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ORIGINAL RESEARCH

Prevalence of Mitral Annulus Disjunction and Mitral Valve Prolapse in Patients With Idiopathic Ventricular Fibrillation

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BACKGROUND: Idiopathic ventricular fibrillation (IVF) is diagnosed in patients with ventricular fibrillation of which the origin is not identified after extensive evaluations. Recent studies suggest an association between mitral annulus disjunction (MAD), mitral valve prolapse (MVP), and ventricular arrhythmias. The prevalence of MAD and MVP in patients with IVF in this regard is not well established. We aimed to explore the prevalence of MAD and MVP in a consecutive cohort of patients with IVF compared with matched controls.

METHODS AND RESULTS: In this retrospective, multicenter cohort study, cardiac magnetic resonance images from patients with IVF (ie, negative for ischemia, cardiomyopathy, and channelopathies) and age- and sex-matched control subjects were analyzed for the presence of MAD (≥2 mm) and MVP (>2 mm). In total, 72 patients (mean age 39±14 years, 42% women) and 72 control subjects (mean age 41±11 years, 42% women) were included. MAD in the inferolateral wall was more prevalent in patients with IVF versus healthy controls (7 [11%] versus 1 [1%], *P*=0.024). MVP was only seen in patients with IVF and not in controls (5 [7%] versus 0 [0%], *P*=0.016). MAD was observed in both patients with (n=4) and without (n=3) MVP.

CONCLUSIONS: Inferolateral MAD and MVP were significantly more prevalent in patients with IVF compared with healthy controls. The authors advocate that evaluation of the mitral valve region deserves extra attention in the extensive screening of patients with unexplained cardiac arrest. These findings support further exploration of the pathophysiological mechanisms underlying a subset of IVF that associates with MAD and MVP.

Key Words: cardiac magnetic resonance imaging ■ idiopathic ventricular fibrillation ■ mitral annulus disjunction ■ mitral valve prolapse ■ ventricular arrhythmias

Idiopathic ventricular fibrillation (IVF) is diagnosed in patients with ventricular fibrillation of unknown origin that remains unidentified after extensive diagnostic testing.[1,2] The diagnosis of IVF depends on the absence of a substrate for ventricular fibrillation by exclusion of both structural cardiac diseases and primary arrhythmia syndromes. In the follow-up of these patients, a continuing search for previously unknown proarrhythmic factors is driven by the evolution of medical knowledge and diagnostic techniques.[3]

Decades ago, mitral valve prolapse (MVP) and mitral annulus disjunction (MAD) had already been associated with ventricular arrhythmias and sudden cardiac arrest in young patients.[4–13] In recent years, MAD

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CLINICAL PERSPECTIVE

What Is New?

- Idiopathic ventricular fibrillation has previously been associated with mitral valve prolapse.
- Recent research has suggested an association between ventricular arrhythmias and mitral annulus disjunction, independently of mitral valve prolapse.
- We found that mitral valve prolapse and mitral annulus disjunction are both significantly more prevalent in patients with idiopathic ventricular fibrillation than in controls.

What Are the Clinical Implications?

- Mitral annulus disjunction and mitral valve prolapse are frequently overlooked and deserve extra attention in the extensive screening of patients with idiopathic ventricular fibrillation.

Nonstandard Abbreviations and Acronyms

IVF	idiopathic ventricular fibrillation
MAD	mitral annulus disjunction

regained attention in association with MVP and ventricular arrhythmias.[8,14–17] MAD is defined as an abnormal atrial displacement of the mitral valve leaflet hinge point, away from the ventricular myocardium. A close relationship has been shown between MVP and sudden cardiac arrest, but recent studies also showed an association with ventricular arrhythmias independently of MVP.[8–10]

Imaging with cardiac magnetic resonance (CMR) and echocardiography is included in the standard workup for patients with IVF. Previous studies have reported a high prevalence of MVP in patients with aborted cardiac arrest of unexplained cause,[9] but until now, no specific attention has been given to the presence of MAD in patients with IVF. We hypothesize that this abnormality might have often been overlooked in the routine clinical workup of patients with IVF. The aim of this study was to describe MAD and MVP prevalence and morphology in a multicenter cohort of patients with IVF and matched controls.

METHODS

Study Population

Patients were derived from a large Dutch registry of patients with IVF. Details of the cohort have been published in previous studies.[2,18] In summary, we enrolled patients with an unexplained cardiac arrest with an initial rhythm of ventricular fibrillation, in whom known cardiac, respiratory, metabolic, and toxicological causes were excluded at first presentation. Comprehensive clinical investigation was performed, and accepted diagnostic criteria were used to exclude specific disease.[19]

For this multicenter, retrospective cohort study, we included patients with IVF who were evaluated in 3 tertiary referral centers in the Netherlands (University Medical Center Utrecht, Amsterdam University Medical Center, and Radboud University Medical Center) between September 2004 and December 2020 and underwent CMR imaging of sufficient image quality (Figure 1). Age- and sex-matched controls with no history of cardiovascular disease were selected from a previous prospectively included cohort of healthy nonathletes.[20,21] The study complied with the Declaration of Helsinki and was approved by the Regional Committee for Medical Research Ethics in all participating centers, and the subjects gave informed consent when appropriate. The data that support the findings of this study are available from the corresponding author upon reasonable request.

CMR Imaging

All included subjects underwent CMR examination on a clinical 1.5T or 3T magnetic resonance scanner using electrocardiographic gating and a phased array cardiac receiver coil according to standardized cardiac protocols.[22] Breath-hold balanced steady-state free-precession cine images covering both the ventricles and atria were acquired (4-chamber long-axis view, 2- and 3-chamber long-axis left ventricle [LV] views and multislice full coverage of the LV in short-axis orientation). The voxel size of the cine sequences used was dependent on the local clinical scan protocol and was typically around 1.5×1.5×5 to 8 mm^3. In addition, late gadolinium enhancement (LGE) imaging was performed at least 10 minutes after intravenous administration of a gadolinium-based contrast agent in identical views. LGE imaging was not performed in control subjects.

Ventricular metrics and ejection fraction were measured in a standardized way using semiautomated contour tracing software.[23] Ventricular end-diastolic volumes were indexed for body surface area. Patients with major LGE (sufficient for a specific diagnosis) were not included in the IVF registry, whereas patients with minor LGE of uncertain pathogenicity were included in this study. The LGE images were reevaluated for any myocardial fibrosis in the LV and papillary muscles by an experienced cardiac radiologist. Mild insertion fibrosis was deemed insignificant for this study.

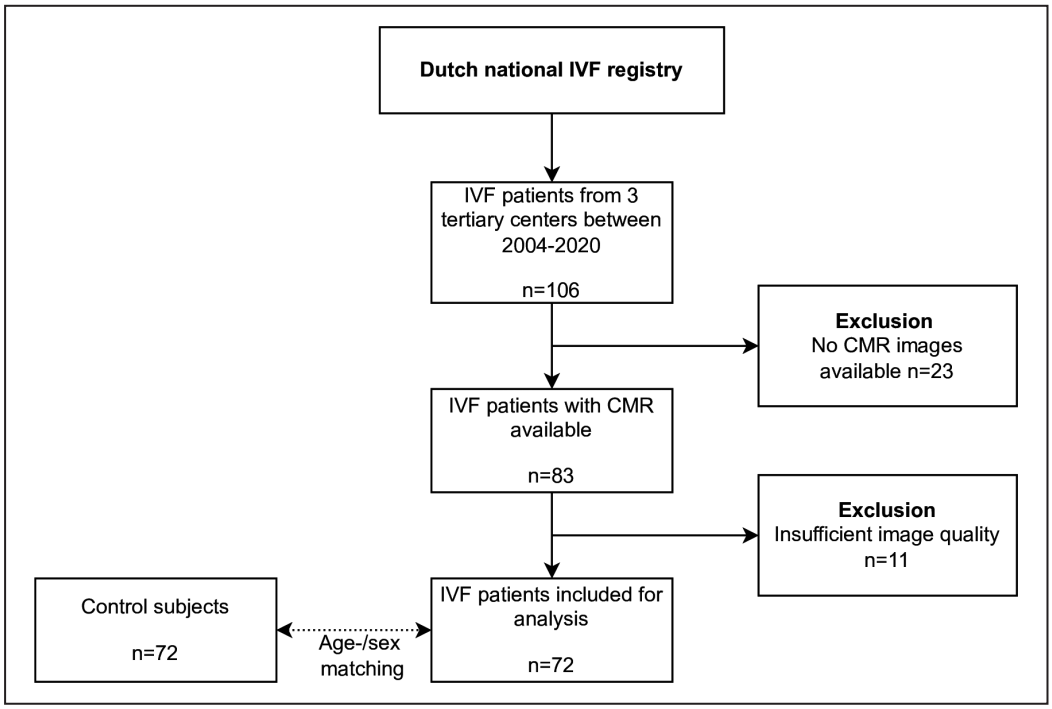

Figure 1. Inclusion flowchart.
Patients with IVF included in a large national registry from 3 tertiary centers were included. CMR indicates cardiac magnetic resonance; and IVF, idiopathic ventricular fibrillation.

Two blinded observers analyzed CMR images for presence and longitudinal distance of MAD and MVP. Longitudinal MAD distance was measured on all 3 long-axis cine views from the left atrial wall mitral valve leaflet junction to the top of the left ventricular wall at end-systole. Presence of MAD was defined as a longitudinal displacement of >1 mm (Figure 2). Presence of MVP was defined as displacement of >2 mm of 1 or both leaflets beyond the annular hinge points at end-systole, measured perpendicular to the annular plane in the 3-chamber view (Figure 2).[24] Presence of the curling sign, defined as an unusual systolic motion of the inferior mitral annulus on the adjacent ventricular wall, was identified by visual assessment (Video S1).[8,25]

Clinical Characteristics

Clinical data were derived from the IVF registry. Enrolled patients all underwent detailed investigation of medical history, physical examination, 12-lead ECG, laboratory testing, echocardiography, coronary angiography (or computed tomography angiography) and CMR. All

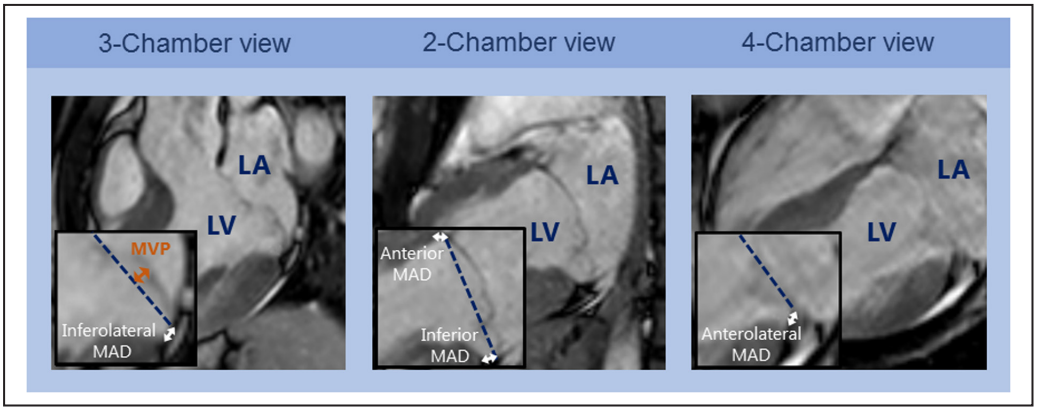

Figure 2. Measurements of longitudinal MAD and MVP distance on CMR imaging.
All images are obtained at end-systole. The blue line connects the annular hinge points of the mitral valve, the white arrows are longitudinal MAD measurements, and the orange arrow is the MVP measurement. CMR indicates cardiac magnetic resonance; LA, left atrium; LV, left ventricle; MAD, mitral annulus disjunction; and MVP, mitral valve prolapse.

patients underwent echocardiographic imaging according to the standard clinical protocol.[26,27] Additional investigations, such as exercise ECG, sodium channel blocker provocation, endomyocardial biopsy, and genetic testing, were performed at the treating physician's discretion.[2,18] T-wave abnormalities were defined as inverted or biphasic T waves. Genetic testing consisted of single targeted gene testing or next generation sequencing of a larger panel of genes, depending on the center where the genetic testing was performed. In line with previous studies, we also included patients with the *DPP6 haplotype*, a genetic variant associated with short-coupled polymorphic ventricular tachycardia/IVF.[1,28] Although we previously proposed that overexpression of the transient outward current (Ito) channel plays an essential role in these patients,[29] the underlying pathophysiological mechanism for ventricular fibrillation remains uncertain.

Follow-up data were retrospectively collected from all patients. All electrocardiographic data on ECGs, cardiac telemetry during admission, exercise ECG, and Holter monitoring were analyzed for the occurrence of premature ventricular complexes (PVCs). A high PVC burden was defined as >1000 PVCs per 24 hours on Holter monitoring. In patients without Holter monitoring, a high PVC burden was defined as >20 PVCs during an exercise test or bigeminy or trigeminy on ECG or cardiac telemetry. Nonsustained ventricular tachycardia was defined as 3 or more ventricular beats with a maximum duration of 30 seconds.[30] Appropriate implantable cardioverter-defibrillator therapy was defined as antitachycardia pacing or shock during a ventricular tachycardia or ventricular fibrillation.

Statistical Analysis

Parametric data were presented as mean±standard deviation, median (interquartile range), or number (percent). Comparisons were performed using a Student *t* test, Mann-Whitney *U* test, or Fisher exact test as appropriate. Analyses were performed with SPSS version 24.0 (IBM, Armonk, NY). Intra- and interobserver variability was expressed by intraclass correlation coefficients. Two-sided *P* values <0.05 were considered significant.

RESULTS

Study Population

After screening 106 patients with IVF from 3 centers, a total of 72 patients (mean age 39±14 years, 42% women) and 72 age- and sex-matched control subjects (mean age 41±11 years, 42% women) were included (Figure 1). In total, 23 patients were excluded because of CMR unavailability, and 11 patients were excluded because of insufficient image quality. An implantable cardioverter-defibrillator for secondary prevention was implanted in all but 1 of the patients with IVF (99%) (Table 1).

Table 1. Baseline Characteristics of Patients With Idiopathic Ventricular Fibrillation

Characteristics	All, n=72
Age, y	39±14
Women, n (%)	30 (42)
Circumstances event, n (%)	
Rest	43 (60)
Exercise	16 (22)
Asleep	9 (12)
Emotions	4 (6)
Genetic testing	
DPP6 haplotype	9 (13)
Electrocardiogram	
Heart rate, bpm	69±13
ICD implantation	71 (99)

Values are n (%) or mean±SD. ICD indicates implantable cardioverter-defibrillator.

Prevalence of Mitral Valve Disease

MAD was commonly measured in the anterior, inferior, and anterolateral wall in both patients with IVF and healthy controls (Table 2). The inferolateral wall was the only distinctive location for the presence of MAD between patients with IVF and controls (7 [11%] versus 1 [1%], *P*=0.024). In addition, patients with IVF showed a higher prevalence of MVP (5 [8%] versus 0 [0%], *P*=0.016). A curling sign of the inferior wall was observed in 3 patients with IVF with MAD and not in controls. One control subject showed MAD in the inferolateral wall of 2 mm, without signs of other mitral valve disease. In 7 patients with IVF with inferolateral MAD, other mitral valve disease was prevalent; 4 (57%) also had MVP, of which 3 women with bileaflet MVP and 4 patients (57%) showed signs of mitral regurgitation. One patient with MVP did not have inferolateral MAD. Characteristics of subjects with MAD and/or MVP are described in Table 3. In 2 subjects with MAD/MVP, a variant of uncertain significance was found with genetic testing (Table S1). Three subjects with MAD/MVP underwent electrophysiology study. Voltage mapping of the LV was not performed. One subject underwent radiofrequency ablation because of frequent PVCs in the anterolateral right ventricular outflow tract. Seven subjects with MAD/MVP underwent exercise stress testing, and none showed non-sustained ventricular tachycardia or multifocal PVCs.

Comparison Between Patients With IVF With and Without Mitral Valve Disease

Mitral regurgitation was more prevalent in patients with MAD and/or MVP compared with patients without (4

Table 2. Comparison Between Patients With IVF and Matched Controls

Characteristics	Patients with IVF, n=72	Controls, n=72	*P* value
Age, y	39±14	41±11	0.290
Women, n (%)	30 (42)	30 (42)	1.000
BSA, m^2	2.0±0.2	1.9±0.2	0.571
Cardiac magnetic resonance			
LVEF, %	57±15	60±7	0.180
LVEDVi, mL/m^2	85±16	93±14	0.005*
Late gadolinium enhancement, n (%)	8 (13)	n/a	n/a
Mitral annulus disjunction, n (%)	40 (56)	44 (61)	0.612
Anterolateral wall, n=141*	17 (24)	13 (18)	0.417
Anterior wall, n=132*	21 (33)	32 (46)	0.156
Inferior wall, n=135*	26 (40)	29 (41)	1.000
Inferolateral wall, n=133*	7 (11)	1 (1)	0.024*
Mitral valve prolapse, n (%)	5 (8)	0 (0)	0.016*
Bileaflet mitral valve prolapse, n (%)	3 (5)	0 (0)	0.096
Curling sign, n (%)	3 (5)	0 (0)	0.096

Values are n (%) or mean±SD. BSA indicates body surface area, IVF, idiopathic ventricular fibrillation; LVEDVi, indexed left ventricular end-diastolic volume; and LVEF, left ventricular ejection fraction.

*Missing values because of unavailable views or insufficient image quality.

[50%] versus 7 [14%], *P*=0.024) (Table 4). In addition, inverted or biphasic T waves were more frequently observed in patients with IVF with MAD/MVP compared with patients without (3 [38%] versus 2 [3%], *P*=0.009). LGE imaging was available for analysis in the majority of patients with IVF (n=61). In 8 (13%) patients with IVF, small LGE spots of uncertain pathogenicity were reported (Table 4). There was no difference in the occurrence of LGE between patients with MAD/MVP compared with patients without (1 [13%] versus 7 [13%], *P*=1.000). One patient with inferolateral MAD showed midwall LGE in the LV basal inferoseptal myocardium (Figure S1). LGE was seen in 7 patients without MAD. The location and pattern of LGE ranged from small midwall or epicardial foci in 3 patients (basal inferolateral twice and basal inferior wall); 3 patients had a small subendocardial scar in the respectively basal inferior, apical septal, and apical inferior segments, and 1 patient had a small transmural scar in the basal inferolateral segment. The patient with possible basal subendocardial LGE could also be slow flow in a basal crypt (Figure S1). The 4 patients with subendocardial to transmural LGE had no coronary artery disease on catheter angiography or coronary computed tomography angiography.

Follow-Up

The mean follow-up duration of the IVF cohort was 7 years (interquartile range, 2–12 years). Patients with MAD/MVP more frequently showed a high PVC burden (6 [75%] versus 7 [13%], *P*=0.001). In patients with MAD/MVP, the PVCs more frequently originated from the basal LV or right ventricular outflow tract (Table S2 and Figure S2). There were no significant differences between patients with IVF with MAD/MVP compared with patients without MAD/MVP with regard to the occurrence of nonsustained ventricular tachycardias or appropriate implantable cardioverter-defibrillator therapy during follow-up (Table 4).

Intra- and Interobserver Agreement

We showed excellent reproducibility of longitudinal MAD distance measurements. The intraobserver agreement on 80 segments from 20 patients was 0.92 (95% CI, 0.88–0.95; *P*<0.001), and the interobserver agreement was also 0.92 (95% CI, 0.88–0.95; *P*<0.001).

DISCUSSION

Our study is the first to compare prevalence of MAD and MVP in a consecutive multicenter cohort of patients with IVF to a healthy control population. The most important finding was the increased prevalence of MAD in the inferolateral wall and MVP compared with controls (Figure 3). Subjects with MAD in the inferolateral wall also showed high prevalence of other mitral valve disease and ventricular ectopy. This is in line with previous studies suggesting a correlation between mitral valve disease and IVF. MAD in the anterior, inferior, and anterolateral wall was commonly measured in both patients with IVF and healthy controls.

Table 3. Characteristics of 8 Subjects With MVP and/or MAD in the Inferolateral Wall on Cardiac Magnetic Resonance Imaging

Subjects, N=7	Sex	MAD, mm				MVP, mm	Bileaflet MVP	Curling sign	MR*	LGE	ECG T-wave abnormalities	Ventricular ectopy
		AL	ANT	INF	IL							
Control 1	M	2	2	3	2	0	No	No	No	N/A	N/A	N/A
IVF survivor 1	F	3	0	0	2	5	Yes	No	Moderate	Basal septal LV	Yes, inferior	No
IVF survivor 2	M	3	0	5	3	3	No	No	Mild	No	No	Yes, basal LV
IVF survivor 3	M	3	0	8	3	0	No	No	Mild	No	No	No
IVF survivor 4	F	3	3	2	2	0	No	Yes	No	No	No	Yes, RVOT
IVF survivor 5	F	1	2	5	3	6	Yes	Yes	No	No	Yes, inferior	Yes, basal LV
IVF survivor 6	M	2	5	1	2	0	No	No	No	No	Yes, inferior	Yes, RVOT
IVF survivor 7	F	2	2	2	2	7	Yes	Yes	Mild	No	No	Yes, LV apex
IVF survivor 8	M	0	0	4	0	4	No	No	No	No	No	Yes, RVOT

MAD, MVP, and the curling sign were assessed on cardiac magnetic resonance imaging. AL indicates anterolateral wall; ANT, anterior wall; IL, inferolateral wall; INF, inferior wall; IVF, idiopathic ventricular fibrillation; LGE, late gadolinium enhancement; LV, left ventricle; MAD, mitral annulus disjunction; MR, mitral regurgitation; MVP, mitral valve prolapse; N/A; not available; and RVOT, right ventricular outflow tract.
*Mitral regurgitation was determined on echocardiography.

Location of Mitral Annulus Disjunction

Previous studies showed that MAD distance can vary considerably along the annulus circumference. This was shown with an extensive CMR protocol design assessing the mitral annulus every 30°.[8] Although we did not assess the mitral annulus every 30° because of unavailability of these acquisitions or 3-dimensional CMR data in this retrospective study, we also observed considerable differences in longitudinal MAD distance over the mitral annulus (Table 3). The aforementioned study showed that MAD located in the inferolateral wall assessed by CMR was an independent risk marker for ventricular arrhythmias.[8] In our cohort, the inferolateral wall visualized in the 3-chamber long-axis view was found to be the only distinctive location for MAD between patients with IVF and controls. In the other walls, gaps of 1 to 3 mm between the LV myocardium and the mitral annulus hinge points were frequently seen in both patients and controls. Where the 3-chamber view (or parasternal long-axis view in echo) is generally considered to be the most standardized for measurements of the mitral valve, the other views are less reproducible when it comes to measurements on the saddle-shaped valve and might therefore be more subjected to errors.[24,31] This might have contributed to our finding that the inferolateral wall was the only distinctive location for MAD between patients with IVF and controls, which is in line with previous studies.[8,9,25,32] Additionally, a recent study applying a comprehensive 3-dimensional analysis on cardiac computed tomography images of 98 structurally normal hearts also showed a high prevalence of MAD in the anterior to anterolateral and inferior to inferoseptal segments (77.5% and 87.8%, respectively), whereas inferolateral MAD was less common in healthy subjects (11.2%).[33]

The cutoff to determine presence of MAD on CMR is another point of discussion. We considered longitudinal distances of >1 mm significant, given the spatial resolution of CMR,[18] but general consensus is lacking. The voxel size of cine sequences acquired in routine clinical care limits reliability of measurements below 1.5 mm. Moreover, longitudinal distances measured by CMR and echocardiography cannot be used interchangeably, as shown by differences in measured distances by the 2 modalities in a previous study.[8] Larger CMR-based population studies are needed to determine the upper limit of normal.

MAD and the Relation to MVP

The concept of MAD as an arrhythmic factor was introduced for the first time around the 1980s.[11,12,34] Since then, it has been closely linked to MVP and other mitral valve diseases.[25] During the past several years, study of MAD has regained interest, and multiple reports indicate that MAD may also be present without MVP.[8,35] This is in

Table 4. Comparison Between Patients With IVF With and Without MAD and/or MVP

Characteristics	IVF with MAD/MVP, n=8	IVF without MAD/MVP, n=64	*P* value
Age, y	38±17	39±14	0.890
LVEF, %	54±15	56±8	0.430
Women, n (%)	4 (50)	25 (39)	0.706
Late gadolinium enhancement, n (%)	1 (13)	7 (13)	1.000
Mitral regurgitation, n (%)	4 (50%)	7 (14%)	0.024
Inverted/biphasic T waves, n (%)	3 (38%)	2 (3%)	0.009
Follow-up data			
Follow-up duration, y	7 [4–11]	7 [2–12]	0.886
PVC count per hour on Holter monitoring, n	228 [71–676]	1 [0–18]	0.016
High PVC burden on ECG, telemetry, exercise test, or Holter	6 (75%)	8 (16%)	0.001
LV basal	2 (25%)	0 (0%)	N/A
RVOT	3 (38%)	3 (6%)	N/A
Other	0 (0%)	5 (10%)	N/A
Multiform	1 (12%)	0 (0%)	N/A
Nonsustained ventricular tachycardia	4 (50%)	17 (31%)	0.423
Appropriate ICD therapy, n (%)	1 (13%)	15 (24%)	0.670
Ventricular tachycardia	1 (13%)	5 (8%)	N/A
Ventricular fibrillation	0 (0%)	10 (16%)	N/A
Atrial fibrillation, n (%)	1 (13%)	5 (9%)	0.567

Values are n (%), mean±SD, or median [interquartile range]. ICD indicates implantable cardioverter-defibrillator; IVF, idiopathic ventricular fibrillation; LV, left ventricle; LVEF, left ventricular ejection fraction; MAD, mitral annulus disjunction; MVP, mitral valve prolapse; PVC, premature ventricular complex; and RVOT, right ventricular outflow tract.

line with our findings, because 43% of patients with IVF with MAD did not show MVP. The distinction between MAD and MVP can, however, be difficult, especially when determining the exact hinge point of a prolapsed mitral valve that parallels the atrial wall. If the prolapse distance is measured from the myocardial edge, MVP will always be found in the presence of MAD.[25] We measured longitudinal MAD distance from the myocardial edge to the annular hinge point and MVP beyond the annular hinge point, allowing a distinction between them.[8] Although the distinction between MAD and MVP can be challenging, the increased prevalence of both entities in IVF that was found in this study is remarkable.

Proarrhythmic Substrate

The exact proarrhythmic mechanism of MAD is unknown. It has been hypothesized that hypermobility of the mitral valve causes mechanical stretch on the myocardial wall. This may directly induce ventricular ectopy, which can potentially trigger ventricular fibrillation. In the long term, mechanical stretch may also result in myocyte hypertrophy and fibrosis, creating another potential cause for myocardial electrical instability and arrhythmias.[9,25] Previous studies related papillary muscle fibrosis to arrhythmic events in the presence of MAD and MVP, but severe arrhythmias were also observed in patients without visible papillary muscle fibrosis on CMR.[8,14,25] In this study, we did not observe any papillary muscle fibrosis in patients with IVF with MAD. However, we more frequently observed ventricular ectopy and T-wave abnormalities in the inferolateral leads in patients with MAD/MVP, which was also observed in previous studies.[9,25] Although PVCs from the basal LV correspond with the anatomical location of MAD, this relationship is less clear for PVCs from the right ventricular outflow tract. The latter were previously reported in MAD, but mainly with concurrent left ventricular outflow tract PVCs.[9] Ventricular ectopy from areas in close proximity to the mitral annular region and papillary muscles has been attributed to mechanical traction in a subgroup of patients with IVF with bileaflet MVP,[9] and the same mechanism of traction-induced ectopy may be present in MAD.[36] Bileaflet MVP was present in 3 female patients with IVF in our cohort, consistent with the previous description of the malignant bileaflet MVP syndrome, which was characterized by bileaflet MVP, frequent ventricular ectopy, and female sex.[9]

Clinical Implications

A previous report demonstrated a case of unexplained cardiac arrest in an otherwise healthy patient, whereby

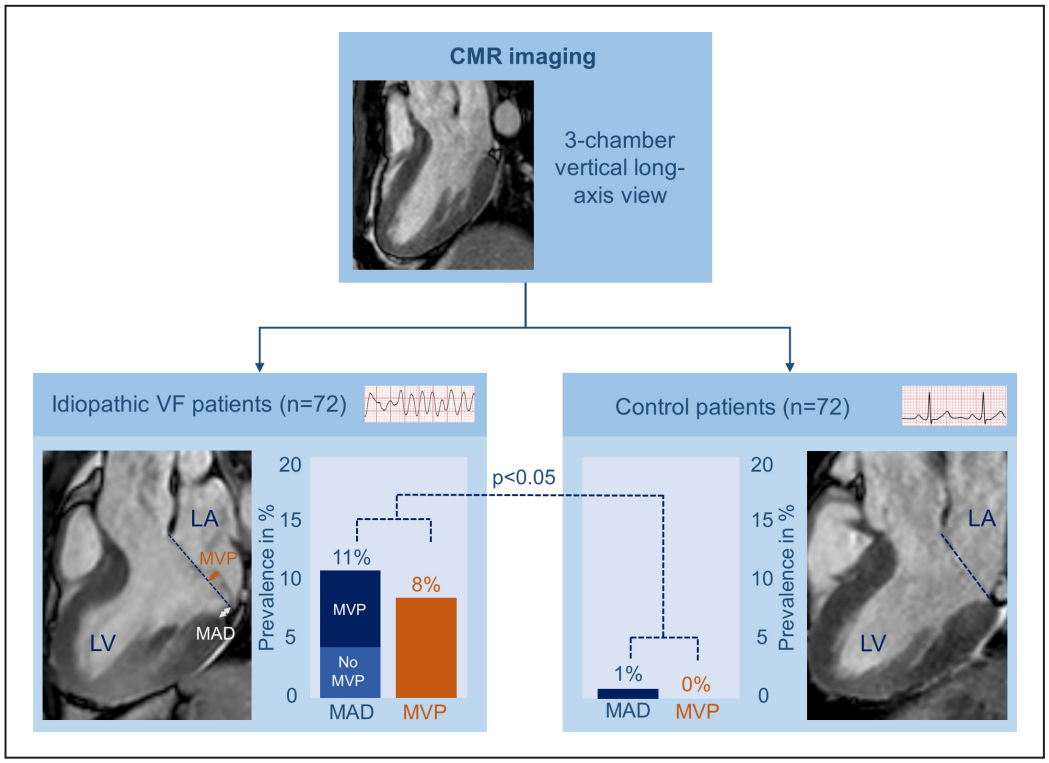

Figure 3. Prevalence of mitral annulus disjunction (MAD) and mitral valve prolapse (MVP) in patients with idiopathic ventricular fibrillation (VF) compared with healthy controls.
In total, 144 patients were enrolled in the study, 72 patients with idiopathic VF and 72 healthy controls. All patients were screened for presence of MAD and MVP on cardiac magnetic resonance (CMR) imaging by 2 blinded observers. MAD in the inferolateral wall was more prevalent in patients with idiopathic VF compared with controls (P=0.024). MVP was also more prevalent in patients with idiopathic VF compared with controls (P=0.016). LA indicates left atrium; and LV, left ventricle.

clear MAD was found upon secondary evaluation of cardiac imaging data.[37] We confirm that in 11% of our IVF cohort, MAD and/or MVP can be observed during focused analysis of CMR images, whereas it was previously left unrecognized in a thorough diagnostic process. In a matched cohort of healthy controls, MAD and MVP were rarely found. Overt MVP in combination with extensive myocardial fibrosis in the annular region and papillary muscles was not observed in our IVF cohort. These subjects were most likely already diagnosed with an arrhythmic mitral valve prolapse according to current clinical standards and did not end up in the IVF cohort.[9,38] Our findings suggest that mitral valve disease may still contribute as a proarrhythmic factor in a subset of patients with IVF. However, one could still argue that minor degrees of MAD are a bystander in IVF. A future, larger prospective study is needed to further evaluate our findings. We advocate that evaluation of the mitral valve region deserves extra attention in the extensive screening of patients with unexplained sudden cardiac arrest. The direct therapeutic consequences for patients with IVF may be limited, because they generally have a clear indication for secondary prevention implantable cardioverter-defibrillator implantation. However, knowledge about the correlation between MAD and arrhythmias may yield prognostic value for patients with IVF and might especially be important to identify a possible arrhythmogenic risk in family members.

Limitations

Although this is one of the largest IVF cohorts worldwide, the number of patients included is relatively small because of the rarity of the disease. Because of the retrospective nature of this study, image plane acquisition was already performed. Therefore, MAD measurements were confined to available CMR views. In addition, LGE imaging was not standardly performed in the older CMRs and in some cases could not be interpreted because of artifacts. Other studies suggest that MAD is also easily detectable on echocardiography, but the quality and focus of the images acquired are of great importance.[8,35] We did not use echocardiography because we concluded that measurement of MAD distance on retrospective exams without focused images was not feasible. Holter monitoring was not routinely performed because of the retrospective setup of the study. In addition, the number of patients

with MAD or MVP was relatively small, hampering strong conclusions on clinical follow-up data. Larger prospective follow-up studies are needed to determine the potential impact of MAD/MVP on the prognosis of patients with IVF.

CONCLUSIONS

Inferolateral MAD and MVP were significantly more prevalent in a large multicenter cohort of patients with IVF compared with healthy controls. Our findings support further exploration of the pathophysiological mechanisms underlying a subset of IVF that associates with MAD and MVP. The clinical implications of the presence of MAD for recurrences of ventricular arrhythmias and treatment strategies remain to be elucidated.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S2
Figures S1–S2
Video S1

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SUPPLEMENTAL MATERIAL

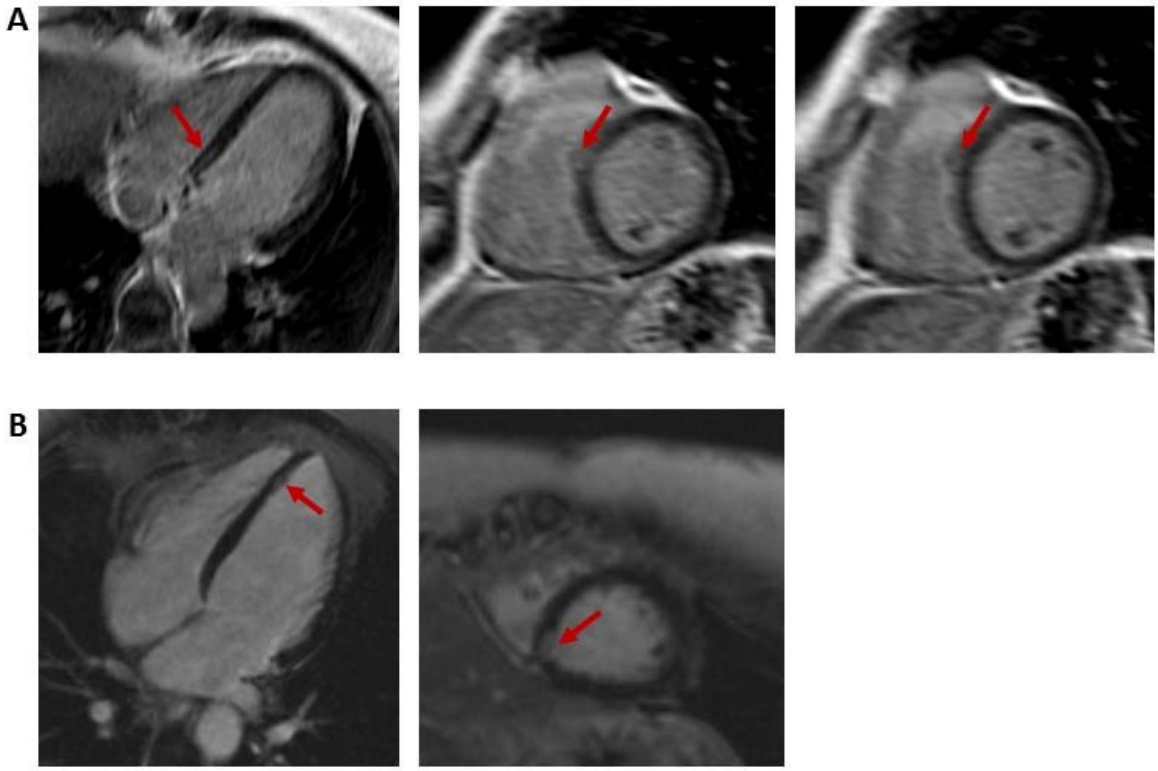
Table S1: Variants of uncertain significance found in patients with MAD/MVP

Patient	**Mutation**	**Gene**		
IVF survivor 3	VUS	TMEM43	c.428C>T	p.(Thr143Met)
	VUS	DSP	c.3230C>A	p.(Ala1077Glu)
IVF survivor 4	VUS	TTN	c.76352dupC	Pro25452fs

Table S2: morphologic PVC criteria in patients with MAD/MVP

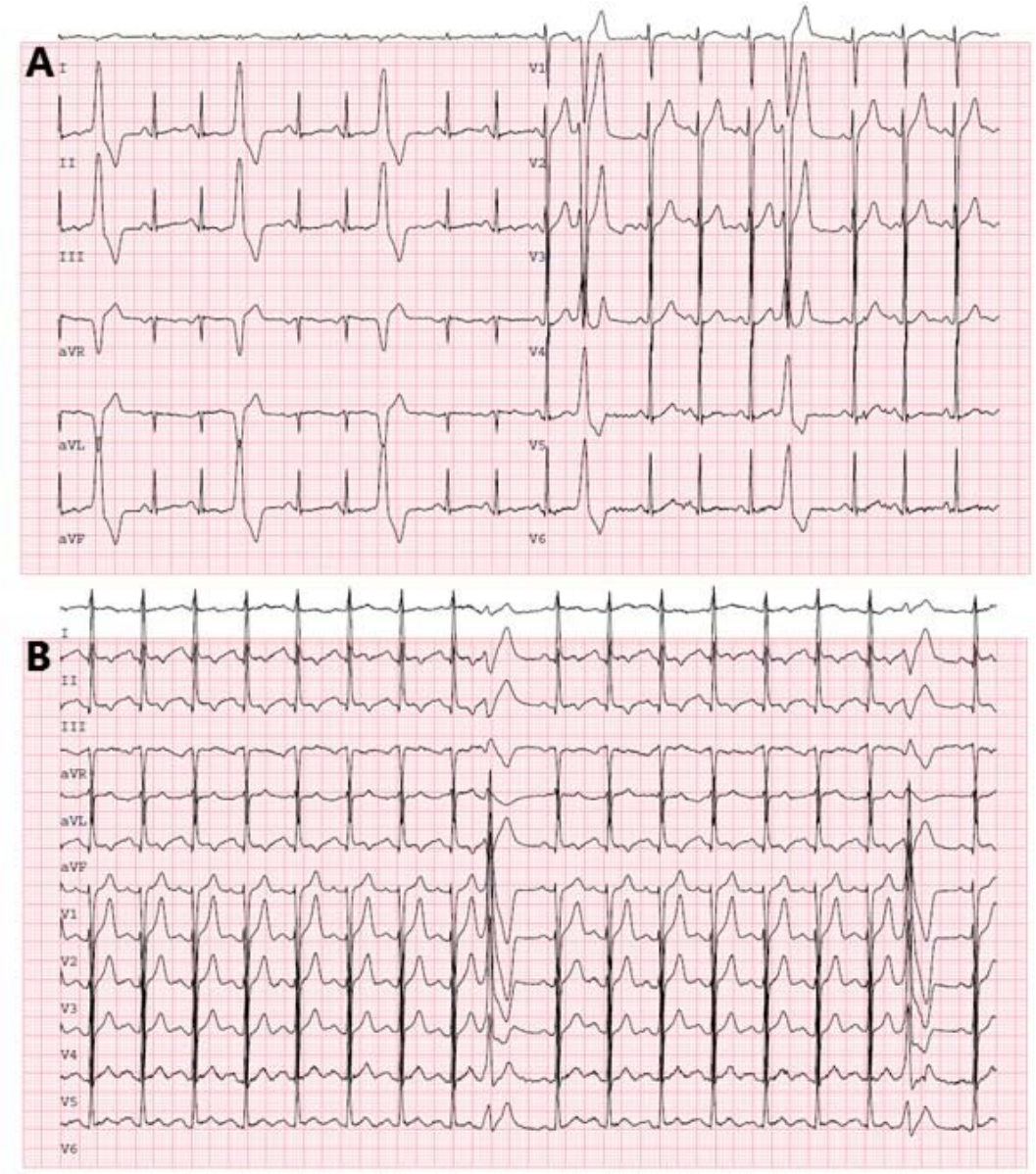
Patient	**VE**	**BBB pattern**	**Precordial transition**	**Axis**	**Estimated origin**
IVF survivor 1	No	N/A	N/A	N/A	N/A
IVF survivor 2	Yes	RBBB	V4	Superior	LV inferoseptal
		LBBB	V5	Inferior	RVOT
IVF survivor 3	No	N/A	N/A	N/A	N/A
IVF survivor 4	Yes	LBBB	V3	Inferior	RVOT (distal)
IVF survivor 5	Yes	RBBB	Positive conc.	Intermediair/ superior	LV mid posterior
IVF survivor 6	Yes	LBBB	V4	Inferior	RVOT (distal)
IVF survivor 7	Yes	RBBB	V5	Superior	LV apex
IVF survivor 8	Yes	LBBB	V4	Inferior	RVOT distal lateral DD LVOT RCC

Figure S1: Example of two IVF patients with LGE



A: One patient with inferolateral MAD showed midwall LGE in the LV basal inferoseptal myocardium. B: One patient without MAD/MVP showed possible basal subendocardial LGE. However, this could also be due to slow flow in a basal crypt.

Figure S2: Example of two patients with MAD/MVP and PVCs



A: The electrocardiogram shows PVCs with a LBBB morphology and an inferior axis of an IVF patient with MAD/MVP. B: The electrocardiogram shows PVCs with an RBBB morphology and a horizontal axis of an IVF patient with MAD/MVP.

Video S1: Representative case of curling in a mitral valve prolapse patient on cine cardiac magnetic resonance. The curling sign is defined as an unusual systolic motion of the inferior mitral annulus on the adjacent ventricular wall.