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The Mitral Annulus Disjunction Arrhythmic Syndrome

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ABSTRACT

BACKGROUND Mitral annulus disjunction (MAD) is an abnormal atrial displacement of the mitral valve leaflet hinge point. MAD has been associated with mitral valve prolapse (MVP) and sudden cardiac death.

OBJECTIVES The purpose of this study was to describe the clinical presentation, MAD morphology, association with MVP, and ventricular arrhythmias in patients with MAD.

METHODS The authors clinically examined patients with MAD. By echocardiography, the authors assessed the presence of MVP and measured MAD distance in parasternal long axis. Using cardiac magnetic resonance (CMR), the authors assessed circumferential MAD in the annular plane, longitudinal MAD distance, and myocardial fibrosis. Aborted cardiac arrest and sustained ventricular tachycardia were defined as severe arrhythmic events.

RESULTS The authors included 116 patients with MAD (age 49 ± 15 years; 60% female). Palpitations were the most common symptom (71%). Severe arrhythmic events occurred in 14 (12%) patients. Longitudinal MAD distance measured by CMR was 3.0 mm (interquartile range [IQR]: 0 to 7.0 mm) and circumferential MAD was 150° (IQR: 90° to 210°). Patients with severe arrhythmic events were younger (age 37 ± 13 years vs. 51 ± 14 years; p = 0.001), had lower ejection fraction (51 ± 5% vs. 57 ± 7%; p = 0.002) and had more frequently papillary muscle fibrosis (4 [36%] vs. 6 [9%]; p = 0.03). MVP was evident in 90 (78%) patients and was not associated with ventricular arrhythmia.

CONCLUSIONS Ventricular arrhythmias were frequent in patients with MAD. A total of 26 (22%) patients with MAD did not have MVP, and MVP was not associated with arrhythmic events, indicating MAD itself as an arrhythmogenic entity. MAD was detected around a large part of the mitral annulus circumference and was interspersed with normal tissue. (J Am Coll Cardiol 2018;72:1600–9) © 2018 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/).

Mitral valve prolapse (MVP) is relatively common, with a prevalence of about 2% and has a good overall prognosis (1–4). However, MVP has been associated with malignant ventricular arrhythmias and sudden cardiac death in a small subset of young and middle-aged patients (5–11). The mechanisms for arrhythmias in patients with MVP are unknown; however, bileaflet MVP, papillary muscle fibrosis, and mitral annulus disjunction (MAD) have been linked to increased arrhythmic risk (9–14).

MAD was first described more than 3 decades ago as an abnormal atrial displacement of the hinge point of the mitral valve away from the ventricular

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myocardium (15), and has since been closely linked to MVP (11,12,16–19). Recent studies demonstrate an association among MAD, ventricular arrhythmia, and papillary muscle fibrosis, but only as a part of MVP disease and not in patients with MAD specifically (11,12,20). Some reports indicate that MAD also may appear without concomitant MVP, but the clinical relevance of this finding is unclear (19–22). Large clinical studies with MAD as the inclusion criterion are lacking, and standardized imaging protocols for detection and quantification of MAD are missing.

The aim of this study was to clinically characterize patients with MAD and to describe the MAD morphology by echocardiography and advanced cardiac magnetic resonance (CMR) imaging. We aimed to explore the relationship between MAD and MVP and to assess potential markers for ventricular arrhythmias.

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METHODS

STUDY POPULATION. In this cross-sectional multicenter study, we screened patients with possible MAD as previously defined (12) by echocardiography at 2 hospitals in Norway, Oslo University Hospital and Drammen Hospital, from August 2015 until June 2017. Sonographers and cardiologists at the 2 recruiting localizations were educated on how to identify MAD. If the echocardiographer suspected MAD, we invited the patient to a comprehensive study protocol evaluation including a new echocardiogram, CMR, 24-h electrocardiogram (ECG) recording, and clinical assessment at Oslo University Hospital. Patients were included if MAD was confirmed by either CMR or study echocardiogram (**Figure 1**).

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.

ECHOCARDIOGRAPHY. Left ventricular and atrial volumes and ejection fraction were measured according to guidelines (Vivid E95 scanner, GE Healthcare, Horten, Norway) (23). Care was taken to identify the mitral annulus and include the basal sections of the left ventricle, but exclude prolapsed volume, in volumetric measurements. Data were analyzed offline (EchoPac version 201, GE Healthcare). MAD distance was measured from the left atrial wall-mitral valve leaflet junction to the top of the left ventricular wall during end-systole in the parasternal long-axis view (**Figure 2**) (12) and was defined as longitudinal MAD distance in the posterolateral wall. Presence of basolateral left ventricular wall curling motion (11,24) was identified by visual assessment (Online Videos 1A [echocardiogram, parasternal long-axis view], 1B [echocardiogram, apical long-axis view], 1C [echocardiogram, apical 4-chamber view], and 2 [CMR, 3-chamber view]). MVP was defined as superior displacement ≥2 mm of any part of the mitral leaflet beyond the mitral annulus according to the American Society of Echocardiography guideline (**Figure 3,** Online Figures 1 to 3) (25,26), and this MVP definition is used in the paper unless otherwise stated. We also classified patients according to the European Society of Cardiology guideline for comparison (27), which defines MVP as superiorly displaced mitral valve coaptation point relative to the mitral ring. We quantified mitral regurgitation according to guidelines (25,27). Echocardiographic analyses were performed by 2 independent echocardiography experts (L.A.D. and E.T.S.) blinded to all clinical data.

CMR IMAGING. The study protocol CMR was performed on a 3-T whole-body scanner (Ingenia, Phillips Healthcare, Best, the Netherlands) with a phased array body coil. To ensure the complete assessment of the mitral annulus circumference, we performed 6 left ventricle long-axis cine sequences with an interslice rotation of 30°. The first projection was aligned through the superior right ventricular free wall insertion into the septum, and was defined as 0° in the annular plane, followed by clockwise labeling of the long-axis slices. Longitudinal MAD distance was measured from the left atrial wall-mitral valve leaflet junction to the top of the left ventricular wall during at end-systole in all long-axis cine sequences and was defined as present if ≥1.0 mm. Longitudinal MAD distance in the posterolateral wall was measured at 120°. The circumferential extent of tissue disjunction along the mitral annulus was obtained from the combination of the 6 long-axis and was defined as circumferential MAD and expressed in degrees of the mitral annulus (Online Figure 4).

We recorded presence of late gadolinium enhancement in the left ventricular myocardium and the papillary muscles. Prior CMR examinations, if available, were analyzed for late gadolinium enhancement (n = 16) and for longitudinal MAD (n = 18) in patients who were not eligible for the study protocol CMR.

VENTRICULAR ARRHYTHMIAS. Patients with aborted cardiac arrest underwent thorough diagnostic workup, including genetic testing for channelopathies

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

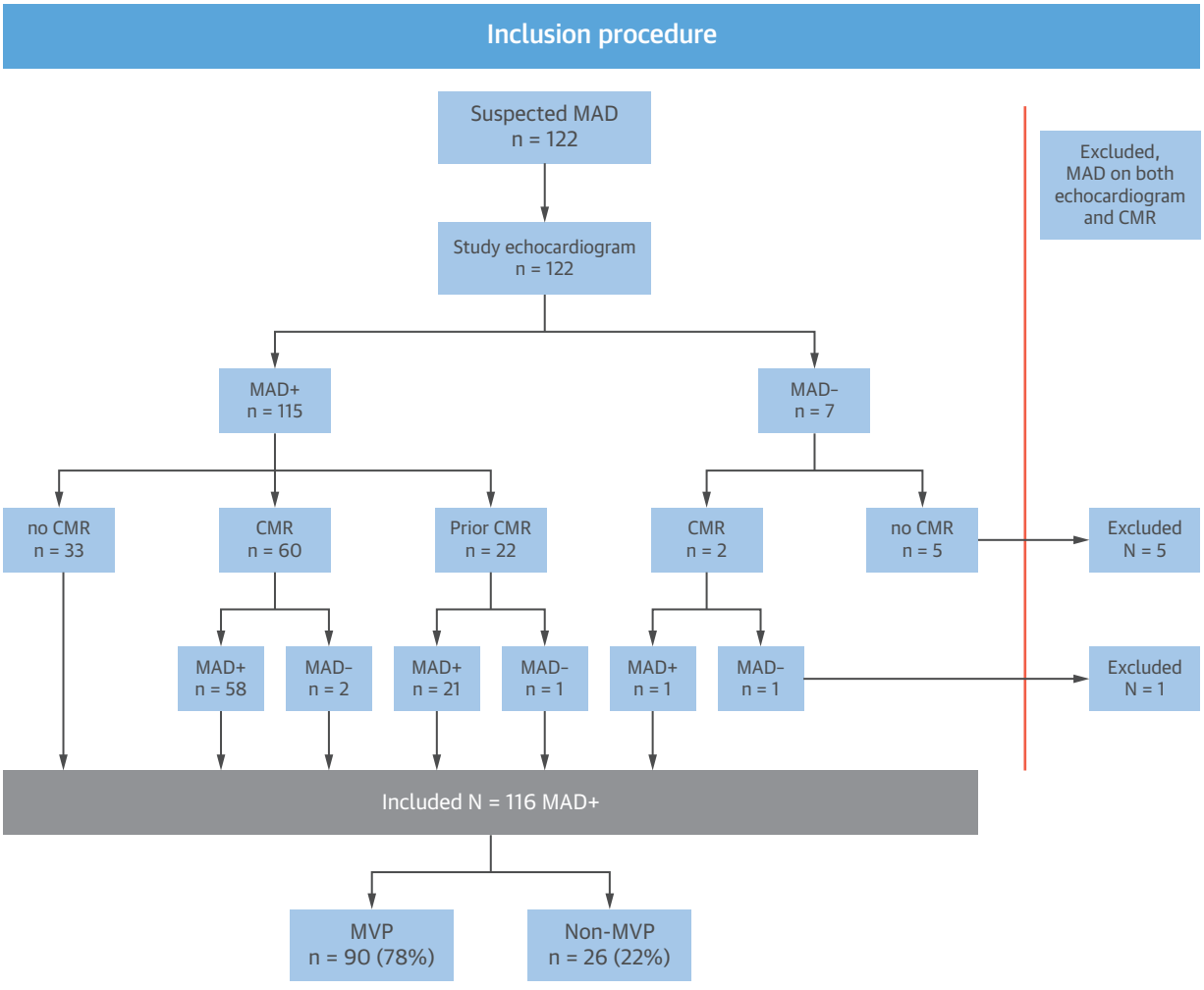
ECG = electrocardiogram

IQR = interquartile range

MAD = mitral annulus disjunction

MVP = mitral valve prolapse

FIGURE 1 Study Flow Chart

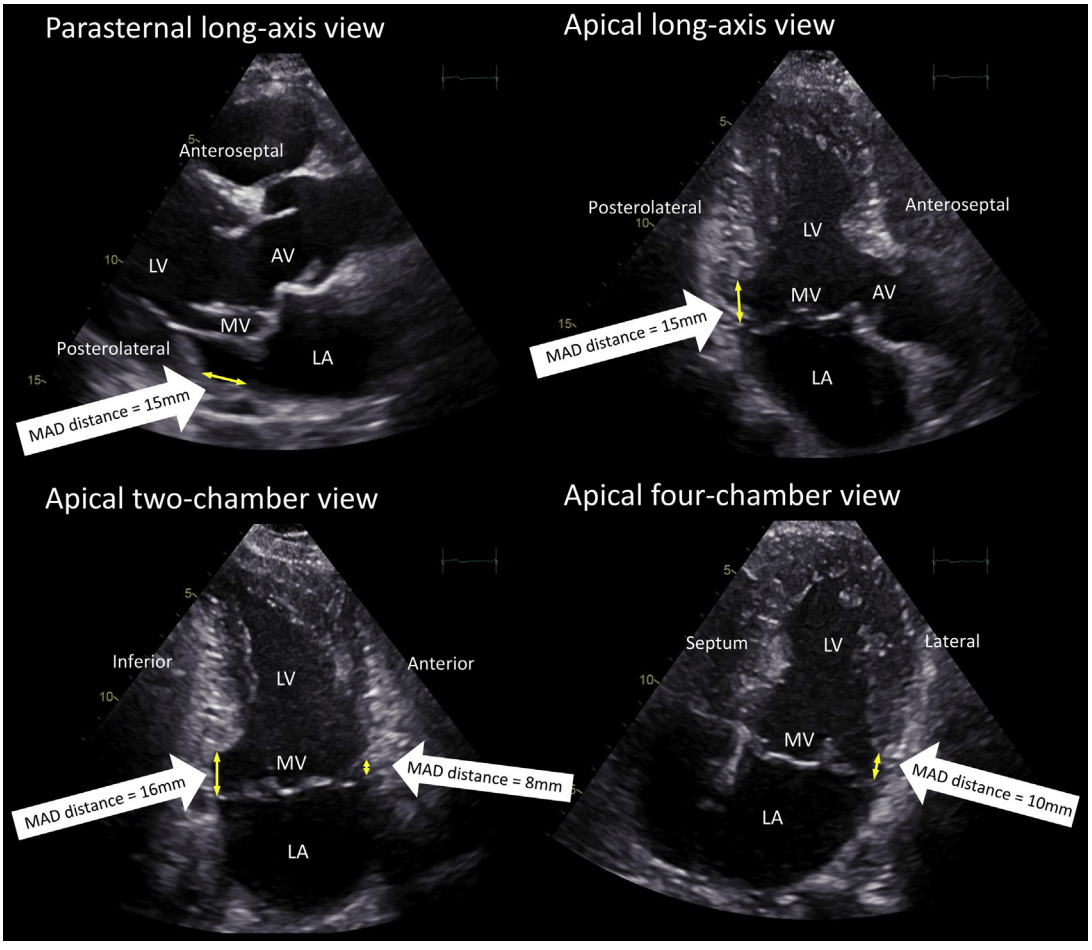


Patients with suspected mitral annulus disjunction (MAD) underwent a multimodality imaging study evaluation before inclusion. Patients were included if MAD was detected in any imaging modality. Echocardiography was performed in all included patients (n = 116), and CMR study protocol in 62 patients. One patient was excluded because MAD could not be confirmed either by echocardiography or CMR. Therefore, 61 patients were eligible for evaluation of circumferential MAD. Additionally, 22 patients had prior CMR examinations with a standard clinical protocol, leaving 83 patients who were evaluated for longitudinal MAD. CMR = cardiac magnetic resonance; MAD = mitral annulus disjunction; MAD+ = mitral annulus disjunction present; MAD– = mitral annulus disjunction not present; MVP = mitral valve prolapse.

and cardiomyopathies to exclude other etiologies of the event. Aborted cardiac arrest and sustained ventricular tachycardia (ventricular rhythm >100 beats/min lasting >30 s) were defined as severe arrhythmic events. Ventricular arrhythmia was defined as a history of severe arrhythmic events in addition to non-sustained ventricular tachycardia (≥3 consecutive ventricular beats <30 s with heart rate >100 beats/min). Data on ventricular arrhythmia were collected from 24-h ECG recordings during study evaluation and from exercise-ECG, telemetry, cardiac devices, and medical records.

STATISTICAL ANALYSIS. Parametric data were presented as mean ± SD, median (interquartile range [IQR]) or number (%). Comparisons were performed using Student's *t*-test, Mann-Whitney *U* test, or Fisher exact test as appropriate. Univariate logistic regression was used to identify markers of ventricular arrhythmia and severe arrhythmic events, and multivariate analysis included significant ($p < 0.05$) variables from the univariate analyses SPSS version 24.0 (SPSS Inc., Chicago, Illinois). Correlation analyses were made using Spearman's rho. Two-sided p values <0.05 were considered significant.

FIGURE 2 Measurement of Longitudinal MAD Distance in a Transthoracic Echocardiogram



All pictures are at end-systole. Longitudinal MAD distance in the posterolateral wall is measured in parasternal long-axis view. **Yellow arrows** = longitudinal MAD measurement. AV = aortic valve; LA = left atrium; LV = left ventricle; MAD = mitral annulus disjunction; MV = mitral valve. See Online Videos 1A, 1B, 1C.

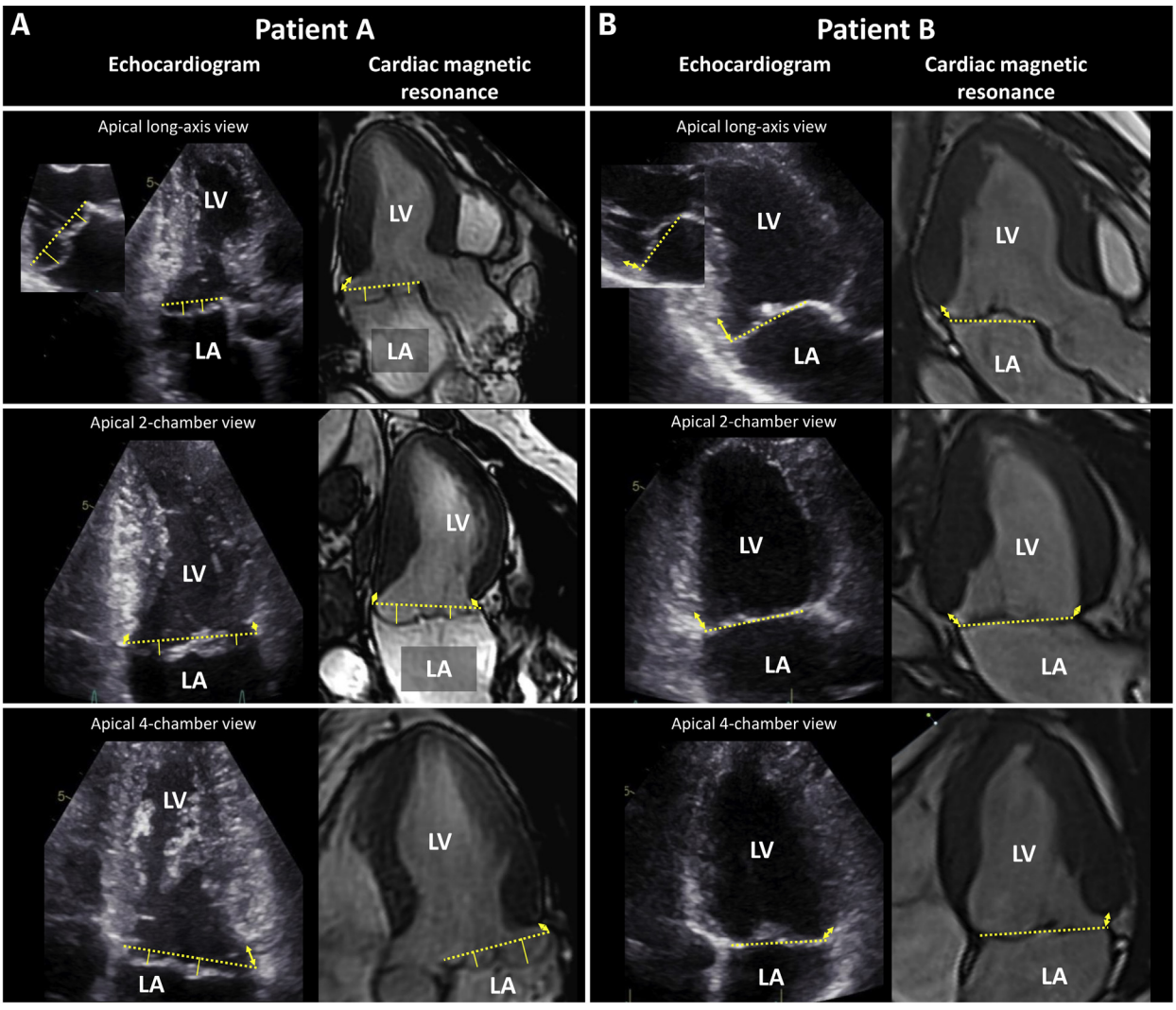
RESULTS

STUDY POPULATION. We screened 122 patients with suspected MAD by a standard clinical echocardiogram and could confirm the presence of MAD in 116 (95%) patients by our study protocol echocardiogram or CMR (**Figure 1**).

The most common indications for the screening echocardiograms were valvular heart disease follow-up (34%), evaluation for cardiac arrhythmias (23%), or palpitations (12%) (Online Table 1). A total of 82 (71%) patients reported palpitations, 47 (41%) patients reported previous pre-syncope, 40 (34%) had ventricular arrhythmia, 15 (13%) had experienced syncope, and 14 (12%) patients had experienced a severe arrhythmic event prior to inclusion (**Table 1,** Online Table 2). Study protocol 24-h ECG was obtained in 81 (70%) patients (66% without ventricular arrhythmia and 78% with ventricular arrhythmia; $p = 0.21$).

MITRAL ANNULUS DISJUNCTION ANATOMY. The typical curling motion of the basolateral left ventricular wall in patients with MAD is demonstrated in Online Videos 1A, 1B, 1C (echocardiogram) and 2 (CMR). In all, 83 (72%) patients had CMR studies (n = 77 with gadolinium contrast examinations). The maximum longitudinal MAD distance by CMR was 7.9 ± 3.2 mm and was most frequently located in the anterior wall (n = 16 [28%]), inferior wall (n = 15 [26%]), or posterolateral wall (n = 5 [9%]).

FIGURE 3 Echocardiogram and Corresponding Cardiac Magnetic Resonance Images of 2 Patients With MAD



(A and B) All pictures are at end-systole. **Yellow dotted lines** demarcate the mitral annulus; **yellow arrows** indicate longitudinal MAD distance where present; **yellow solid lines** are prolapse depth where present. Patient A has mitral valve prolapse, mild mitral regurgitation, and no documented ventricular arrhythmias. Patient B has no mitral valve prolapse, mild mitral regurgitation, and previous aborted cardiac arrest. Abbreviations as in **Figure 2**. See Online Videos 1A, 1B, 1C and 2.

Circumferential MAD by CMR varied from 30° to 240°, with a median of 150° in those with MAD visible on CMR (n = 59). Circumferential MAD was exclusively found along the posterior mitral valve leaflet hinge point and not along the sector of the anterior mitral valve leaflet, where the leaflet hinge point anatomically is connected to the mitral-aortic continuum. Longitudinal MAD distance varied along the mitral annulus circumference, from 1 mm up to 15 mm in the individual patient. In 33 (52%) patients, MAD was scattered around the circumference with interspersed apparently normal annulus tissue. Although there was almost complete concordance between CMR and echocardiography in assessing prevalence of MAD (**Figure 1**), there was only a moderate correlation between absolute longitudinal MAD distance measurements ($R = 0.47$; $p < 0.001$ for longitudinal MAD distance in the posterolateral wall by CMR vs. echocardiography).

MITRAL VALVE PROLAPSE IN PATIENTS WITH MAD. MVP was present in 90 (78%) patients, and interestingly, was absent in 26 (22%) patients with MAD (**Table 1, Figures 1 and 3**). The number of premature ventricular contractions per 24 h (187 [IQR: 33 to 1,035] vs. 267

TABLE 1 Characteristics of Patients With MAD and Severe Arrhythmic Events (n = 14) and No Severe Arrhythmic Events (n = 102)

	Total (N = 116)	No Severe Arrhythmic Events* (n = 102)	Severe Arrhythmic Events* (n = 14)	p Value	OR†	95% CI	p Value
Age, yrs	49 ± 15	51 ± 14	37 ± 13	0.001	0.93	0.89–0.97	0.002
Female	70 (60)	61 (60)	9 (64)	1.00			
Implantable cardiac-defibrillator	13 (11)	2 (2)	11 (79)	<0.001			
Symptoms							
NYHA functional class							
I	85 (73)	75 (74)	10 (71)	Ref			
II	25 (22)	21 (21)	4 (29)	0.73			
III	6 (5)	6 (6)	0 (0)	1.00			
IV	0 (0)						
Reported symptoms							
Chest pain	33 (28)	30 (29)	3 (21)	0.75			
Palpitations	82 (71)	73 (72)	9 (64)	0.55			
Pre-syncope	47 (41)	43 (42)	4 (29)	0.40			
Syncope	15 (13)	13 (13)	2 (14)	1.00			
Arrhythmia							
Aborted cardiac arrest	10 (9)	0 (0)	10 (71)	N/A			
Ventricular tachycardia	4 (3)	0 (0)	4 (29)	N/A			
Nonsustained ventricular tachycardia	26 (22)	26 (25)	6 (43)	0.10			
Premature ventricular contractions per 24 h	238 (41–875)	188 (33–761)	572 (72–5,114)	0.56			
Atrial fibrillation	19 (16)	19 (19)	0 (0)	0.12			
Echocardiography							
Ejection fraction, %	56 ± 7	57 ± 7	51 ± 5	0.002	0.86	0.77–0.96	0.008
Left ventricular end-diastolic volume, ml	135 ± 44	137 ± 44	123 ± 39	0.27			
Longitudinal MAD in posterolateral wall, presence	96 (83)	83 (81)	13 (93)	0.46			
Longitudinal MAD distance in posterolateral wall, mm	6.0 (2.0–8.0)	6.0 (2.0–8.0)	6.0 (4.0–10.0)	0.19			
Mitral regurgitation							
Effective regurgitant orifice area, cm^2	0.05 (0–0.19)	0.05 (0–0.20)	0.04 (0–0.10)	0.38			
Grade 0	36 (31)	32 (31)	4 (29)	Ref			
Grade 1	42 (36)	35 (34)	7 (50)	0.53			
Grade 2	20 (17)	18 (18)	2 (14)	1.00			
Grade 3	18 (16)	17 (17)	1 (7)	0.67			
Mitral valve prolapse (ASE)	90 (78)	84 (82)	6 (43)	0.003	0.22	0.06–0.75	0.02
Bileaflet mitral valve prolapse (ASE)	55 (47)	50 (49)	5 (36)	0.40			
Mitral valve prolapse (ESC)	63 (54)	59 (58)	4 (29)	0.048	0.49	0.13–1.82	0.29
Cardiac magnetic resonance							
Circumferential MAD, °‡	150 (90–210)	150 (90–210)	120 (120–120)	N/A			
Longitudinal MAD distance in posterolateral wall, mm§	3.0 (0–7.0)	3.0 (0–7.0)	5.0 (0–6.0)	0.62			
LGE‖	29 (38)	24 (37)	5 (46)	0.74			
LGE in LV myocardium§	13 (17)	12 (19)	1 (9)	0.68			
LGE in anterolateral papillary muscle§	10 (13)	6 (9)	4 (36)	0.03	7.35	1.15–47.02	0.04
LGE in posteromedial papillary muscle§	16 (21)	13 (20)	3 (27)	0.69			

Values are mean ± SD, n (%), or median (interquartile range). p values are calculated by Student's *t*-test, Mann-Whitney *U* test, or Fisher exact test as appropriate. *Aborted cardiac arrest and sustained ventricular tachycardia were defined as severe arrhythmic events. †Adjusted odds ratio (OR) by multivariate logistic regression. Ejection fraction, mitral valve prolapse, and LGE in anterolateral papillary muscle are adjusted for age. ‡n = 61 (3 patients with severe arrhythmic events and 58 patients with no severe arrhythmic events) underwent CMR with study protocol and possibility to assess circumferential MAD, and no statistical comparisons have been performed in this group. §n = 77 (11 patients with severe arrhythmic events and 66 patients with no severe arrhythmic events) underwent CMR with LGE. ‖n = 79 (10 patients with severe arrhythmic events and 69 patients with no severe arrhythmic events) underwent CMR with 3-chamber long-axis projection and possibility to assess longitudinal MAD in the posterolateral wall.

ASE = American Society of Echocardiography; CMR = cardiac magnetic resonance; CI = confidence interval; ESC = European Society of Cardiology; LGE = late gadolinium enhancement; MAD = mitral annulus disjunction; N/A = not applicable; ref = reference.

[IQR: 56 to 867]; p = 0.72) and the prevalence of ventricular arrhythmia (n = 30 [33%] vs. n = 10 [39%]; p = 0.65) did not differ between MAD patients with and without concomitant MVP. MAD patients with MVP were older than those without MVP (age 51 ± 14 years vs. 43 ± 15 years; p = 0.02), more frequently had moderate or severe mitral regurgitation (n = 36 [40%] vs. n = 2 [8%]; p = 0.002), had larger left ventricular end-diastolic volume (140 ± 44 ml vs. 118 ± 37 ml; p = 0.02), and had a nonsignificant trend toward higher ejection fraction (57% ± 7% vs. 54% ± 6%; p = 0.07). There were no significant differences

between MAD patients with and without MVP with regard to longitudinal MAD distance in the posterolateral wall assessed by CMR (5.0 mm [IQR: 0 to 7.0 mm] vs. 1.0 mm [IQR: 0 to 5.0 mm]; $p = 0.09$) or circumferential MAD (150° [IQR: 90° to 210°] vs. 120° [IQR: 75° to 180°]; $p = 0.23$).

By applying the more conservative European Society of Cardiology definition of mitral valve prolapse, only 63 (54%) patients with MAD had MVP. Similarly to MVP defined by the American Society of Echocardiography guideline, there was no difference in prevalence of ventricular arrhythmias between MAD patients with and without concomitant MVP by the European definition (**Table 1**, Online Table 2).

FREQUENCY AND MARKERS OF VENTRICULAR ARRHYTHMIA. Fourteen patients had experienced severe arrhythmic events prior to inclusion (10 with aborted cardiac arrest and 4 with sustained ventricular tachycardia) (**Table 1**, Online Table 3). Cardiac arrest had occurred at wakeful rest in 3, during leisure activity in 3, during exercise in 3, and at induction of general anesthesia in 1. Sustained ventricular tachycardia occurred at wakeful rest in all 4. None of the patients with aborted cardiac arrest had consulted a cardiologist prior to the event, and diagnostic work-up revealed no other etiology of cardiac arrest. Interestingly, absence of concomitant MVP was associated with severe arrhythmic events, along with younger age, lower ejection fraction, and papillary muscle fibrosis (**Table 1**).

In all, 40 (34%) patients had ventricular arrhythmias by our definition (severe arrhythmic events or nonsustained ventricular tachycardia). Markers of ventricular arrhythmia were younger age, previous syncope, more premature ventricular contractions, papillary muscle fibrosis, and larger longitudinal MAD distance in the posterolateral wall assessed by CMR (Online Table 2). Longitudinal MAD distance in the posterolateral wall and papillary muscle fibrosis assessed by CMR remained markers of ventricular arrhythmia in multivariate analysis (Online Table 2). Longitudinal MAD distance in the posterolateral wall by CMR correlated with premature ventricular contractions per 24 h (rho = 0.46; $p < 0.001$).

DISCUSSION

Our study demonstrates novel findings in patients with MAD and adds an important delineation of MAD to the overlapping mitral valve syndromes. The most important finding was the high occurrence of ventricular arrhythmias in patients with MAD, independently of concomitant MVP (**Central Illustration**). One-tenth of patients had life threatening arrhythmic events, and frequent premature ventricular contractions was the most common cause of seeking medical advice. One-fifth of the patients did not have MVP, suggesting that MAD is related to symptomatic disease and arrhythmogenesis independent of concomitant MVP. We showed that MAD is a 3-dimensional circumferential continuum interspersed with regions of apparently normal mitral annulus, but with a considerable interindividual variation.

CLINICAL PRESENTATION AND VENTRICULAR ARRHYTHMIAS. Palpitations were by far the most commonly reported symptom, and frequent premature ventricular contractions were detected in the majority of patients. Frequent premature ventricular contractions are common in the general population, with a multifactorial etiology and most often with a benign prognosis. However, a subset of these patients may have underlying MAD with increased risk of arrhythmic events, and these patients can easily be identified by echocardiography.

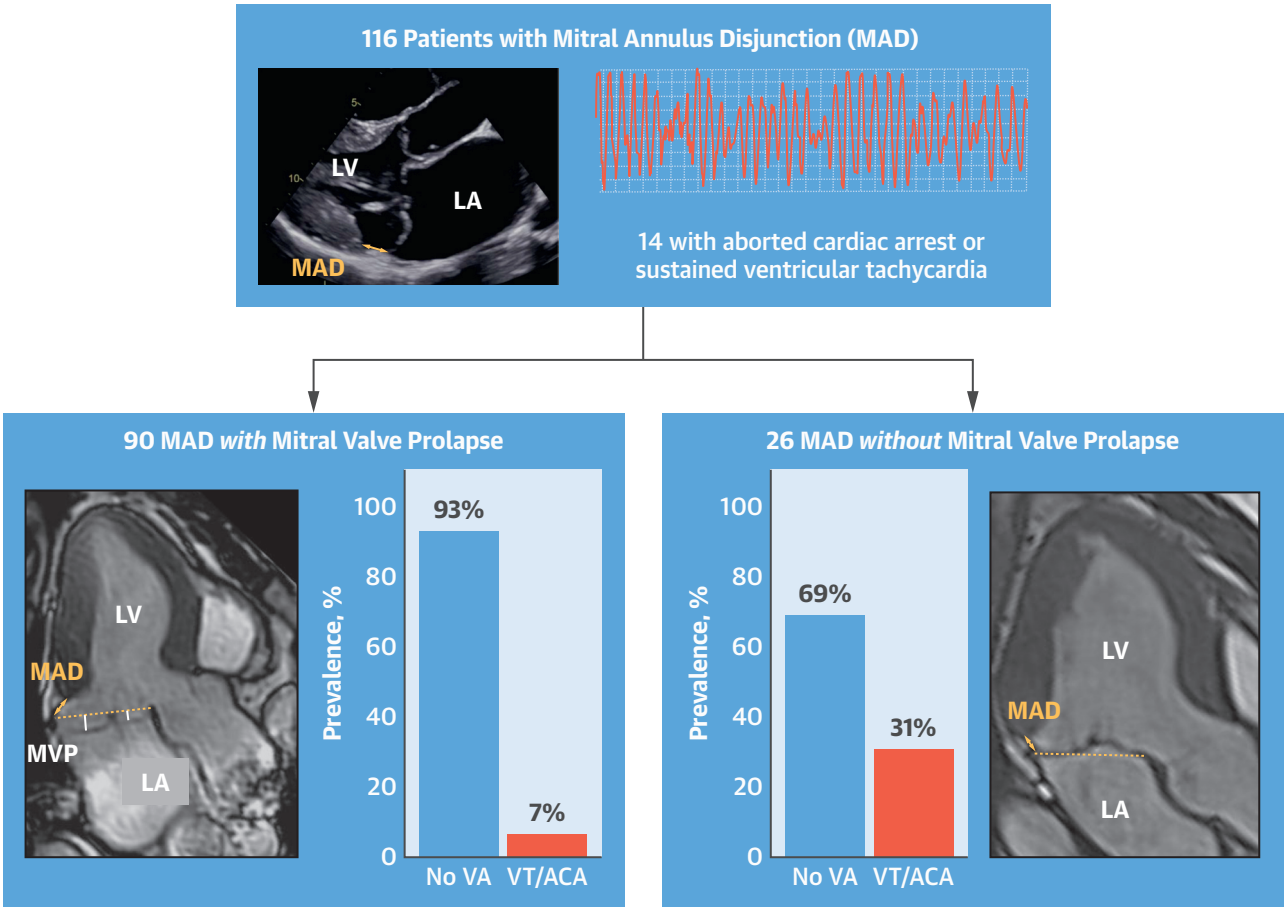
We identified young age, lower ejection fraction, and papillary muscle fibrosis as markers for severe arrhythmic events. However, we acknowledge that the relatively low number of severe arrhythmic events limits the interpretation of these risk factors and that lower ejection fraction may be a result of the aborted cardiac arrest rather than a prerequisite.

Interestingly, MAD patients with MVP were less likely to have experienced severe arrhythmic events, although the presence of MVP did not exclude severe arrhythmic events (**Central Illustration**). This finding may be explained by the closer follow-up of patients with concomitant MVP allowing identification of individuals at risk and appropriate treatment. Furthermore, a selection bias by a higher referral rate to our center of patients with unexplained aborted cardiac arrest is a possible explanation. Nevertheless, it is of utmost importance that a finding of MAD itself, even without concomitant MVP, is a clear risk marker of arrhythmic events. In the absence of other known risk factors for sudden cardiac death, our findings suggest the existence of a novel clinical syndrome, that is, MAD arrhythmic syndrome.

Greater longitudinal MAD distance located in the posterolateral wall assessed by CMR was an independent risk marker for all ventricular arrhythmias (severe arrhythmic event and nonsustained ventricular tachycardia). This parameter can easily be measured from current standard CMR studies. The clinical importance of this finding, however, remains to be determined, because this endpoint also included relatively benign arrhythmias.

Recent studies have hypothesized papillary muscle fibrosis and stretch as arrhythmic mechanisms in

CENTRAL ILLUSTRATION **Mitral Annulus Disjunction (MAD) Arrhythmic Syndrome**



Dejgaard, L.A. et al. J Am Coll Cardiol. 2018;72(14):1600–9.

One hundred and sixteen patients with mitral annulus disjunction (MAD) were enrolled in the study, of which 14 had experienced aborted cardiac arrest (ACA) or sustained ventricular tachycardia (VT) **(top)**. **(Top left)** An echocardiogram with pronounced MAD. **(Top right)** An original electrocardiogram (ECG) from an implantable loop recorder from one of the study participants. A total of 90 patients with MAD had concomitant mitral valve prolapse (MVP) **(bottom left)**, while 26 patients with MAD did not have MVP **(bottom right)**. Severe ventricular arrhythmias (ACA or VT) were frequent in the study participants, and were more prevalent in MAD without MVP, chi-square test, $p = 0.003$.

patients with MVP (9,10). This theory is supported by observations of premature ventricular contractions originating from the papillary muscles and from the mitral annulus in patients with MVP (9,10,13,28-30). Interestingly, our study supports an association between papillary muscle fibrosis and severe arrhythmic events, and we show an association among premature ventricular contractions, severe arrhythmic events, and MAD independently of concomitant MVP. Therefore, our study indicates that MAD itself may play an important role in arrhythmogenesis.

It has been debated whether the risk of ventricular arrhythmia in patients with MVP and mitral regurgitation changes after mitral valve surgery (31,32). A reduction in mitral regurgitation could play a role in mitigating arrhythmic risk by decreased left ventricular overload. Further studies are needed to address these issues.

MITRAL ANNULUS DISJUNCTION AND RELATION TO MITRAL VALVE PROLAPSE. MAD has previously been described as a finding connected to MVP. Our study is the first large clinical trial on patients with MAD as the inclusion criterion. We demonstrated that 22% of our patients with MAD did not have MVP. Our novel findings suggest a spectrum of mitral valve involvement in patients with MAD. Still, the causality

among MAD, MVP, and mitral ring dysfunction is unclear (11,18). We speculate that MAD may be a precursor of degenerative mitral valve disease and of MVP. The disjunctive areas along the mitral annulus may represent weak spots vulnerable for long-standing mechanical stress, as age and larger longitudinal MAD distance in the posterolateral wall were associated with MVP. Development of MVP would assume additional pathology in the other parts of the mitral valve apparatus, such as degeneration of chordae and valve leaflets (33). However, not all MVP patients have concomitant MAD (18), and we show that MAD occurs without MVP, indicating that MAD and MVP can be separate disease entities and that the mitral valves can remain normal in patients with MAD.

MAD IN 3 DIMENSIONS. We described MAD anatomically and used a focused CMR protocol in this study, which facilitated the assessment of the entire mitral annulus. Therefore, we were able to report that MAD can be present in up to two-thirds of the mitral ring circumference, which is more extensive than previously described (18). Furthermore, longitudinal MAD distance varied considerably along the annulus circumference, and a large proportion of the patients had interpolated segments of nondisjunctive annulus along the circumference.

To what extent MAD represents abnormal or normal variation in embryological development or is an expression of mitral valve ring disease has been debated in postmortem studies (15,19,21,22). The traits of the tissue in the MAD zone (i.e., between the ventricular myocardium and the mitral valve hinge points) remains unsatisfactory explained. Pathoanatomical studies have shown fibrotic mitral annulus tissue, but possible electrical capabilities and direct involvement in arrhythmogenesis remain elusive (11,15,19).

CLINICAL IMPLICATIONS. MAD was associated with ventricular arrhythmias ranging from frequent premature ventricular contractions to cardiac arrest. Physicians should consider MAD in younger patients with no other apparent cause for premature ventricular contractions and refer these patients to an echocardiographic study. MAD is readily detectable by echocardiography, with the typical curling motion of the left ventricular basal posterolateral wall. Importantly, in patients with incidental findings of MAD, a careful history of palpitations, syncope, and 24-h ECG recording may be appropriate. Furthermore, physicians should be attentive to possible MAD in patients followed for MVP and mitral regurgitation. CMR may add to risk stratification by detecting papillary muscle fibrosis and measuring longitudinal MAD distance in the posterolateral wall. Future studies should evaluate pharmaceutical and device therapy in these patients.

STUDY LIMITATIONS. This study had a cross-sectional design, and arrhythmic events were partly collected retrospectively. As we included symptomatic patients seeking medical advice, we cannot evaluate the MAD prevalence or arrhythmic risk in MAD patients in the general population. Increased awareness of MAD and alertness toward a possible connection with arrhythmias in the recruiting centers represent possible selection biases, and the clinical presentation of patients with MAD should be investigated in larger and unselected populations. The 24-h ECG recordings were not performed in all patients; however, there was no difference between frequency of 24-h ECG recordings in patients with or without arrhythmias.

Ejection fraction is, among several factors, dependent on grade of mitral regurgitation. Systolic "curling motion" of the posterolateral left ventricular wall may result in smaller end-systolic volume, resulting in a slightly higher EF. This is particularly likely to occur if care is not taken during volumetric measurements to correctly identify a superiorly displaced mitral annulus in patients with MAD. A few patients with severe arrhythmic events had an implantable cardiac-defibrillator at inclusion and were not eligible for the CMR study protocol, and may therefore have been under-represented in studies on circumferential MAD.

CONCLUSIONS

Patients with MAD presented with frequent premature ventricular contractions; one-third had ventricular arrhythmias and one-tenth had severe arrhythmic events. A total of 22% of the patients with MAD did not have MVP, and arrhythmias were frequent irrespective of MVP, indicating an arrhythmic risk of MAD itself. MAD was detected around a large part of the mitral annulus circumference, with considerable individual variation and with interpolated nondisjunctive annulus.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: MAD identified by echocardiography or magnetic resonance imaging can involve varied proportions of the annular circumference with or without overt mitral prolapse and is associated with ventricular arrhythmias.

TRANSLATIONAL OUTLOOK: Future studies should address the cause of MAD and the mechanism of arrhythmias to which patients with this condition are prone.

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

APPENDIX For supplemental videos, figures, and tables, please see the online version of this paper.