP. In addition, we aimed to investigate the morphological substrate of TWI using tissue characterization by CMR. We hypothesized that TWI is associated with diffuse myocardial fibrosis, forming the substrate for VA in patients with MVP.

Methods

Study population

In this multicentre cross-sectional study, patients were consecutively included from August 2015 until March 2018, at Oslo University Hospital, Rikshospitalet and Drammen Hospital, Norway and at the University Hospital Brussels, Universitair Ziekenhuis Brussel, Belgium. A subset of patients have been reported previously.[4,8] Patients undergoing echocardiography at these centres were screened for MVP and MAD by experienced physicians and sonographers. Patients with confirmed MVP and MAD were invited to a comprehensive study evaluation, which included medical history recording, clinical examination, 12-lead ECG, 24 h Holter monitoring, echocardiography and CMR as previously described.[4,8] Patients with history of severe VA underwent a comprehensive diagnostic work-up as clinically indicated. We excluded patients with obstructive coronary artery disease and non-mitral moderate or severe valvular disease, patients with severe VA of other plausible causes (cardiac channelopathies and cardiomyopathies) and those successfully treated by catheter ablation for VA before inclusion. All patients gave their written informed consent for participation. The study complied with The Declaration of Helsinki and was approved by the Regional Committee for Medical Research Ethics in Norway (2015/596/REKnord) and by the Ethical Committee of UZ Brussels in Belgium (2016/407). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Electrocardiogram and ventricular arrhythmias

We analysed 12-lead resting ECGs for the presence and extent of inverted T-wave in inferior (II, III, and aVF), lateral (I, aVL, V5, and V6), and anterior leads (V3 and V4). We excluded ECGs recorded <5 days after an episode of severe VA and TWI secondary to bundle branch block. TWI was defined as inverted T-wave ≥0.1 mV and considered pathological when present in ≥2 adjacent ECG leads.[9] We defined extended TWI as negative T-wave present in ≥3 ECG leads. We reported duration of the QRS complex and fragmentation of a narrow QRS complex defined as the presence of an additional R wave or notching in the nadir of the S wave[10] and calculated QTc duration according to Bazett's formula. All ECG analyses were performed blinded to clinical data.

The number of PVCs in 24 h by Holter monitoring was recorded as PVCs count.

We defined VA as non-sustained VT (≥3 consecutive ventricular beats >100 beats/min for <30 s) or documented history of severe VA. Severe VA were defined as history of documented sustained VT (runs of consecutive ventricular beats >100 beats/min for >30 s) or aborted cardiac arrest at inclusion.

Echocardiography

Transthoracic echocardiography was performed using a commercial cardiac ultrasound system (Vivid 7, Vivid E9 or Vivid E95; GE Vingmed Ultrasound, Horten, Norway) and images were analysed offline blinded for clinical data (EchoPac, version 202, GE Vingmed Ultrasound, Horten, Norway). We acquired standard parasternal long- and short-axis images, apical 4-, 2-, and 3-chamber views. MV regurgitation was quantified according to guidelines and graded as mild, moderate, or severe.[11]

Cardiac magnetic resonance

The CMR study protocol was performed using a 3-T scanner (Ingenia, Philips Healthcare, Best, the Netherlands) and images were analysed using Sectra Workstation IDS7 v18.1 (Sectra AB, Linköping, Sweden) at Oslo University Hospital, Rikshospitalet, Norway.

We performed balanced steady-state free precession cine sequences in six left ventricular long axis image planes separated by 30° and in consecutive short axis image planes of 8 mm slice thickness as previously described.[4] The CMR study protocol included modified Look-Locker inversion recovery sequences in standard long axis and three short axis image planes both prior to (native) and 10 min after intravenous injection of 0.20 mmol/kg gadoterate meglutamine (Dotarem™, Guerbet, Villepinte, France).

We measured native and post-contrast T1 relaxation time on midventricular short axis slices by placing the region of interest in the interventricular septum and in the lateral left ventricular wall and a circular region of interest in the left ventricular blood pool. We calculated myocardial extracellular volume (ECV) as the ratio between myocardial and blood pool T1 relaxivity change multiplied by a factor equal to 1-haematocrit.[12] All T1-mapping CMR studies were performed on the same scanner.

We defined MVP as atrial displacement of any part of the mitral leaflets of ≥2 mm from the line connecting annular hinge points at end-systole.[11] We inspected the entire mitral annulus circumference for the presence of MAD of ≥1 mm by measuring MAD distance from the left atrium-MV leaflet junction to the top of the left ventricular myocardium at end-systole. Greatest MAD assessed from 90° to 240° was reported as inferolateral MAD distance.

We assessed the presence of LGE on sequential post-contrast short axis slices of the left ventricle from the atrioventricular valve plane to the apex and we measured left ventricular volumes and ejection fraction using standard techniques.[13]

In patients not eligible for our CMR study protocol, previously obtained clinical CMR examinations were retrospectively analysed using Sectra Workstation IDS7 v18.1 [Sectra AB, Linköping, Sweden (in Oslo)] or Circle [Circle Cardiovascular Imaging, Calgary, Alberta, Canada (in Brussels] for the presence of LGE at basal left ventricular wall and papillary muscles.

Statistics

Continuous variables were presented as mean±standard deviation (SD) or median [inter-quartile range (IQR)] and compared using Student's *t*-test, one-way ANOVA, or Mann–Whitney *U* non-parametric test, as appropriate. Categorical variables were presented as frequencies (%) and compared using χ^2 test or Fisher's exact test as appropriate. Association between indices of diffuse myocardial fibrosis and electrical and imaging parameters was assessed using univariate linear regression and Pearson correlation analysis. Odds ratios and 95% confidence interval (CI) were calculated for VA, LGE and TWI using univariate and multivariate logistic regression analysis. Statistical analysis was performed using Stata/SE 16.0 (StataCorp LLC, Texas); *P* values were two-sided and values <0.05 were considered significant. *P* values for CMR parameters were adjusted for centre cluster confounding.

Results

We included 162 patients with MVP (58% women, age 50 ± 16 years) (*Table 1*). Sixteen (10%) patients had documented severe VA at inclusion (13 with aborted cardiac arrest and 3 with sustained VT) and 18 (11%) patients were implanted with a cardiac device (15 patients with an implantable cardiac defibrillator and 3 patients with a pacemaker).

T-wave inversion and severe ventricular arrhythmias

We found 34 (21%) patients with TWI ≥2 leads of which 20 (59%) patients had extended TWI (≥3 leads), while the remaining had TWI in 1 lead or no TWI.

Extended TWI was associated with severe VA ($P = 0.02$) (*Table 1*) and the risk of severe VA increased with the number of leads with TWI [OR 1.91, 95% CI (1.04–3.52), $P = 0.04$] (*Graphical Abstract*). Extended TWI was also associated with longer duration of QTc (*Table 1*). Other ECG abnormalities were not associated with higher arrhythmic risk including duration of the QRS complex (91 ± 12 vs. 95 ± 13 ms, $P = 0.28$), prevalence of QRS fragmentation [3/16 with VA (19%) vs. 20/146 without VA (14%), $P = 0.70$] and QTc duration (416 ± 28 vs. 411 ± 37 ms, $P = 0.63$).

T-wave inversion and myocardial fibrosis

A CMR study was available in 120 (74%) patients. CMR was performed prospectively at inclusion in 114 (70%) patients, while in the remaining 6 (4%) patients, we used a previous CMR study performed on clinical indication. CMR with LGE was available in 113 (70%)

Table 1 Characteristics of 162 patients with MVP dichotomized according to the presence of TWI in ≥3 ECG leads (*n* = 20) and TWI in <3 ECG leads (*n* = 142)

	Total (*n* = 162)	TWI < 3ECG leads (*n* = 142)	TWI ≥ 3ECG leads (*n* = 20)	*P* value
Clinical characteristics				
Age, years±SD	50 ± 16	50 ± 16	45 ± 15	0.20
Female, *n* (%)	93 (57)	78 (55)	15 (75)	0.10
Syncope, *n* (%)	29 (18)	26 (18)	3 (15)	1.00
Palpitations, *n* (%)	116 (72)	100 (70)	16 (80)	0.60
Arrhythmias				
VA, *n* (%)	66 (41)	54 (38)	12 (60)	0.06
Severe VA, *n* (%)	**16 (10)**	**11 (8)**	**5 (25)**	**0.02**
Electrocardiogram				
QRS duration, ms±SD	95 ± 13	95 ± 14	90 ± 8	0.12
QRS fragmentation, *n* (%)	23 (14)	22 (15)	1 (5)	0.31
QTc, ms±SD	**412 ± 37**	**409 ± 37**	**429 ± 31**	**0.02**
24 h Holter monitoring				
PVCs count,[a] *n*±SD	2.34 ± 1.09	2.29 ± 1.08	2.71 ± 1.17	0.16
Cardiac magnetic resonance[b]				
Bileaflet MVP, *n* (%)	**43 (27)**	**34 (24)**	**9 (45)**	**0.02**
Inferolateral MAD distance	**7 ± 3**	**7 ± 3**	**10 ± 3**	**0.005**
LVEDVi, mL/m^2±SD	82 ± 24	81 ± 22	89 ± 33	0.26
LVESVi, mL/m^2±SD	35 ± 12	34 ± 12	40 ± 17	0.12
LV EF, %±SD	58 ± 7	58 ± 7	55 ± 7	0.18
LGE, *n* (%)	54 (33)	46 (32)	8 (40)	0.48
Basal LV wall LGE, *n* (%)	34 (21)	30 (21)	4 (20)	1.00
Papillary muscles LGE, *n* (%)	21 (13)	17 (12)	4 (20)	0.30
Average T1 time, ms±SD	1267 ± 43	1262 ± 43	1290 ± 42	0.09
Septal T1 time, mc±SD	1273 ± 47	1268 ± 46	1298 ± 46	0.08
Lateral T1 time, ms±SD	1257 ± 45	1253 ± 44	1280 ± 42	0.09
Average ECV, %±SD	**27 ± 3**	**26 ± 3**	**29 ± 4**	**0.01**
Septal ECV, %±SD	**27 ± 3**	**26 ± 3**	**29 ± 4**	**0.02**
Lateral ECV, %±SD	**27 ± 3**	**26 ± 3**	**29 ± 5**	**0.03**

Continuous variables are presented as mean (SD) and categorical variables as frequencies (%). *P* values are calculated by Student's *t*-test, χ^2, or Fisher's exact test as appropriate. Bold values denote statistical significance.

BSA, body surface area; ECG, electrocardiogram; ECV, extracellular volume; EF, ejection fraction; LV, left ventricular; LVEDVi, LV end-diastolic volume indexed to BSA; LVESVi, LV end-systolic volume indexed to BSA; LGE, late gadolinium enhancement; MAD, mitral annulus disjunction; MVP, mitral valve prolapse; TWI, T-wave inversion; PVCs, premature ventricular contractions; VA, ventricular arrhythmias.

[a]Log base 10 transformation of the PVCs count was performed to assure normal distribution.

[b]CMR was available in 120 patients and LGE in 113 patients, T1-mapping CMR sequences were available in 56 patients.

patients and 56 (35%) patients underwent study protocol CMR with T1-mapping sequences.

Of the 113 patients with LGE CMR, 54 (48%) patients had fibrosis by LGE (34 in the left ventricular inferolateral wall and 37 in the papillary muscles). LGE was not associated with extended TWI (≥3 leads) (*Table 1*). Furthermore, odds of LGE presence did not increase with the number of leads with TWI [OR 1.07, 95% CI (0.80–1.45), $P = 0.62$] nor when adjusted for centre cluster confounding [multivariate OR 1.41, 95% CI (0.80–2.48), $P = 0.24$].

Lateral ECV values were higher in patients with extended TWI (≥3 leads) (*Table 1*), also when adjusted for age and sex [lateral ECV: multivariate OR 1.32, 95% CI (1.00–1.74), $P = 0.048$]. Lateral ECV increased with the number of ECG leads displaying TWI (*Graphical Abstract*).

Myocardial fibrosis and ventricular arrhythmias

Among the 113 patients with CMR LGE protocol, 50 (44%) patients had VA and among the 56 patients with TI-mapping, 15 (28%) patients had VA.

Patients with VA had more frequently papillary muscles LGE compared to those without VA (50% vs. 19%, $P = 0.001$). Furthermore, patients with VA had higher lateral T1 relaxation time and higher lateral ECV (*Figure 1A and B*; *Table 2*). The association between lateral T1 and VA was present even in the group of patients without LGE (*Figure 1C*).

Lateral ECV and T1 relaxation time were associated with VA in a multiple logistic regression independently of age, sex, LGE, left ventricular end-diastolic volume index and severe mitral regurgitation [lateral ECV: multivariate OR 1.37, 95% CI (1.02–1.84), $P = 0.03$; lateral T1: multivariate OR 1.04, 95% CI (1.01–1.07), $P = 0.008$].

Number of PVCs per 24 h by Holter monitoring increased with lateral T1 time and lateral ECV values (*Figure 2*; *Table 2*).

T-wave inversion, fibrosis and mitral valve abnormalities

Patients with extended TWI (≥3 leads) had higher prevalence of bileaflet MVP ($P = 0.02$) (*Table 1*), and had greater inferolateral MAD distance ($P = 0.005$) (*Table 1*).

Lateral ECV was marginally higher in patients with bileaflet MVP than in those without (28 ± 4% vs. 26 ± 3%, $P = 0.06$) (*Table 2*) and correlated positively with inferolateral MAD distance ($P = 0.03$) (*Graphical Abstract*).

Discussion

In this study, we confirmed the association between TWI and severe VA and added to the current knowledge by showing that arrhythmic risk increased with the extent of TWI. Interestingly, the extent of TWI

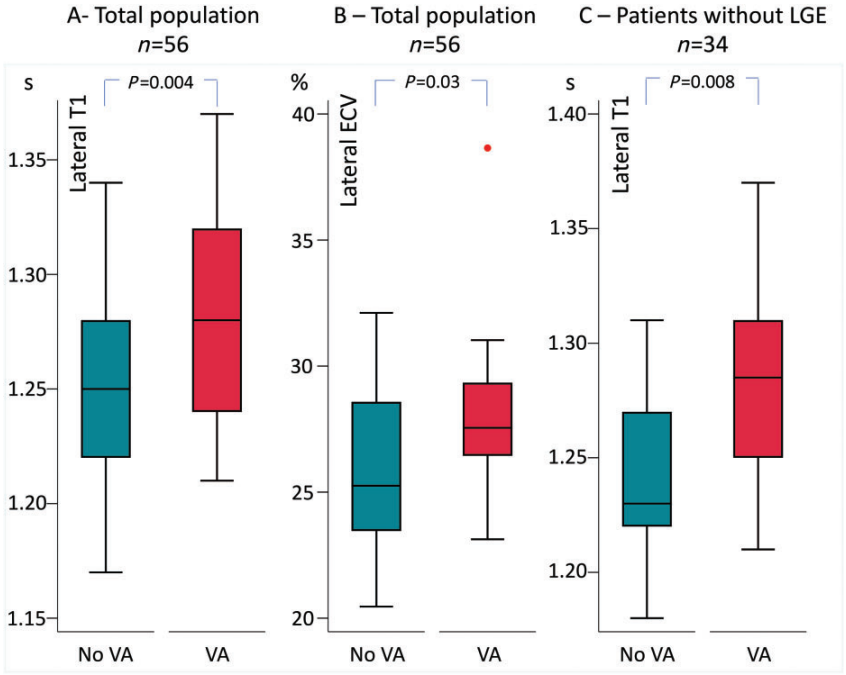


Figure 1 Lateral diffuse myocardial fibrosis by T1-mapping cardiac magnetic resonance in patients with and without VA. Boxplots representing lateral T1 and ECV values in patients with and without VA. (*A*) Lateral T1 in the total study population. (*B*) Lateral ECV in the total study population. (*C*) Lateral T1 in patients without LGE. *P* values are calculated by Student's *t*-test. ECV, extracellular volume; LGE, late gadolinium enhancement; VA, ventricular arrhythmias.

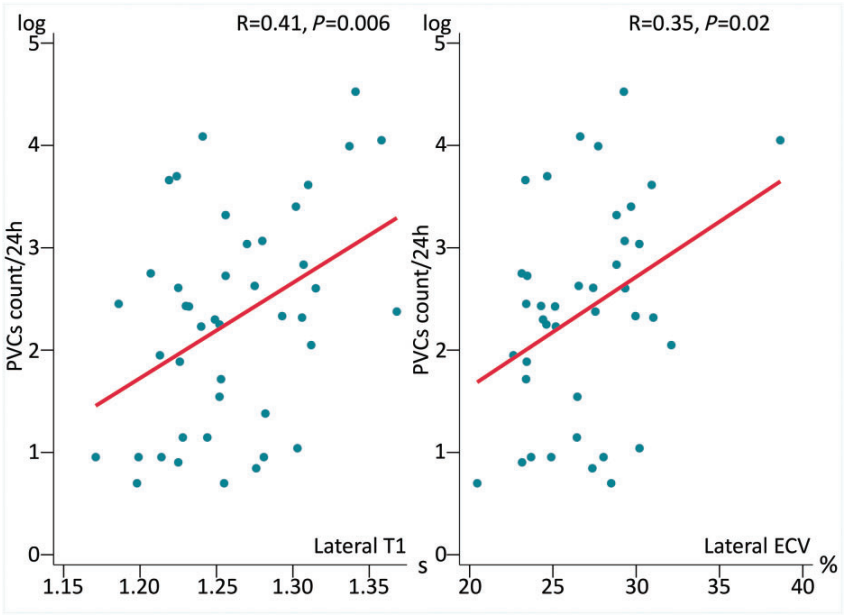


Figure 2 Correlation between PVCs count/24 h by Holter monitoring and lateral T1 and ECV values by T1-mapping cardiac magnetic resonance. Correlation plots between PVCs count/24 h as evaluated by Holter monitoring (*y*-axis) and lateral T1 (left panel) and ECV values (right panel) by T1-mapping cardiac magnetic resonance (*x*-axis). Log base 10 transformation of the PVCs count was performed to assure model linearity assumptions. Correlation coefficient *R* and *P* values are calculated by Pearson correlation analysis. ECV, extracellular volume; PVCs, premature ventricular contractions.

correlated with the degree of diffuse myocardial fibrosis by T1-mapping CMR suggesting diffuse fibrosis to be the substrate of electrical changes. Importantly, patients with VA had more diffuse myocardial fibrosis even in the absence of LGE, suggesting diffuse myocardial fibrosis alone as an arrhythmogenic factor independently of fibrosis detected by LGE. Whether diffuse fibrosis is an early sign or concomitant with LGE detected focal fibrosis remains to be explored.

Prevalence of repolarization abnormalities and arrhythmic risk

We found TWI ≥2 leads in 21% and extended TWI in 13% of patients with MVP. The prevalence found in our study is comparable with a recent study showing TWI in 20% of cases in a general MVP population.[14] Other previous studies[2,3] found a prevalence of repolarization abnormalities (inverted or biphasic T-wave in inferior leads) as high as 80% when including high-risk patients with a frequent bileaflet MVP. Our study confirmed the association between extended TWI and bileaflet MVP, supporting the theory that TWI is associated with more severe mitral valve disease.

We showed that the risk of severe VA increased with greater number of ECG leads displaying TWI. Several studies have indicated T-wave changes as a characteristic of the arrhythmic MVP phenotype and its association with increased arrhythmic risk.[2,3,14] Our study supported the link between TWI and severe VA and added the finding of a continuous increase in risk by more extended repolarization abnormalities.

Tissue characterization for identification of substrate of repolarization abnormalities

For the first time, we were able to link more extended TWI to lateral diffuse myocardial fibrosis by T1-mapping CMR. These findings indicate that diffuse fibrosis forms the substrate for ECG repolarization abnormalities and relate the ECG changes to possible arrhythmogenic substrates.

In contrast to T1-mapping CMR, we found no association between the presence of LGE and ECG repolarization abnormalities. The presence of LGE is a qualitative and observer-dependent finding based on differences in signal intensity between adjacent myocardium regions[15] and is categorized in presence or absence of fibrosis. LGE might not be sensitive enough to detect small amount of fibrosis. Our findings of TWI relation to fibrosis by T1-mapping suggest that the continuum of myocardial fibrosis is more precisely characterized by T1-mapping CMR.[16] Furthermore, missing CMR data in patients at highest arrhythmic risk might have impacted the association between LGE and TWI.

Substrate for arrhythmias in mitral valve prolapse

We showed that patients with MVP and VA had higher indices of diffuse myocardial fibrosis, linking diffuse fibrosis to arrhythmic risk. The arrhythmic relation to diffuse fibrosis was further supported by a positive correlation between lateral diffuse fibrosis and PVCs count in

Table 2 Linear regression between diffuse fibrosis by T1-mapping cardiac magnetic resonance and clinical, electrical, and imaging parameters

	Univariate B (95% CI) Lateral T1 (ms)	*P* value	Univariate B (95% CI) Lateral ECV (%)	*P* value
Clinical characteristics				
Age[a] (years)	4.95 (−3.43–13.33)	0.24	0.52 (−0.12–1.16)	0.11
Sex, female	0.95 (−24.20–26.10)	0.69	1.66 (−0.15–3.47)	0.07
Syncope	39.96 (−0.88–80.79)	0.06	1.36 (−1.69–4.41)	0.38
Palpitations	14.58 (−11.81–40.96)	0.27	0.96 (−1.01–2.94)	0.33
Arrhythmias				
VA	**36.68 (11.37–61.99)**	**0.005**	**2.07 (0.16–3.98)**	**0.03**
Severe VA	−25.87 (−116.61–64.87)	0.57	−1.29 (−7.88–5.31)	0.70
Electrocardiogram				
TWI	**27.94 (1.81–54.07)**	**0.04**	**2.31 (0.42–4.19)**	**0.02**
QRS duration (ms)	0.49 (−0.46–1.44)	0.30	0.01 (−0.07–0.08)	0.89
QRS fragmentation	−16.48 (−54.22–21.27)	0.39	−1.54 (−4.40–1.31)	0.28
QTc (ms)	**0.44 (0.05–0.83)**	**0.03**	**0.06 (0.03–0.08)**	**<0.001**
24 h Holter monitoring				
PVCs count,[b] *n*	**18.21 (5.51–30.94)**	**0.006**	**1.17 (0.16–2.18)**	**0.03**
Cardiac magnetic resonance				
Bileaflet MVP	21.17 (−3.98–46.33)	0.10	1.75 (−0.08–3.58)	0.06
Inferolateral MAD distance	**4.50 (1.26–7.73)**	**0.007**	**0.27 (0.02–0.52)**	**0.03**
LVEDVi[c] (mL/m^2)	1.93 (−0.86–4.72)	0.17	0.13 (−0.08–0.33)	0.21
LVEDVi[c] (mL/m^2)	4.49 (−1.20–10.19)	0.12	0.32 (−0.09–0.74)	0.13
LV EF[c] (%)	−4.01 (−15.42–7.39)	0.68	−0.45 (−1.28–0.37)	0.28
LGE	12.10 (−13.16–37.36)	0.34	1.10 (−0.75–2.95)	0.24
Basal LV wall LGE	23.64 (−4.80–52.08)	0.10	**2.24 (0.18–4.29)**	**0.03**
Papillary muscles LGE	20.39 (−21.03–61.81)	0.33	**3.30 (0.37–6.23)**	**0.03**

P values are calculated by univariate linear regression analysis. Bold values denote statistical significance.
ECV, extracellular volume; EF, ejection fraction; LGE, late gadolinium enhancement; LV, left ventricular; LVEDVi, LV end-diastolic volume indexed; LVESVi, LV end-systolic volume indexed; MAD, mitral annulus disjunction; MVP, mitral valve prolapse; PM, papillary muscles; PVCs, premature ventricular contractions; TWI, T-wave inversion; VA, ventricular arrhythmias.
[a]Per 10 years increments.
[b]Log base 10 transformation of the PVCs count was performed to assure model linearity assumptions.
[c]Per 5-units increments.

24 h by Holter monitoring, supporting one previous study.[6] This finding also suggests the lateral left ventricular wall to be predominantly affected in MVP. Our findings support the hypotheses that mechanical stretch of the basal inferolateral left ventricular wall and adjacent segments induces specific regional myocardial changes in MVP.[17,18]

In this study, we showed the value of assessing diffuse myocardial fibrosis for depicting arrhythmic risk also in patients without LGE.[6] This finding is important by indicating that different types of fibrosis may play a role in MVP. LGE is considered to reflect replacement fibrosis while parameters assessed by T1-mapping CMR reflect interstitial fibrosis. LGE is a recognized arrhythmic marker in MVP patients,[3] with inferolateral left ventricular wall and papillary muscles LGE related to highest arrhythmic risk.[4,5] However, LGE has limited abilities in predicting arrhythmic risk as also shown in our previous study[4] where LGE was absent in more than half of patients with MVP and severe VA thus indicating other mechanisms for the electrical instability. Detection of interstitial fibrosis in patients with MVP may further improve risk stratification.[16]

Myocardial fibrosis and relation to mitral valve abnormalities

The prevalence of bileaflet MVP was higher in patients with extended TWI. Our finding supports the hypothesis that stretching of the papillary muscles and of the adjacent ventricular wall by a severely degenerated valve leads to myocardial fibrosis.[19] Our results further add to these theories by showing the association between bileaflet MVP and ECG abnormalities and the marginally significant relation of bileaflet MVP to CMR diffuse fibrosis.

Interestingly, we showed that a greater inferolateral MAD distance was linked to extended TWI and more lateral diffuse myocardial fibrosis. These findings suggest that greater MAD distance imposes greater mechanical stretch on the lateral ventricular wall, leading to myocardial fibrosis presented on the ECG as extended repolarization abnormalities.

Clinical implications

We propose that detection of ECG TWI could help identify patients with underlying diffuse myocardial fibrosis who might benefit from

closer heart rhythm monitoring. Importantly, diffuse myocardial fibrosis in MVP patients could indicate arrhythmic risk even in the absence of LGE. Assessment of myocardial fibrosis by T1-mapping CMR may help in arrhythmic risk stratification of patients with MVP.

Limitations

This was an ambispective cross-sectional study with a prospective CMR study protocol in addition to retrospective CMR examinations and partly pre-existing data collection with inherent design-associated limitations and possible selection bias.

The limited number of severe VA could have influenced the robustness of the statistical analysis. We included MVP patients from referral centres and the prevalence of arrhythmias was therefore overestimated compared to a general population. Furthermore, the referral bias resulted in a high proportion of patients with an arrhythmic MVP phenotype and our findings may not be applicable to populations with other characteristics.

Lack of CMR examinations in survivors of severe VA already implanted with an implantable cardioverter-defibrillator and not suitable for CMR scanning may have caused underestimation of the prevalence of fibrosis in the individuals at highest risk. Only one patient with history of severe VA performed T1-mapping CMR. Therefore, we were not able to investigate a direct association between diffuse fibrosis by T1-mapping CMR and severe VA.

CMR with evaluation of the presence of LGE was not available in all and T1-mapping sequences were available only in a subgroup of patients which could have influenced the results. Patients with VA were clearly distinguished by higher native T1 values. However, small differences of native T1 values between diseased and normal myocardium might limit the clinical application of this technique.[20]

We cannot exclude other causes of TWI as the phenomenon of cardiac memory in the presence of frequent PVCs or transitory states responsible for dynamic TWI.

CMR protocol did not include velocity encoding necessary for regurgitation quantification and therefore the degree of mitral regurgitation was analysed using echocardiography.

Conclusions

Extended ECG TWI was associated with higher risk of severe VA and was present in 13% of patients with MVP. The extent of TWI was associated with higher degree of lateral diffuse fibrosis, suggesting diffuse fibrosis as the underlying substrate for ECG repolarization abnormalities. Lateral diffuse myocardial fibrosis indicated higher arrhythmic risk even in the absence of focal fibrosis by LGE. These results suggest that ECG TWI reflects myocardial diffuse fibrosis associated with increased arrhythmic risk in patients with MVP.

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Conflict of interest: none declared.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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