Usefulness of 3-Tesla Cardiac Magnetic Resonance to Detect Mitral Annular Disjunction in Patients With Mitral Valve Prolapse

Benjamin Essayagh, MD[a], Laura Iacuzio, MD[a], Filippo Civaia, MD[a], Jean-Francois Avierinos, MD, PhD[b], Christophe Tribouilloy, MD, PhD[c,d], and Franck Levy, MD[a,*]

Mitral annulus disjunction (MAD) is characterized by a separation between the atrial wall mitral junction and the left ventricular (LV) free wall. Little is known regarding cardiac magnetic resonance (CMR) performance to detect MAD and its prevalence in mitral valve prolapse (MVP). Based on 89 MVP patients (63 women; mean age 64 ± 13) referred for CMR assessment of MR, either from myxomatous mitral valve disease (MMVP) (n = 40; 45%) or fibroelastic disease (n = 49; 55%), we sought to assess the frequency of MAD and its consequences on LV morphology. Patients were classified in 2 groups according to MAD presence (MAD+) or absence (MAD−). MAD (measuring 8 ± 4 mm) was diagnosed in 35% (31 of 89) of MVP patients, more frequently in MMVP than fibroelastic disease (60% vs 14%). MAD+ was associated with MMVP; bileaflet MVP and nonsustain ventricular tachycardia but not with the severity of MR. Diagnostic accuracy of transthoracic echocardiography for the detection of MAD was fair (65% sensitivity, 96% specificity) with CMR as reference. MAD+ showed significantly enlarged basal and mid LV diameters and enlarged mitral-annulus diameter. In patients with late gadolinium enhancement, presence of LV fibrosis at level of papillary muscle was more frequent in MAD+. After adjustment on age and MR severity, MMVP, and enlarged end-systolic mitral annulus diameter were independently associated with MAD+. In conclusion, MAD was present in about 1/3 of MVP patients, mostly in MMVP and independent of MR severity. Enlarged mitral-annulus and basal LV diameters, nonsustain ventricular tachycardia and papillary muscle fibrosis were associated with MAD presence. **(Am J Cardiol 2019;124:1725−1730)**

Degenerative mitral regurgitation (MR), defined as prolapse of at least one leaflet, is one of the most prevalent valvular disease requiring surgery in Europe.[1−3] Any abnormality of the mitral valve components including leaflets, mitral annulus (MA), subvalvular apparatus, left ventricle (LV), and left atrium (LA), may lead to mitral valve dysfunction.[4] Mitral annulus disjunction (MAD) is characterized by a detachment of the roots of MA from the LV myocardium, leading to a separation between the atrial wall mitral junction and LV free wall. MAD is mostly associated with myxomatous mitral valve prolapse (MMVP) but is also found in fibroelastic disease (FED),[5−7] though most studies excluded non-MMVP patients. Recent data suggest that MAD could be associated to LV morphological and functional remodeling including myocardial hypertrophy or fibrosis, which could be the substrate of ventricular arrhythmias and sudden cardiac death. Echocardiography is the first-line imaging method but shows several limitations such as misalignment or insufficient image quality. Recent echocardiographic studies reported conflicting results on prevalence, consequences, and significance of MAD. Cardiac magnetic resonance (CMR) provides unique morphological information and is considered a gold standard for cardiac chamber quantification. Thus, the aim of this study using CMR was to assess the frequency of MAD and its consequences on LV morphology in MVP patients.

Methods

The study was conducted at the Monaco Heart center, Monaco. We, retrospectively evaluated 89 patients with echocardiographic diagnosis of MVP, consecutively referred for CMR assessment of MR, over a 24-months period. Exclusion criteria were more than mild aortic stenosis, aortic regurgitation or mitral stenosis, intracardiac shunt, and standard contraindications to CMR. Institutional review board approval was obtained before conducting the study. The study was conducted in accordance with institutional policies, national legislation, and the revised Helsinki declaration. MVP etiology was either MMVP (n = 40) or FED (n = 49). MMVP and FED were defined according to current description.[8] Bileaflet prolapse was defined as the prolapse of the anterior and the posterior MV leaflet, by opposition to the prolapse of the posterior MV leaflet only.[9] All patients underwent a comprehensive CMR study. Patients were imaged with a 3-Tesla Siemens Skyra scanner (Siemens; Erlangen, Germany), 18 channels body flex coils

[a]Centre Cardiothoracique de Monaco, Monaco; [b]Department of Cardiology, University Hospital La Timone, Marseille, France; [c]Department of Cardiology, University Hospital Amiens, Amiens, France; and [d]INSERM U-1088, Jules Verne University of Picardie, Amiens, France. Manuscript received July 15, 2019; revised manuscript received and accepted August 26, 2019.

See page 1730 for disclosure information.

*Corresponding author: Tel: (+377) 92 16 80 00; fax: (+377) 92 16 82 99.
E-mail address: flevy@ccm.mc (F. Levy).

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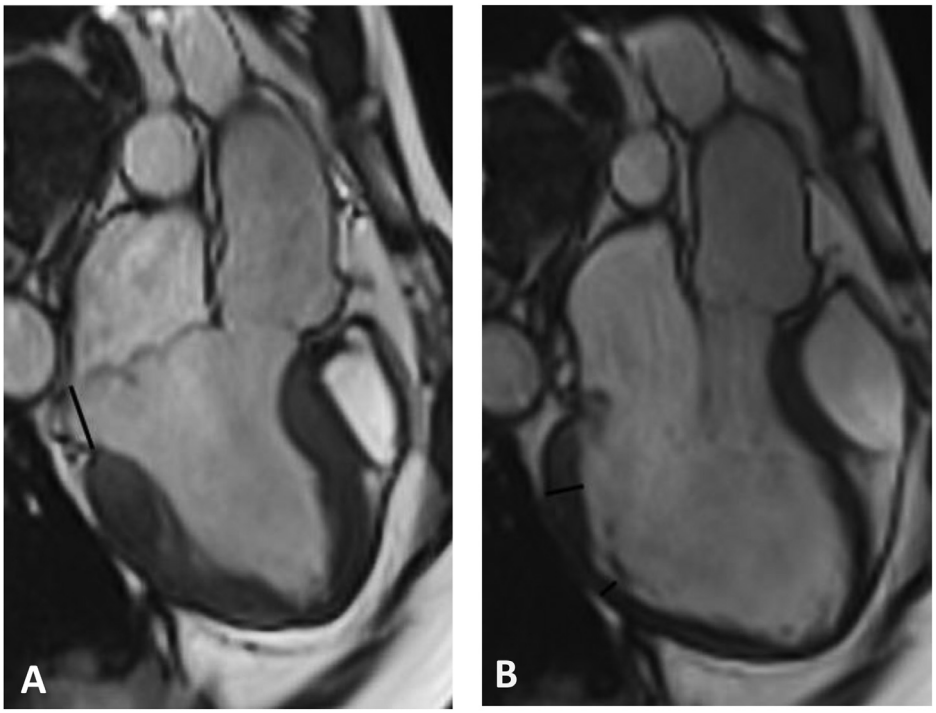

Figure 1. Cardiac magnetic resonance measures in patients with mitral valve prolapse. (*A*) On 3-chamber view long-axis views, length of MAD was measured from the left atrium-posterior mitral valve leaflet junction to the top of the LV wall during in end-systole, and (*B*) LV wall thickness was measured during end-diastole at base and mid-ventricular segment posterior wall.

and 45 mT/m gradients. Assessment of cardiac function was performed with a cine steady-state free precession pulse sequence, with retrospective gating, in end-expiration breath-hold. The following projections were acquired: 2-chamber, 4-chamber, parallel contiguous short axis (to cover the entire LV from the mitral plane to the apex). On the cine images, LV ejection fraction, LV mass, end-diastolic, and end-systolic volumes were calculated using the standard formula. Data were analyzed by dedicated software Circle CVI 42 (version 5.1 Circle Cardiovascular Imaging, Calgary, Canada). Aortic phase contrast was performed 10 mm above the tip of the aortic valve perpendicular to the aorta. Aortic outflow volume was derived from quantitative flow measurements. Regurgitant volume was calculated as the difference between LV total stroke volume obtained from CMR acquisition and aortic forward flow volume (obtained from phase contrast analysis). Gadolinium administration and delayed enhancement were used according to the standard protocol. Briefly, late gadolinium enhancement images were acquired using a high-resolution 3 dimensional electrocardiographic−gated free breathing, respiratory navigator gated inversion recovery spoiled gradient echo sequence in the short-axis orientation 20 minutes after intravenous administration of 0.1 mmol/kg Gadobutrol (Gadovist). MAD was defined as a separation between the LA-valve junction and the atrial aspect of the LV posterior free wall. Patients were classified in 2 groups according to presence (MAD+) or absence of MAD (MAD−). As previously described,[10–12] the length of MAD was measured from the LA-posterior MV leaflet junction to the top of the LV wall during, from the long axis views in end-systole (Figure 1). The upper limit of MAD was defined at the level of P2 scallop insertion of the LA wall, whereas the lower limit was defined at the level of LA connection with LV myocardium. The prolapse distance was measured as the maximum prolapse distance during peak systole beyond the MA. Curling was defined as an unusual systolic motion of the posterior mitral ring on the adjacent myocardium. When present, a quantitative assessment was provided, by tracing a line between the top of LV wall and the LA wall-posterior MV leaflet junction, and from this line a perpendicular line to the lower limit of the MA was traced and expressed in millimeters (Figure 1). Severe curling was defined as a curling ≥3.5 mm, as previously described.[12] LV mid-systolic diameter was measured at base, mid and apex, in 4-chamber view and 2-chamber view. LV wall thickness was measured during end-diastole at base and mid-ventricular segment of septal, lateral, inferior, anterior, posterior, and anteroseptal wall (Figure 1). The ratio of LV basal to mid-ventricular wall thickness ≥1.5 was used as a surrogate of basal LV hypertrophy.[12] Mitral annular diameter was measured during end-diastole and end-systole in 2-chamber view. Paradoxical systolic annulus expansion was defined as a positive difference of end-systolic diameter minus end-diastolic diameter. Atrial fibrillation and ventricular arrhythmias were diagnosed by the cardiologist in charge of the patient (by 12 lead-electrocardiogram, 24-hour Holter monitoring or exercise stress test) or during hospital stay where electrocardiogram was continuously monitored and recorded. Ventricular arrhythmia was defined by the presence of more than 3 consecutive ectopic ventricular beats. Data for study population and CMR

measurements are presented as number (percent) or mean ± standard deviation after testing for normal distribution (Kolmogorov-Smirnov test). Unpaired continuous variables were compared using the Student's test or Wilcoxon's rank-sum test. Comparison of categorical variables was performed with a Chi-square test of Fisher's exact test. All covariates associated with the presence of MAD on univariate were included in a multivariable logistic regression model to determine variables independently associated with MAD. These covariates were age, MMVP, bileaflet MVP, MA systolic diameter, and MR severity. Agreement for the presence of MAD between CMR and transthoracic echocardiography (TTE) was assessed using the weighted Kappa statistic in a subgroup of 80 patients who underwent a comprehensive TTE and CMR study within 48 hours in our institution. All statistical analyses were performed using commercially available software (MedCalc, version 16.8, Mariakerke, Belgium). All p values are the results of 2-tailed tests. A value of $p < 0.05$ was considered significant.

Results

Eighty-nine patients (63 women; mean age 64 ± 13) with MVP were consecutively referred for CMR assessment of MR. Baseline demographic and clinical characteristics of the 89 patients are displayed in Table 1. MAD was diagnosed in 35% (31 of 89) of MVP patients, measuring 8 ± 4 mm [2 to 16 mm]. A typical curling motion (mean length 4 ± 4 mm) was found in 64%, considered severe (≥3.5 mm) in 75%. MAD was more frequent in MMVP than in FED (60% vs 14%; $p < 0.0001$). Ventricular arrhythmia was significantly more frequent in MAD + patients (29% vs 10%, $p = 0.037$) and in MMVP than in FED (87% vs 13%). MAD was longer in patients with ventricular arrhythmias (5 ± 5 mm vs 2 ± 4 mm; $p = 0.038$) and in bileaflet MVP (9 ± 4 mm vs 7 ± 2 mm; $p = 0.018$). None of the patients had history of sustained ventricular tachycardia nor resuscitated sudden cardiac death. Incidence of atrial fibrillation was similar between groups. Diagnostic accuracy of TTE for the detection of MAD was fair (65% sensitivity, 96% specificity, 88% positive predictive value, and 87% negative predictive value) with CMR as reference. Most of the discordances were false-negative classifications of TTE (8 of 23). MAD length was similar using either TTE or CMR (8 ± 3 mm vs 8 ± 5 mm, respectively; $p = 0.89$). On univariate analysis, presence of MAD was associated with MMVP ($p < 0.0001$), Bileaflet prolapse ($p < 0.0001$), and nonsevere MR ($p = 0.023$). Patients with MAD tended to be younger ($p = 0.08$). Left chambers size was similar between groups ($p = 0.86$ and $p = 0.88$) (Table 2). LV ejection fraction was significantly lower in MAD+ patients ($p = 0.044$). Prolapse distance on the posterior leaflet was significantly higher in presence of MAD (6.9 ± 4.8 vs 1.4 ± 2.9 mm; $p = 0.0001$). MR regurgitant volume was similar between groups (47 ± 32 vs 56 ± 23 ml/beat, $p = 0.141$). A majority of MAD+ patients (55%; 17/31) had nonsevere MR and were more frequently asymptomatic. In the 34 patients who had nonsevere MR (≤ grade 2), MAD was present in 17 (50%), mostly in MMVP (14; 82%). Length of MAD tended to be higher in severe MR than in nonsevere MR (3.8 ± 4.5 vs 2.3 ± 4.3 mm; $p = 0.13$). In the 55 patients with severe MR, LV ejection fraction was comparable in both groups (66 ± 6% vs 66 ± 6%; $p = 0.94$). MA was significantly enlarged in MAD+ in both end-systole ($p < 0.0001$) and end-diastole ($p = 0.004$). Significant paradoxical systolic annulus expansion tended to be more frequent in MAD+ (Table 3). Though LV volumes were similar in both groups, basal and mid LV 4-chamber diameters were significantly enlarged in MAD+ patients ($p = 0.014$ and $p = 0.044$, respectively). In MAD+ patients, a significant but weak correlation was

Table 1
Characteristics of the study population and comparison between patients with (MAD+) and without mitral annulus disjunction (MAD−)

Variables	Overall population N = 89	MAD+ N = 58	MAD− N = 31	p Value
Baseline characteristics				
Age (years)	64 ± 13	65 ± 11	60 ± 15	0.082
Women	63 (71%)	44 (76%)	19 (61%)	0.221
Body surface area (m^2)	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	0.466
Asymptomatic	52 (58%)	29 (50%)	23 (74%)	0.042
Myxomatous mitral valve disease	40 (45)	16 (28)	24 (74)	0.000
Coronary artery disease	9 (10%)	9 (16%)	0 (0%)	0.024
Ventricular arrhythmias	15 (17%)	6 (10)	9 (29%)	0.037
Atrial fibrillation	20 (23%)	14 (24%)	6 (19%)	0.791
Mitral regurgitation CMR quantification				
Mitral regurgitation severity				
Grade I/ II	34 (38%)	17 (29%)	17 (55%)	0.023
Grade III/ IV	55 (62%)	41 (71%)	14 (45%)	
Regurgitant volume, ml/beat	53 ± 27	56 ± 23	47 ± 32	0.141
Regurgitation fraction (%)	40 ± 16	42 ± 13	36 ± 19	0.087
Mitral valve prolapse characteristics				
Posterior mitral valve prolapse	37 (42%)	12 (21%)	25 (81%)	<0.001
Bileaflet mitral valve prolapse	28 (31%)	9 (15%)	19 (61%)	<0.001
Prolapse distance (mm)				
Anterior leaflet	1.9 ± 3.4	0.9 ± 2.5	3.7 ± 4.1	0.001
Posterior leaflet	3.3 ± 4.5	1.4 ± 2.9	6.9 ± 4.8	<0.001

Table 2
Cardiac magnetic resonance (CMR) morphological parameters in the study population and comparison between patients with (MAD+) and without mitral annulus disjunction (MAD−)

Variables	Overall population n = 89	MAD + n = 58	MAD - n = 31	p Value
Left ventricular CMR morphological parameters				
Left Ventricular End-diastolic volume index, ml/m^2	107 ± 24	107 ± 25	107 ± 24	0.882
Left Ventricular End-systolic volume index, ml/m^2	37 ± 13	36 ± 13	39 ± 12	0.310
Left Ventricular EF, n (%)	66 ± 7	67 ± 7	64 ± 7	0.044
Left Ventricular mass, g/m^2	85 ± 17	87 ± 16	83 ± 18	0.303
Left Atrial volume index, ml/m^2	82 ± 28	83 ± 26	82 ± 33	0.856
Left Ventricular mid-systolic diameter, mm				
Basal 4-chamber diameter	38.3 ± 8	36.7 ± 7.2	41.3 ± 8.7	0.014
Mid-ventricular 4-chamber diameter	34.2 ± 8.7	33.1 ± 9.7	36.4 ± 5.8	0.044
Apical 4-chamber diameter	23.5 ± 6.5	22.5 ± 6.6	25.3 ± 5.9	0.907
Basal 2-chamber diameter	38.4 ± 7.9	37.5 ± 7.8	4.1 ± 8	0.537
Mid-ventricular 2-chamber diameter	35.6 ± 8.9	34.2 ± 9.1	38.3 ± 7.9	0.556
Apical 2-chamber diameter	26.7 ± 6.6	25.6 ± 6.8	28.9 ± 5.7	0.369
Left ventricular end-diastolic wall thickness, mm				
Septal wall				
Basal segment	10 ± 3	10 ± 3.1	10 ± 3	0.744
Mid segment	8 ± 2.1	8 ± 2.2	7 ± 1.9	0.096
Ratio mid/basal wall thickness	1.4 ± 0.8	1.3 ± 0.3	1.6 ± 1.3	0.154
Ratio ≥1.5	30 (33%)	15 (26%)	15 (48%)	0.038
Lateral wall				
Basal segment	10 ± 2.7	10 ± 2.5	11 ± 2.8	0.063
Mid segment	7 ± 2	7 ± 2.2	6 ± 1.5	0.260
Ratio mid/basal wall thickness	1.5 ± 0.5	1.4 ± 0.5	1.7 ± 0.5	0.020
Ratio ≥1.5	43 (48%)	23 (40%)	20 (65%)	0.029
Inferior wall				
Basal segment	9 ± 2.2	9 ± 2.3	9 ± 2	0.523
Mid segment	7 ± 1.6	7 ± 1.6	7 ± 1,5	0.204
Ratio mid/basal wall thickness	1.3 ± 0.3	1.3 ± 0.3	1.4 ± 0.4	0.050
Ratio ≥1.5	31 (35%)	18 (31%)	13 (42%)	0.354
Gadolinium				
Gadolinium injection	26 (29%)	16 (28%)	10 (32%)	0.635
Late gadolinium enhancement	11 (12%)	5 (9%)	6 (19%)	0.181
In papillary muscle	6 (7%)	1 (2%)	5 (16%)	0.018
In myocardium	5 (6%)	4 (7%)	1 (3%)	0.654

found between length of MAD and LV basal 4C systolic diameter (r = 0.44; p = 0.01; Figure 2). Presence of MAD was associated with a significantly increased ratio of basal to mid-ventricular wall thickness only in the lateral wall (Table 2). A ratio ≥1.5 used as a surrogate of basal LV hypertrophy[14] was more prevalent in MAD+ patients in the septal (p = 0.04) and lateral walls (p = 0.03). Similar results were found in the subgroup of MAD + patients with MMVP (n = 24), excluding MAD+ patients with FED. In the 11 of 26 patients (42%) with late gadolinium enhancement, presence of LV fibrosis at the level of papillary muscle (PM) was more frequent in case of MAD as 83% (5 of 6) of the patients with PM fibrosis had MAD. After adjustment on age and MR severity, MMVP (hazard ratio 5.04; 95% confidence interval [1.66 to 15.31], p = 0.004) and end-systolic MA diameter (hazard ratio 1.17; 95% confidence interval [1.05 to 1.30], p = 0.005) were independently associated with the presence of MAD.

Discussion

Our study using 3-Tesla CMR shows that MAD was present in about 1/3 of MVP patients, more frequently in MMVP than in FED, independently of MR severity.

Table 3
Mitral annulus characteristics in the study population and comparison between patients with (MAD+) and without mitral annulus disjunction (MAD−)

Variables	Overall population n = 89	MAD− n = 58	MAD + n = 31	p Value
End-diastolic diameter, (mm)	45.3 ± 4.9	44.1 ± 4.3	47.5 ± 5.4	0.004
End-systolic diameter, (mm)	45.4 ± 5.7	43.8 ± 4.9	48.5 ± 5.8	<0.0001
Diastolic to systolic diameter difference, (mm)	0.12 ± 3.30	-0.33 ± 3.16	0.97 ± 3.45	0.08
Paradoxical systolic annulus expansion	43 (48%)	24 (41%)	19 (61%)	0.081

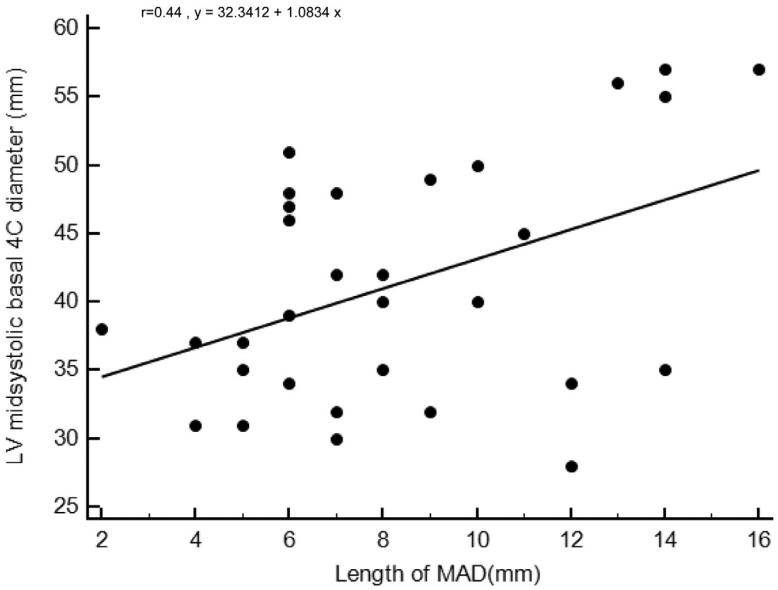

Figure 2. Relation between length of mitral annulus disjunction (MAD) and left ventricular (LV) midsystolic basal 4 chamber diameter. A positive correlation was found between the length of MAD expressed in millimeters and the LV midsystolic basal diameter, expressed in millimeters.

Enlarged MA and basal LV diameters, ventricular arrhythmias and papillary muscle fibrosis were associated with the presence of MAD. Comprehensive CMR study of MVP should include a careful description of MAD, alongside with other risk factors of ventricular arrhythmia such as focal fibrosis, irrespectively of MR severity.

Prevalence of MAD in the general population ranges from 7%[5] to 9%.[13] Initial reports found a prevalence of MAD of 92% in MVP, suggesting that MAD was specifically associated with MVP.[5] More recent studies reported lower prevalence of MAD in MVP, ranging from 28% using TTE[13] to 42% in 3D transesophageal echocardiography.[14] Our CMR findings are consistent with previous echocardiographic data showing a prevalence of MAD in MVP of 35%. Moreover, we report that diagnostic performance of TTE might not be optimal for the detection of MAD compared with CMR. Konda et al[13] reported that MAD could exist in the absence of MVP. However, MAD appears to be more frequently found in MMVP (from 44% to 98%[3,11,13]), with highest incidence of MAD in advanced MVP, defined as increased valve thickness, volume of both leaflets, valve mobility, and MA dilatation. By CMR examination, our study confirms a higher prevalence of MAD in MMVP than in FED (60% vs 14%). By TTE[11,13] as transesophageal echocardiography[15] examination, presence of MAD was not associated with the severity of MR. The present study confirms the absence of correlation between MAD and MR severity assessed by CMR which is considered superior to TTE in assessing MR severity.[15] Some authors believe that assessment of MAD length obtained by different imaging modalities are not interchangeable and should be compared and interpreted with caution.[16] CMR assessment of MAD may be the preferred imaging method, offering unique spatial resolution and reproducibility. In previous echocardiographic studies,[11,13,14] MAD length ranged from 8 to 10 mm. Our study reports similar values between CMR and TTE. In some patients, MVP may present with ventricular arrhythmias and sudden cardiac death, even in the absence of significant MR. The relation between MAD and ventricular arrhythmias was suspected recently,[11] with an increased frequency of ventricular extra beats and nonsustain ventricular tachycardia in the presence of MAD detected in echocardiography. A CMR study[17] confirmed that MAD should be considered as an arrhythmogenic entity, irrespective of the presence of MVP or MR. Similarly, we found a significantly increased incidence of ventricular arrhythmias in MAD patients (29% vs 10%), predominantly in MMVP. Incidence of ventricular arrhythmias also increased with MAD length, with a proposed cut-off value of 8.5 mm to predict the risk of ventricular arrhythmias with a sensitivity of 67% and specificity of 83%.[11] In our series, all our patients with ventricular arrhythmias had a MAD length ≥5 mm. Arrhythmic MVP was recently described and is characterized by myxomatous leaflets and left ventricular fibrosis. Recently, Hourdain et al[18] added that "severe myxomatous MVP," combining MMVP with thickened leaflet, bileaflet prolapse, and MAD, was associated with increased risk of sudden death. Using CMR, Perazzolo et al[12] showed that MAD was a common feature in arrhythmic MVP. In such patients, fibrosis is mostly located close to the annulus in the basal LV wall[12] (PM and inferior wall). In our study, most of the patients with PM fibrosis (83%) had MAD. The hypothesis is that excessive mobility of the leaflet caused by posterior systolic curling might create a mechanical stretch of the inferobasal wall and PM, eventually leading to myocardial hypertrophy and scarring.[12] Electrophysiologic studies comfort this hypothesis, as the presence of PM fibrosis on CMR was found to be associated with the papillary origin of ventricular arrhythmias in patients with MVP.[19] Arrhythmic MVP patients showed relative hypertrophy of the inferobasal wall compared with the adjacent mid portion.[12] We found an excessive wall thickening specifically located at the basal posterior and septal wall, which could be potential substrates for ventricular remodeling and consequent electric instability.[16] In patients with MVP, a reduced LV contraction, especially in its base, has been

reported by angiographic studies.[20] Basal LV dilatation may cause greater systolic wall tension in the LV base compared with the middle and apical segments by Laplace's law, which may lead to regionally attenuated contraction in the LV base.[21] MVP patients, in particular bileaflet and MMVP, have prominent MA dilatation with only modest LV dilatation.[21] Using TTE, MA dilatation appeared to be correlated to basal predominance of LV dilatation leading to basal-reduced LV contraction.[21] Our study confirms, using CMR, that basal and mid LV 4-chamber diameters are enlarged in patients with MAD. Thus, life-threatening arrhythmic MVP combines several markers of risk that can be obtained on CMR, such as MV characteristics (thickness, MMVP, and bileaflet prolapse), description of MAD (presence, extension, and length) and LV remodeling and fibrosis (location, extension).

The present study was performed using CMR. This technique requires expertise and CMR suffers several limitations such as limited availability, local expertise or the presence of cardiac pacemakers and implantable cardioverter-defibrillators. Another limitation is cardiac arrhythmia. Nevertheless, sufficient image quality was obtained in patients with atrial fibrillation and controlled heart rate. Gadolinium injection was not performed systematically and complete CMR with injected gadolinium contrast enhancement was performed only in 29% of the patients included. This study was performed retrospectively and conducted in a single surgical center.

Disclosures

The authors have no conflicts of interest to disclose.

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