Original research

Ventricular arrhythmias during exercise in patients with mitral valve prolapse

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ABSTRACT

Background Mitral valve prolapse (MVP) can be associated with ventricular arrhythmias (VA), but little is known about the relationship between VA and exercise in these patients. The aim of this study was to assess the occurrence and severity of VA during exercise tests in patients with MVP, and to explore the association between VA during exercise and the occurrence of arrhythmic events during follow-up.

Methods In this multicentre study, 375 patients with MVP (58 (48–69) years, 53% male) who underwent a clinically indicated exercise test were included. Severity of VA during exercise was defined as: (1) no VA, (2) minor VA (premature ventricular contractions ≥5% or non-sustained ventricular tachycardia (nsVT) <120 beats per minute) and (3) major VA (nsVTs ≥120 beats per minute).

Results During exercise test, 242 (65%) patients showed no VA, 88 (24%) minor VA and 45 (12%) major VA. Patients with minor and major VAs showed more often bileaflet prolapse and mitral annular disjunction (MAD) than patients with no VA (p<0.001). Over a median follow-up of 101 months (IQR 58–138 months), 35 patients (9%) developed a severe arrhythmic event, defined as sustained VA or ventricular fibrillation, implantation of an implantable cardioverter-defibrillator and VA ablation. At the Kaplan-Meier curve analysis, patients with major VA showed the worst arrhythmic event-free survival (log-rank p<0.001). On multivariable analysis, left ventricular end-systolic diameter, MAD and VA severity during exercise were independently associated with this outcome.

Conclusions In patients with MVP, the occurrence of VA during exercise is associated with more advanced mitral valve abnormalities, including MAD, and with higher rates of severe arrhythmic events during follow-up. Performing an exercise test, combined with the clinical and echocardiographic assessments, may therefore offer important complementary information useful for patient management.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mitral valve prolapse (MVP) can be associated with ventricular arrhythmias (VA), but little is known about the relationship between VA and exercise in these patients.

WHAT THIS STUDY ADDS

⇒ Patients with MVP who experienced major VA during an exercise test showed the worst arrhythmic event-free survival.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Performing an exercise test in these patients may offer important complementary information useful for patient management.

INTRODUCTION

Mitral valve prolapse (MVP) is known to be associated with a wide spectrum of ventricular arrhythmias (VA), from frequent premature ventricular contractions (PVCs) to (non-sustained) ventricular tachycardia ((ns)VT), and in rare cases, sudden cardiac death (SCD).[1 2] The pathophysiology of this association is largely unknown, but several risk factors for the development of VA in patients with MVP have been proposed, including female gender,[2] T-wave inversion,[1] bileaflet prolapse,[3] mitral annular abnormalities,[4–6] impaired left ventricular (LV) function[6] and presence of myocardial fibrosis, particularly at the papillary muscles (PM) level.[7] Several studies[8 9] have shown that in patients with MVP and VA, the dominant PVC morphology originated most frequently from the PM, supporting the hypothesis that an increased mechanical traction on the PM by the prolapsing valve could be a trigger for VA. Moreover, recurrent traction on the PM could lead to myocardial fibrosis, which could be a substrate for severe VA. During exercise, the mechanical forces on the PM increase, and it could be therefore hypothesised that during exercise testing, patients with MVP might show an increase in VA.

Recent meta-analyses[10 11] showed that exercise-induced VAs are associated with an increased risk of all-cause and cardiovascular mortality. However, so far, none of these studies have included patients with MVP. The aim of the current study was therefore to assess the development of VA during exercise testing in patients with MVP. Furthermore, the association between the presence and severity of VA during exercise testing and patient clinical and echocardiographic characteristics was explored, as well as the occurrence of severe arrhythmic events during follow-up.

METHODS

Study population and clinical characteristics

Patients with MVP who underwent exercise testing based on clinical indication at the Leiden University Medical Center (LUMC, Leiden, the Netherlands) and at the Mayo Clinic (Rochester, Minnesota, USA) were included. The following exclusion criteria were applied: (1) exercise test performed without standard saving of the ECGs and without automatic savings of arrhythmias, (2) inducible ischaemia, (3) concomitant presence of other structural heart disease as cause for VA, including ischaemic/hypertrophic/dilated cardiomyopathy and congenital heart disease, (4) previous valvular intervention (including mitral valve (MV) surgery), (5) major VA prior to the exercise test, including PVC/VT ablation or implantable cardioverter-defibrillator (ICD) implantation.

The hospital information systems were used to collect the demographic and clinical characteristics of the patients. The following baseline information was obtained: age, sex, symptoms (palpitations, dyspnoea, (near)syncope, angina pectoris), comorbidities (diabetes mellitus, chronic obstructive lung disease, coronary artery disease), renal function and antiarrhythmic medication.

During follow-up starting from the date of the exercise test, the occurrence of severe arrhythmic events (primary endpoint) was collected and defined as the occurrence of sustained VT or ventricular fibrillation (VF), ICD implantation and PVC/VT ablation.

Echocardiography

Transthoracic 2D echocardiography was performed in all patients at rest around the time of the exercise test in the left lateral decubitus position using commercially available ultrasound equipment. The parasternal long-axis view was used to assess LV dimensions, MV annular diameter and mitral annular disjunction (MAD).[12] The presence of MAD was confirmed along the whole cardiac cycle but measured in systole defined as a separation between the left atrial (LA) wall at the level of the posterior MV junction and LV free wall, and a significant MAD was set with a cut-off value of >5 mm.[13] Apical two and four-chamber views were used to measure LV end-diastolic and end-systolic volumes according to Simpson's biplane method to calculate LV ejection fraction (LVEF).[12] LA remodelling was quantified by the maximum LA volume measured in systole in the two and four-chamber views indexed to body surface area (LAVI).[12] Right atrial and ventricular pressures were determined as previously described and used to evaluate the systolic arterial pulmonary pressure.[14] To assess the right ventricular (RV) systolic function, tricuspid annular plane systolic excursion was measured.[12]

MVP was diagnosed as leaflet displacement >2 mm beyond the mitral annulus in the long-axis plane[15] and divided into two aetiologies: Barlow's disease and fibroelastic deficiency (FED). Barlow's disease was defined as bileaflet or multisegment prolapse with excessive tissue, elongated/ruptured chordae and severe annular dilatation.[16] FED was defined as a single segment prolapse with thin leaflets and/or thickening of the leaflet limited to the prolapsing segment.[16] Mitral regurgitation (MR) was graded according to current guidelines using a multiparametric approach.[15]

Exercise test

All patients underwent an exercise test with a ramp protocol based on age, length and weight to reach at least 100% of the predicted watt and a target heart rate of 85% of the age-predicted maximum heart rate. The ECG was continuously monitored and saved at standard time points.

Evaluation of VAs

12-lead ECGs recorded at rest, during exercise and during the recovery phase were evaluated for the presence of VA, including simple and complex PVCs and nsVT or sustained VT. nsVT was defined as a run of consecutive ventricular beats with a heart rate ≥100 beats per minute lasting 3 beats to 30s and sustained VT as a rhythm originating from the ventricle with a heart rate ≥100 beats per minute lasting >30 s or requiring termination because of haemodynamic instability.[5] Previous studies tested different definitions of VA during exercise,[17–20] but ultimately identified the 'presence of any PVC or nsVT during stress testing' as the most informative.[10 11] For the current study, we decided to stratify the patients according to the complexity of VA during exercise testing (the cut-off values are derived from the consensus statement on arrhythmic MVP[21]): (1) no VA defined as no or sporadic PVCs (<5%) and no nsVT/VT, (2) minor VA defined as frequent PVCs (≥5%) with or without nsVTs <120 beats per minute and (3) major VA defined as nsVTs >120 beats per minute or sustained VA (VT or VF) with or without PVCs. The percentage of PVCs during the exercise test was calculated by dividing the number of PVCs by the number of QRS complexes on all saved ECGs.

Statistical analysis

Categorical variables are expressed as absolute numbers and percentages. Continuous variables are presented as mean±SD in case of a reasonably symmetrical distribution and as median with IQR in case not. Differences in continuous and categorical clinical and echocardiographic characteristics between patients with no/minor/major VAs were assessed using the one-way analysis of variance test (numerical data with normal distribution), Kruskal-Wallis test (numerical data without normal distribution) and χ^2 test or Fisher-Freeman-Halton exact test (categorical data), when appropriate.

To calculate the severe arrhythmic event rates during follow-up for the separate groups based on VA severity, the Kaplan-Meier method was employed. The log-rank test was used for the comparison of cumulative event rates between the different groups. The origin was defined as the date of the exercise test. Follow-up started at this date and ended at the first occurrence of a severe arrhythmic event (primary endpoint). Patients without an event were censored at their last known follow-up or at their date of death.

Univariable Cox proportional hazards analyses were performed to test the association of the severity of VA during exercise and of other relevant clinical and echocardiographic parameters (namely based on the criteria for valve intervention indication of current guidelines[22]) with the primary endpoint. From this univariable analysis, statistically significant ($p<0.05$) and clinically relevant variables were selected and introduced as covariables in the multivariable Cox proportional hazards models. Due to the low number of severe arrhythmic events during follow-up, only four variables could be included in the multivariable model. Therefore, several models were tested, including variables representing MV abnormalities alternatively, in combination with LV parameters. For both univariable and multivariable analyses, HRs with 95% CIs are reported. Statistical analysis was performed using SPSS V.25.0 (IBM). For all tests, a two-sided p value <0.05 was considered statistically significant.

Table 1 Clinical characteristics of the total population and among patients with different severity of VA during exercise test

	Total population n=375	No VA n=242	Minor VA n=88	Major VA n=45	P value
Age at exercise test, years	58 (48–69)	59 (48–70)	56 (41–67)	64 (50–69)	0.061*
Male, n (%)	197 (53)	123 (51)	46 (52)	28 (62)	0.372†
Aetiology, n (%)					<0.001†
Fibroelastic deficiency	147 (39)	114 (47)	21 (24)	12 (27)	
Barlow's disease	228 (61)	128 (53)	67 (76)	33 (73)	
Palpitations, n (%)	151 (40)	76 (31)	48 (55)	27 (60)	<0.001†
Dyspnoea, n (%)	97 (26)	63 (26)	20 (23)	14 (31)	0.577†
(Near)syncope, n (%)	43 (12)	26 (11)	9 (10)	8 (18)	0.364†
Angina pectoris, n (%)	64 (17)	49 (20)	12 (14)	3 (7)	0.052†
Diabetes mellitus, n (%)	20 (5)	15 (6)	3 (3)	2 (4)	0.695‡
Chronic obstructive pulmonary disease, n (%)	15 (4)	10 (4)	3 (3)	2 (4)	1.000‡
Atrial fibrillation, n (%)	83 (22)	54 (22)	15 (17)	14 (31)	0.180†
Coronary artery disease, n (%)	59 (16)	40 (17)	13 (15)	6 (13)	0.830†
eGFR, mL/min/1.73 m^2	81 (62–95)	80 (60–95)	83 (66–93)	82 (63–93)	0.661*
Medication, n (%)					
Beta-blockers	156 (42)	97 (40)	39 (44)	20 (44)	0.724†
Other antiarrhythmics	54 (14)	37 (15)	12 (14)	5 (11)	0.744†
Indication exercise test					<0.001†
Evaluation palpitations	113 (30)	51 (21)	36 (41)	26 (58)	
Assessment of symptoms	169 (45)	122 (50)	32 (36)	15 (33)	
Exclusion of ischaemia	83 (22)	61 (25)	19 (22)	3 (7)	
Other reason	10 (3)	8 (3)	1 (1)	1 (2)	
Resting heart rate, beats per minute	72 (63–84)	73 (61–85)	71 (63–79)	72 (65–83)	0.848*
Maximal heart rate, beats per minute	151 (135–166)	150 (133–166)	155 (143–166)	151 (125–171)	0.284*
Exercise test result based on heart rate, n (%)					0.089‡
Maximal	274 (73)	185 (76)	61 (69)	28 (62)	
Near maximal	33 (9)	23 (10)	7 (8)	3 (7)	
Submaximal	37 (10)	22 (9)	5 (6)	10 (22)	
Exercise capacity based on watt, n (%)					0.004†
Below average	45 (12)	24 (10)	15 (17)	6 (13)	
Average	155 (41)	114 (47)	29 (33)	12 (27)	
Above average	116 (31)	64 (26)	29 (33)	23 (51)	

Data are presented as number (percentage) in case of categorical data or median (IQR) in case of continuous data with no normal distribution.
*Kruskal-Wallis test.
†χ^2 test.
‡Fisher-Freeman-Halton exact test.
eGFR, estimated glomerular filtration rate; VA, ventricular arrhythmia.

RESULTS

Clinical characteristics

A total of 375 patients with MVP (116 patients from the LUMC and 259 patients from Mayo Clinic) who underwent a clinically indicated exercise test were included (median age 58 years (IQR 48–69), 53% male). The majority of patients (71%) could reach the predicted maximal exercise capacity. Using the above-mentioned definition of VA severity during exercise, 242 (65%) patients showed no or only sporadic PVCs, 88 (23%) patients showed minor VA and 45 (12%) patients showed major VA (all nsVTs). The baseline clinical characteristics of the total population, stratified based on the severity of VA during exercise, are presented in table 1. When comparing the three groups, patients with minor and major VAs during exercise were more often diagnosed with Barlow's disease (76% and 73%, respectively) than patients with no VA (53%, p<0.001). The presence of comorbidities was relatively low in the whole population and did not significantly differ between the three groups. More than half of the patients used antiarrhythmic medications, mainly beta-blockers; however, the use of beta-blockers and other antiarrhythmic drugs did not significantly differ between the groups.

Echocardiographic characteristics

Table 2 summarises the echocardiographic characteristics of the total study population and the three groups based on VA severity during exercise. As compared with patients with no VA, patients with minor and major VAs during exercise had a larger LV end-diastolic diameter (54 (IQR 49–58) mm and 53 (IQR 50–58) mm vs 51 (IQR 48–56) mm, p=0.006) and slightly lower LVEF (62% (IQR 58–66) and 62% (IQR 57–65) vs 64% (IQR 60–67), p=0.004), although still within the normal range. While LAVI and MV annulus diameter did not significantly differ between the groups, the prevalence of MAD was higher in patients with minor and major VAs during exercise as compared with patients with no VA (43% and 49% vs 30%, p=0.010). The degree of MR, pulmonary artery pressure and RV function did not significantly differ between the three groups.

Table 2 Echocardiographic characteristics of the total population and in comparison among patients with different severity of VA during exercise test

	Total population n=375	No VA n=242	Minor VA n=88	Major VA n=45	P value
LV end-diastolic diameter, mm	52 (48–56)	51 (48–56)	54 (49–58)	53 (50–58)	0.006*
LV end-systolic diameter, mm	32 (29–35)	32 (28–35)	33 (30–37)	33 (29–36)	0.063*
LV ejection fraction, %	63 (58–66)	64 (60–67)	62 (58–66)	62 (57–65)	0.004*
LA volume index, mL/m^2	37 (29–49)	36 (28–48)	37 (29–49)	42 (34–53)	0.053*
MV annulus diameter, mm	36 (32–40)	36 (31–40)	37 (33–40)	36 (33–40)	0.154*
Mitral annular disjunction, n (%)	132 (35)	72 (30)	38 (43)	22 (49)	0.010†
MR grade, n (%)					0.592‡
Mild	201 (53)	135 (56)	45 (51)	21 (47)	
Moderate	79 (21)	48 (20)	18 (21)	13 (29)	
Moderate-severe	55 (15)	33 (14)	13 (15)	9 (20)	
Severe	40 (11)	26 (11)	12 (14)	2 (4)	
Systolic pulmonary pressure, mm Hg	28 (24–34)	28 (24–34)	28 (23–34)	29 (26–35)	0.326*
TAPSE, mm	23 (21–25)	23 (21–25)	22 (20–25)	23 (21–25)	0.870*

Data are presented as number (percentage) in case of categorical data or median (IQR) in case of continuous data with no normal distribution.
*Kruskal-Wallis test.
†χ^2 test.
‡Fisher-Freeman-Halton exact test.
LA, left atrial; LV, left ventricular; MR, mitral regurgitation; MV, mitral valve; TAPSE, tricuspid annular plane systolic excursion; VA, ventricular arrhythmia.

Survival analysis

During follow-up, 35 patients developed a severe arrhythmic event (median of 101 months (IQR 58–138) after the exercise test)(table 3). In total, 340 patients were censored, of which 296 (79%) were due to end of follow-up without a severe arrhythmic event and 44 (12%) because of death. Several patients experienced multiple severe arrhythmic events, but only the first was used for survival analysis. Sustained VA occurred in 24 patients (15 patients had VT, five patients had VF and four patients had both VT/VF during follow-up), 18 patients received an ICD, while 14 patients underwent PVC/VT ablation. The Kaplan-Meier curve analysis for the occurrence of a severe arrhythmic event revealed that patients with major VA during exercise had significantly worse event-free survival compared with patients with no and minor VAs (log-rank χ^2=45.0; p<0.001) (figure 1).

In addition, table 4 reports the associates of the severe arrhythmic endpoint at the univariable and multivariable Cox regression analyses. In the multivariable analysis, age was introduced in combination with the significant and clinically relevant parameters from the univariable Cox regression analysis. Several models were tested, including parameters reflecting MV abnormalities (Barlow's disease, MV annulus diameter and MAD) together with parameters representing LV remodelling (LV end-systolic diameter and LVEF) (online supplemental table 1). Among these parameters, MAD was the only one which remained independently associated with the outcome regardless of the LV parameter that was included. In all analyses, the severity of VA remained independently associated with a severe arrhythmic event during follow-up. Specifically, patients with minor VA had a 2.5 times higher hazard for developing a severe arrhythmic event during follow-up (HR 2.553, 95% CI 1.060 to 6.150), while patients with major VA showed an even higher hazard (eight times higher) for the primary outcome (HR 7.973, 95% CI 3.437 to 18.498).

DISCUSSION

The clinical course of MVP is mostly benign in the absence of (severe) MR, but a small subgroup of patients remains at higher hazard of severe VA and SCD. A combined approach of clinical,

Table 3 Summary of the severe arrhythmic events during follow-up in the total population and among patients with different severity of VA during exercise test

	Total population n=375	No VA n=242	Minor VA n=88	Major VA n=45	P value
Severe arrhythmic event,* n (%)	35 (9)	10 (4)	11 (13)	14 (31)	<0.001†
VT and/or VF, n (%)					0.025‡
VT	15 (4)	6 (3)	3 (3)	6 (13)	
VF	5 (1)	1 (0.5)	2 (2)	2 (4)	
VT and VF	4 (1)	0 (0)	2 (2)	2 (4)	
PVC/VT ablation, n (%)	15 (4)	6 (3)	4 (5)	5 (11)	0.029‡
ICD implantation, n (%)	18 (5)	4 (2)	5 (6)	9 (20)	<0.001‡

Overview of the total severe arrhythmic events (endpoint of the study) and the different types of severe arrhythmic events. Data are presented as number (percentage) in case of categorical data.
*The first arrhythmic event was used in case of multiple severe arrhythmic events (eg, VT and later ICD implantation).
†χ^2 test.
‡Fisher-Freeman-Halton exact test.
ICD, implantable cardioverter-defibrillator; PVC, premature ventricular contraction; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.

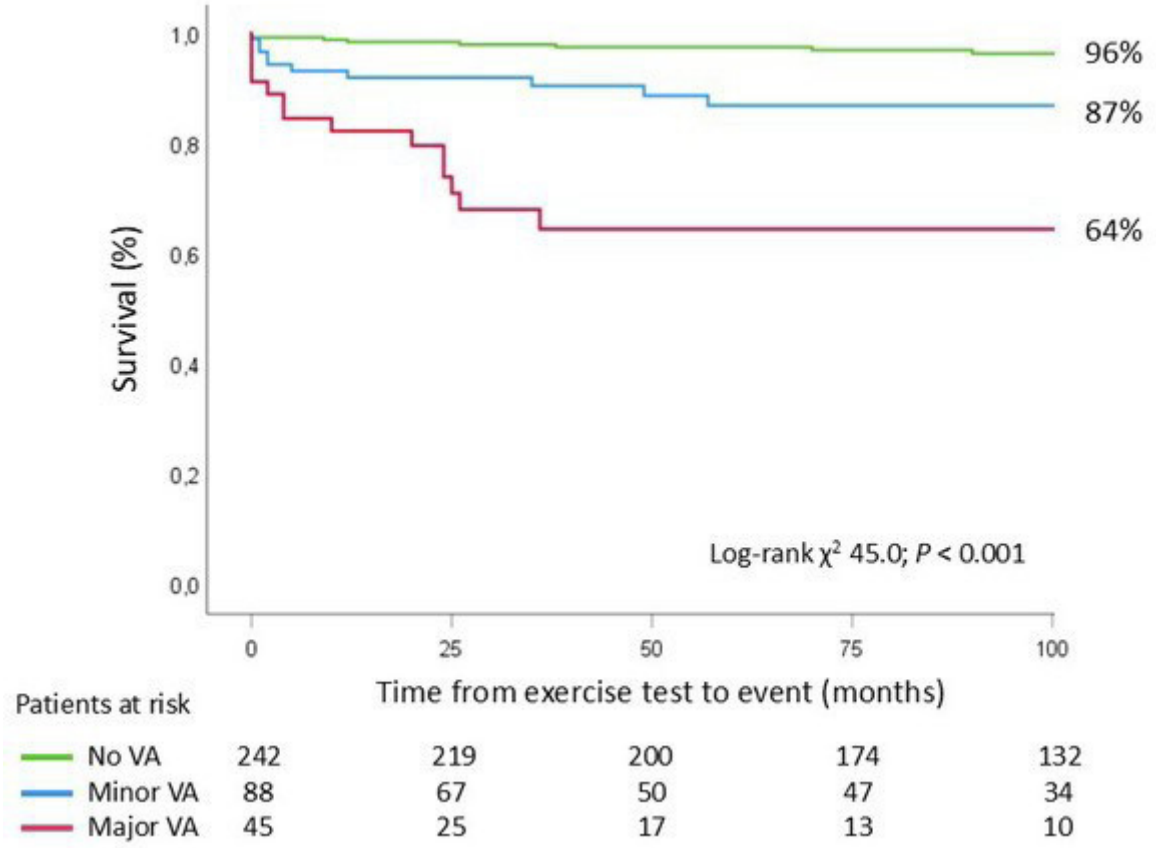

Figure 1 Survival analysis for a severe arrhythmic event during follow-up comparing patients with no, minor and major VAs during exercise. Kaplan-Meier curve estimated for the cumulative event rates of the occurrence of a severe arrhythmic event (VT, VF, ICD implantation or PVC/VT ablation) during follow-up. ICD, implantable cardioverter-defibrillator; PVC, premature ventricular contraction; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.

electrocardiographic (including 24-hour Holter monitoring), cardiac MRI and echocardiographic characteristics is currently used in these patients in an attempt to stratify those at high and low risks for VA.[21] However, the value of performing an exercise test has not yet been evaluated within the risk stratification strategies of these patients. The current study explored the occurrence of VA during exercise in patients with MVP referred for an exercise test. The main findings are: (1) in our study cohort, 45% of the patients with MVP who underwent exercise testing had either minor or major VAs during exercise testing, (2) minor and major VAs occurring during exercise tests were more often observed in patients with Barlow's disease, (3) the occurrence of minor and major VAs during exercise tests showed a higher hazard of severe arrhythmic events during follow-up and remained independently associated with this outcome after adjustment for age, LV function and MV abnormalities.

Prevalence of VA during exercise

Development of VA during exercise test has been previously described in several populations, with a prevalence of VA during exercise ranging from 3% to 23% in healthy subjects[20] and up to 54% in patients with different degrees of coronary artery disease.[23] Prevalence of VA during exercise may also vary according to the definition used and the corresponding cut-off value to define relevant VA. Some studies[18 19] have considered the absolute numbers of PVCs and nsVTs, while other studies[20 24] used a ratio based on the amount of PVCs and QRS complexes or the number of PVCs per minute. In the current study, in order to use relatively restrictive criteria and as specific as possible for this patient population, the chosen definition was based on the recent consensus statement on arrhythmic MVP.[21]

Only very few small studies[25 26] explored the occurrence of VA during exercise in patients with MVP. A small study performed by DeMaria *et al*[25] in 1976 compared 31 patients with MVP with 40 healthy controls and showed that patients with MVP developed more PVCs during the exercise test as compared with controls. In particular, five patients with MVP who had no VA during rest showed VA during exercise, and in two patients with MVP, the frequency of existing VA increased during exercise. A more recent study by Five *et al*[26] explored the association between lifetime exercise dose (measured with metabolic equivalents of task hours/week) and severe VA in a retrospective cohort of 136 patients with MVP. The authors concluded that in these patients, no association could be demonstrated between moderate lifetime exercise dose and severe VA, but higher dose of lifetime exercise could be associated with severe VA.[26]

Parameters associated with VA during exercise in patients with MVP

In the general population, VA during exercise is associated with older age, male gender, cardiovascular risk factors and structural heart disease.[10 11] However, patients with MVP were not included in these studies. In patients with MVP, the occurrence of VA has been associated with female gender,[2] T-wave inversion,[1] fragmented QRS complex,[27] bileaflet prolapse,[3] MV

Table 4 Univariable and multivariable Cox regression analyses of the occurrence of a severe arrhythmic event during follow-up

	Univariable analysis		Multivariable analysis		Multivariable analysis	
	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)
Age, years	0.016	0.974 (0.954 to 0.995)	0.194	0.985 (0.963 to 1.008)	0.189	0.985 (0.962 to 1.008)
Male	0.657	1.163 (0.595 to 2.273)				
Barlow's disease	0.004	3.642 (1.510 to 8.783)				
Coronary artery disease	0.149	0.417 (0.127 to 1.366)				
Atrial fibrillation	0.662	0.831 (0.363 to 1.904)				
eGFR	0.061	1.009 (1.000 to 1.019)				
Resting heart rate	0.343	0.986 (0.959 to 1.015)				
LV end-systolic diameter	<0.001	1.095 (1.052 to 1.140)	0.004	1.063 (1.020 to 1.108)		
LV ejection fraction	0.017	0.955 (0.919 to 0.992)			0.390	0.983 (0.945 to 1.023)
LA volume index	0.340	1.008 (0.992 to 1.024)				
MV annulus diameter	<0.001	1.108 (1.051 to 1.169)				
Mitral annular disjunction	<0.001	3.838 (1.909 to 7.716)	0.021	2.423 (1.141 to 5.145)	0.008	2.723 (1.299 to 5.710)
VA						
No VA*						
Minor VA	0.005	3.412 (1.448 to 8.044)	0.037	2.553 (1.060 to 6.150)	0.020	2.801 (1.174 to 6.682)
Major VA	<0.001	10.518 (4.643 to 23.828)	<0.001	7.973 (3.437 to 18.498)	<0.001	8.384 (3.586 to 19.601)

*Reference group.
eGFR, estimated glomerular filtration rate; LA, left atrial; LV, left ventricular; MV, mitral valve; VA, ventricular arrhythmia.

annular abnormalities,[4–6] impaired LV function[6] and presence of myocardial fibrosis at the PM level or close to the MV annulus.[7] The current study showed that some of these parameters were also associated with the occurrence of VA during exercise. The comparison between patients with no VA and with minor/major VAs during exercise revealed that the latter were more often diagnosed with Barlow's disease, more often had MAD and showed slightly larger LV end diastolic diameter and lower LVEF (although within the normal range and on average >60%). These characteristics may be considered to decide whether to refer patients with MVP for exercise testing as an integral part of their risk stratification strategies.

Exercise-induced VA: mechanism and impact on outcome

Although VA during exercise is common in the general population, their prognostic impact remains uncertain.[28] Nevertheless, several studies,[10 11] including subjects both with and without cardiovascular disease, concluded that exercise-induced PVCs were associated with increased risk of all-cause and cardiovascular mortality. Still, so far, no studies have included patients with MVP to assess whether VA during exercise has prognostic implications. The current study showed that patients with MVP with major VA during exercise had a significantly worse arrhythmic event-free survival as compared with patients without or minor VA.

There are several possible explanations for the association of major VA during exercise test and the occurrence of severe VA during follow-up in patients with MVP. The excessive mobility of the MV leaflets results in an increased mechanical stretch of the PM and of the basolateral LV myocardium, which can result in chronic myocardial damage and secondary fibrosis creating a substrate for re-entrant arrhythmias.[29] This has been demonstrated in autopsy-based and cardiac magnetic resonance studies.[3 9 30] Bui *et al*,[9] using cardiac magnetic resonance, demonstrated significant diffuse interstitial myocardial fibrosis in patients with MVP. Similarly, Garbi *et al*[30] observed during autopsy signs of cardiomyopathy (LV interstitial fibrosis and degeneration of myocytes) in SCD patients with MVP. Another study by Basso *et al*[3] re-examined all cases with MVP as the only cause of SCD from a large autoptic registry of young patients and concluded that fibrosis of the PM and inferobasal LV wall correlated with the VA origin. An additional mechanism is possible, namely the acute stretch of the PM in case of MVP. This mechanical stress leads to electrophysiological changes that facilitate the occurrence of non-re-entrant VA, most frequently PVCs, from the PM and the (chronically) damaged subendocardial Purkinje tissue, whose peripheral arborisation abundantly covers the PM. These PVCs, particularly those arising from the Purkinje tissue, have been shown to trigger VF in patients with MVP.[29]

Although the above-mentioned functional and structural abnormalities might be already present, the majority of patients with MVP might not show complex VA at rest. However, during exercise, repetitive stretch on the subvalvular mitral apparatus

might favour the occurrence of VA. The current study suggests that an exercise test might be considered as an additional tool, together with clinical, electrocardiographic (including Holter monitoring) and echocardiographic assessment, to screen patients with MVP and possibly identify those who deserve additional analyses, such as cardiac MRI, and more stringent surveillance.

Study limitations

Several study limitations should be mentioned. First, the current study was retrospective with limitations inherent to its design; prospective larger studies are advocated to confirm the findings of this study. Second, patients with MVP with a clinically indicated exercise test were included, resulting in a relatively small group with the possibility of selection bias; therefore, current findings cannot be easily generalised for all patients with MVP. Third, the number of events was relatively limited, restricting the number of covariates that could be reliably included in the multivariable models. Fourth, although we adjusted for key clinical and echocardiographic variables, the possibility of unmeasured confounding cannot be excluded. Fifth, cardiovascular magnetic resonance to evaluate the presence of myocardial fibrosis was not systematically performed and was therefore not mentioned in this study. Sixth, the origin of the dominant PVC/VA could not be determined in all patients and was therefore not reported. Seventh, since Holter monitoring was not systematically available in all patients around the same period of the exercise test, the additional value of exercise testing on top of Holter monitoring could not be tested. Eighth, some results have a wide CI; these findings should be interpreted with appropriate caution. Ninth, although we report HRs from Cox regression, it is important to recognise that HRs represent the relative instantaneous event rate and can be influenced by built-in selection over time. Therefore, they should not be interpreted as simple cumulative risks over the follow-up period.

CONCLUSION

In patients with MVP, the occurrence of significant VA during exercise is associated with more advanced MV abnormalities, including MAD, and with higher rates of severe arrhythmic events during follow-up. Performing an exercise test, in combination with clinical and echocardiographic assessment, may provide complementary information by revealing features associated with higher likelihood of arrhythmic events and therefore help improve clinical management and guide decision-making.

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