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ORIGINAL ARTICLE

Primary Atriopathy in Mitral Valve Prolapse: Echocardiographic Evidence and Clinical Implications

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BACKGROUND: Prominent multi-scallop systolic leaflet displacement toward the left atrium (atrialization) is typically observed in bileaflet mitral valve prolapse (MVP) with mitral annular disjunction. We hypothesized that mitral leaflet atrialization is associated with an underlying left atrial (LA) myopathy characterized by progressive structural and functional abnormalities, irrespective of mitral regurgitation (MR) severity.

METHODS: We identified 334 consecutive patients with MVP, no prior atrial fibrillation, and comprehensive clinical and echocardiographic data. LA function was assessed by LA reservoir strain, LA function index, and LA emptying fraction. We also classified the stage of LA remodeling based on LA enlargement and LA reservoir strain (stage 1: no remodeling; stage 2: mild remodeling; stage 3: moderate remodeling; and stage 4: severe remodeling). The primary end point was the composite risk of sudden arrhythmic death, heart failure hospitalization, or the new onset of atrial fibrillation.

RESULTS: Bileaflet MVP with no or mild MR had a lower LA reservoir strain (P=0.04) and LA function index (P<0.001) compared with other MVP subtypes. In multivariable linear regression adjusted for cardiovascular risk factors and MR ≥moderate, bileaflet MVP remained significantly associated with lower LA function parameters (all P<0.05). There was a significant increase in the risk of events as the LA reservoir strain and LA remodeling stage increased (P<0.001). In multivariable analysis, stage 4 of LA remodeling remained significantly associated with a higher risk of events compared with stage 1 (hazard ratio, 6.09 [95% CI, 1.69–21.9]; P=0.006).

CONCLUSIONS: In a large MVP registry, bileaflet involvement is associated with reduced LA function regardless of MR severity, suggesting a primary atriopathy in this MVP subtype. Abnormal LA function, particularly when assessed through a multiparametric approach, is linked to a higher risk of cardiovascular events and may improve risk stratification in MVP, even in those without significant MR.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atrial fibrillation ■ cardiovascular diseases ■ echocardiography ■ mitral valve prolapse

See Editorial by Dhont and Bertrand

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For Sources of Funding and Disclosures, see page 499.

CLINICAL PERSPECTIVE

In addition to traditional morphofunctional characteristics related to the mitral valve (MV) apparatus and the left ventricle, an underlying atriopathy may also affect the prognosis of MV prolapse. Based on various indices of left atrial function, this study demonstrates that bileaflet MV prolapse is related to reduced left atrial function independently of mitral regurgitation, supporting the hypothesis of a primary atriopathy in this MV prolapse subtype. The left atrial–focused multiparametric echocardiographic approach provides incremental prognostic value to predict the risk of cardiovascular events. Therefore, the assessment of left atrial function in MV prolapse, particularly in those with bileaflet involvement and without significant mitral regurgitation, can help identify high-risk patients and optimize their clinical and imaging surveillance.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
LA	left atrial/atrium
LAEF	left atrial emptying fraction
LAFI	left atrial function index
LASr	left atrial reservoir strain
LV	left ventricular/ventricle
MAD	mitral annular disjunction
MR	mitral regurgitation
MV	mitral valve
MVP	mitral valve prolapse
STE	speckle-tracking echocardiography

Mitral valve prolapse (MVP) is a common valvulopathy affecting 2% to 3% of individuals worldwide.[1] While the prognosis of MVP is primarily determined by concomitant severe mitral regurgitation (MR), a subset of MVP patients without significant MR remain at increased risk of atrial fibrillation (AF), cardiomyopathy, and sudden cardiac death.[2–4] Specifically, arrhythmic MVP has been associated with bileaflet involvement, mitral annular disjunction (MAD), and focal fibrosis in the papillary muscles or inferolateral base of the left ventricle (LV).[4–7] Nonetheless, identification of those MVPs at highest risk despite a lack of severe MR who may require closer clinical surveillance remains elusive.

The mitral valve (MV) apparatus is a dynamic organ with complex interactions with surrounding cardiac structures.[1,8] To date, emphasis has been placed on the LV response to chronic degenerative MR or to the abnormal traction exerted by the prolapsing leaflets on the myocardium.[9] However, less is known about abnormal valvular mechanics and left atrial (LA) structure and function. Prominent multi-scallop systolic leaflet displacement toward the left atrium or atrialization is a typical feature of bileaflet MVP with MAD.[10,11] Whether this atrialization relates to impairment of LA function, irrespective of MR severity, remains unclear. A multiparametric assessment of LA function using noninvasive imaging could help unveil the existence of an underlying primary atriopathy associated with MVP, independent of MR.

Prior studies focused on severe degenerative MR support the prognostic role of LA volume and function in predicting overall mortality in MVP.[12,13] However, the prognostic impact of LA function on cardiovascular-only outcomes, including atrial arrhythmic events and cardiac death, remains to be determined, particularly in the absence of significant MR. Novel and less load-dependent imaging parameters, such as LA strain as quantified by speckle-tracking echocardiography (STE), may provide incremental risk prediction of cardiovascular events in MVP.

We hypothesized that bileaflet MVP with concomitant MAD is associated with an underlying LA myopathy characterized by progressive structural and functional abnormalities, irrespective of MR severity. To test this hypothesis, we compared LA function according to different valvular phenotypes using various echocardiographic indices of LA function. Moreover, we sought to assess the prognostic role of LA function with the subsequent risk of cardiovascular events, including AF.

METHODS

The data supporting the findings are available from the corresponding author upon reasonable request.

Study Population

We identified 614 MVPs who underwent comprehensive Doppler echocardiography as part of clinical care at the University of California, San Francisco from 2013 to 2020. Patients were included if they had transthoracic echocardiographic images available for review and a comprehensive assessment of LA structure and function (Figure 1). Patients were excluded if they had a previous MV intervention (repair/replacement), greater than mild aortic valve disease, or a diagnosis of AF or heart failure before or at study entry. Clinical, ECG, history of premature ventricular contractions or ventricular tachycardia by Holter or event monitor, and standard echocardiographic data were retrieved from medical records and organized in an electronic database as part of the University of California, San Francisco MVP registry. The University of California, San Francisco Institutional Review Board approved the study and waived informed consent.

Echocardiography

Two-dimensional transthoracic echocardiograms were performed using commercially available ultrasound systems.

MVP was defined as superior displacement of one or both mitral leaflets >2 mm beyond the mitral annulus in a parasternal or apical 3-chamber long-axis echocardiographic view.[14]

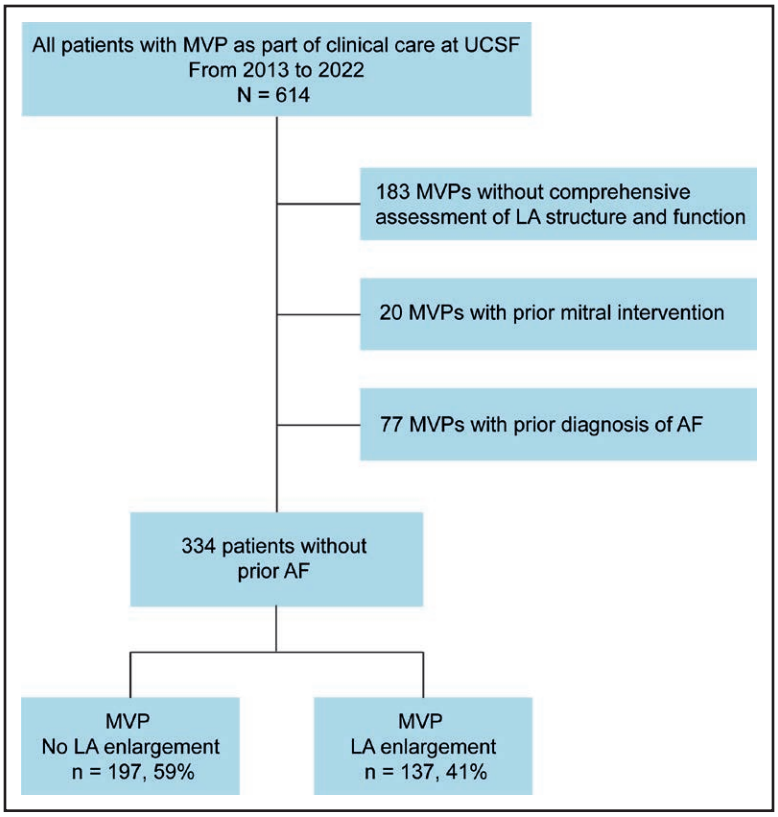

Figure 1. Study flow chart.
AF indicates atrial fibrillation; LA, left atrial; MVP, mitral valve prolapse; and UCSF, University of California San Francisco.

MVP phenotype was further subdivided into flail, bileaflet, or single-leaflet prolapse (anterior versus posterior). MAD, a structural abnormality of the mitral annulus, was defined as previously described (see Supplemental Material).[3] The severity of MR was determined using a multiparametric approach, as recommended by guidelines.[15] MR severity was confirmed by cardiac magnetic resonance in 4 MVP cases (1.2%) who underwent additional imaging as part of their clinical care. LA and LV end-diastolic/end-systolic volumes, LV mass, and LV ejection fraction were measured and indexed to body surface area.[16] We recorded peak early (E) and late (A) diastolic velocities from the mitral inflow and calculated the E/A ratio.[17] The average E/e' ratio was calculated from the mitral annular early diastolic velocity (e').[17] Indexed LA volumes were used to calculate the LA emptying fraction (LAEF) using the formula: ([LAESVi—LAEDVi]/LAESVi)×100, where LAESVi is the LA end-systolic volume index and LAEDVi is the LA end-diastolic volume.[18,19] LA function index (LAFI), which combines LAEF, indexed LA volume, and stroke volume, was then calculated as previously described.[18,19] Pulmonary artery systolic pressure was derived from the peak tricuspid regurgitation velocity jet and the estimated right atrial pressure.[15] Right ventricular systolic function was assessed qualitatively.

Speckle-Tracking Echocardiography

STE analysis was performed offline using commercially available software (EchoPAC, GE Healthcare) to measure LA reservoir strain (LASr) and LV longitudinal strain. Endocardial tracing was performed in apical 4-, 3-, and 2-chamber views for both LA and LV strains (see Supplemental Material). All patients were in normal sinus rhythm when STE measurements were performed. Variability analyses were previously reported for LA and LV measurements at our institution.[19]

Staging of LA Remodeling

Stages of LA remodeling (see Supplemental Material) were defined according to LA volume index and LASr, well-recognized structural and functional parameters of progressive atrial myopathy.[20]

Study End Point

The primary clinical end point was the composite of cardiovascular events, including cardiac mortality (nonarrhythmic and arrhythmic), heart failure hospitalization, or the new onset of AF. Outcome data were collected through review of medical records.

Statistical Analysis

Continuous variables were expressed as mean±SD or median (interquartile range) and tested for normality of distribution and homogeneity of variances with the Shapiro-Wilk and Levene tests, respectively. Continuous variables with a normal distribution were compared between groups with the Student *t* test. Continuous variables nonnormally distributed were compared with the Wilcoxon-Mann-Whitney *U* test or Kruskal-Wallis test, followed by Dunnett's post hoc test. Categorical variables were presented as frequencies and percentages and were

compared with the χ^2 test or Fisher's exact test as appropriate. Univariable and multivariable linear regression analyses were performed to identify the predictors of LA function. The prespecified parameters of LA function included LASr, LAFI, and LAEF. Furthermore, we tested the interaction of mitral-related anatomic abnormalities (MAD and bileaflet MVP) and LV global longitudinal strain in relation to LASr using linear regression analyses. The multivariable model included all clinically relevant variables and those significantly associated (ie, $P<0.05$) with parameters of LA function in univariable analysis. Results were presented as standardized beta coefficient (β) with SE. Collinearity within the multivariable model was assessed by calculating the variance inflation factor.

Kaplan-Meier curves and log-rank tests of the time-to-event data were used to compare the survival function according to the LA function. A Cox proportional hazards model adjusted for age, sex, hypertension, diabetes, moderate or severe MR, LV ejection fraction <50%, and MV intervention or implantable cardioverter defibrillator placement (included as a time-dependent variable) was used to determine the independent association of LA function with the primary end point. Results were presented as a hazard ratio with a 95% CI. Net reclassification index was used to determine the incremental prognostic value of the LA function parameters in predicting the 5-year risk of cardiac events. A 2-tailed $P<0.05$ was considered significant. Statistical analyses were performed with Stata software version 14.2 (StataCorp, College Station, TX).

RESULTS

Study Population

After excluding MVP cases with suboptimal image quality, prior MV intervention, heart failure, or AF (Figure 1), there were 334 MVPs in our study sample. Clinical, ECG, and echocardiographic characteristics are presented in Table 1. LA enlargement (ie, LA volume index >34 mL/m^2) was present in 41% of the study population. MVPs with LA enlargement were older and had a higher prevalence of hypertension compared with MVPs without LA enlargement (Table 1). There were no significant differences between groups with regard to ventricular arrhythmias or the presence of T-wave inversions (Table 1). There was a greater proportion of flail or bileaflet involvement, larger LV volumes and mass index, more significant MR, and consequently a higher (albeit normal) average E/e' ratio in MVPs with LA enlargement (Table 1). The prevalence of MAD was similar according to LA enlargement (42% versus 38%; $P=0.43$; Table 1). Among the 213 (64%) MVPs with a measurable pulmonary artery systolic pressure, pulmonary pressures were overall normal but higher in those with increased LA size. LV and right ventricular systolic function were similar in those MVPs with and without LA enlargement (Table 1).

MVP Subtype, MAD, and LA Myopathy

Considering the impact of MR severity on LA function, parameters of LA function were compared across MVP subtypes according to MR severity (Figure 2). In both categories of MR severity (no/mild and moderate/severe), median LASr and LAFI were lower in bileaflet MVP compared with other MVP subtypes (Figure 2A through 2D), whereas LAEF was similar across MVP subtypes (Figure 2E and 2F). In MVPs with no/mild MR, median LASr and LAFI were significantly lower in the bileaflet compared with posterior and anterior MVP (all $P<0.05$; Figure 2A and 2C).

We further explored the role of MAD as a determinant of LA function in addition to bileaflet involvement (Figure S1). Bileaflet MVP with MAD had significantly lower LASr compared with other subgroups ($P=0.005$), but there were no significant differences in LAFI ($P=0.09$) or LAEF ($P=0.27$; Figure S1). Furthermore, when examined based on LA staging, the combination of both mitral anatomic abnormalities was associated with advanced LA myopathy ($P=0.03$; Table S1).

In multivariable linear regression analysis, factors significantly associated with lower LA function as quantified by LASr included bileaflet MVP, MAD, and LV global longitudinal strain (all $P<0.05$), but not moderate-severe MR (Table 2). In contrast, significant MR was an important contributor of LAFI and LAEF in addition to bileaflet involvement. There was no significant interaction between bileaflet MVP, MAD, or LV global longitudinal strain in relation to LASr (all $P>0.67$). Results remained consistent when the LV mass index was included instead of the LV volume index (Table S2). E/e', included in our multivariable model, is known to be artificially increased in patients with moderate-severe MR. After excluding such patients in a sensitivity analysis and adjusting for more accurate E/e' values, bileaflet involvement remained a significant predictor of LA function (Table S3). The mean variance inflation factor ranged between 1.25 and 1.28 across all models, indicating a low level of multicollinearity.

LA Myopathy and Clinical Outcome

During a median follow-up of 5.4 years, the primary clinical end point occurred in 44 patients (13%), of whom 4 (9%) had cardiac death (including 1 sudden arrhythmic death), 1 (2%) had congestive heart failure, and 39 (88%) had new onset AF. Of these events, 1 patient lacked information about the date of death, leaving 43 events for the time-to-event analysis. Additionally, 46 (14%) patients underwent surgical intervention, including 38 MV repairs (one of which involved an implantable cardioverter defibrillator placement due to ventricular tachycardia following repair) and 8 replacements.

Figure 3 shows the overall risk of the composite events according to LA function parameters. There was a gradual and significant increase in the risk of events with the decrease in tertiles of LASr and LAFI (all $P<0.05$;

Table 1. Characteristics of the Study Population

	All patients, N=334	MVP without LA enlargement, n=197 (59%)	MVP with LA enlargement*, n=137 (41%)	*P* value
Clinical characteristics				
Age, y	56±16	55±17	60±16	0.005
Female, n (%)	167 (50)	93 (47)	74 (54)	0.22
Body surface area, m²	1.81±0.23	1.79±0.23	1.85±0.24	0.02
Hypertension, n (%)	124 (37)	65 (33)	59 (43)	0.06
Diabetes, n (%)	24 (7)	17 (9)	7 (5)	0.22
Coronary artery disease, n (%)	26 (7)	14 (7)	12 (9)	0.58
Smoking, n (%)	107 (32)	65 (33)	42 (31)	0.65
Arrhythmic characteristics				
Ventricular tachycardia, n (%)	37 (11)	19 (10)	18 (13)	0.32
PVC, n (%)	3 (1)	1 (1)	2 (2)	0.57
Echocardiographic characteristics				
MVP anatomy				0.03
Flail, n (%)	19 (5)	8 (4)	11 (8)	
Bileaflet, n (%)	146 (43)	78 (40)	68 (50)	
Posterior, n (%)	123 (37)	77 (39)	46 (34)	
Anterior, n (%)	46 (13)	34 (17)	12 (9)	
Mitral regurgitation grade				<0.001
None/trace, n (%)	90 (27)	69 (35)	21 (15)	
Mild, n (%)	144 (43)	93 (47)	52 (38)	
Moderate, n (%)	72 (22)	28 (14)	44 (32)	
Severe, n (%)	27 (8)	7 (4)	20 (15)	
MAD, n (%)	133 (39)	75 (38)	58 (42)	0.43
LA volume index, mL/m²	34±18	24±6	50±21	<0.001
LASr, %	31±9	34±9	28±8	<0.001
LA function index	0.37±0.19	0.48±0.17	0.21±0.11	<0.001
LA emptying fraction, %	52±11	56±10	47±12	<0.001
LV end-diastolic volume, mL/m²	69±20	62±15	80±23	<0.001
LV end-systolic volume, mL/m²	29±10	27±8	34±13	<0.001
LV mass index, g/m²	83±24	75±21	93±25	<0.001
LV-GLS, %	−20±4	−20±3	−21±4	0.18
E/A ratio	1.3±0.6	1.2±0.6	1.4±0.6	<0.001
E/e' ratio	9.5±4.2	8.6±3.4	10.8±4.8	<0.001
LV ejection fraction, %	57±7	56±7	58±8	0.14
PASP (n=213), mm Hg	28±12	25±2	31±12	<0.001
RV systolic function				0.56
Normal, n (%)	322 (96)	187 (95)	135 (98)	
≥Mildly reduced, n (%)	12 (4)	9 (5)	3 (2)	

Values are presented as mean±SD.

LA indicates left atrial; LASr, LA reservoir strain; LV, left ventricular; LV-GLS, LV global longitudinal strain; MAD, mitral annular disjunction; MVP, mitral valve prolapse; PASP, pulmonary artery systolic pressure; PVC, premature ventricular contraction; and RV, right ventricular.

*Defined by LA volume index >34 mL/m².

Figure 3A and 3B), while there was no significant difference according to tertiles of LAEF (*P*=0.09; Figure 3C).

After multivariable adjustment for risk factors including moderate-severe MR, the mid- and lower tertiles of LASr remained significantly associated with a higher risk of events compared with the upper tertile of LASr (Table 3). There was no significant risk of events between the tertiles of LAFI or LAEF (Table 3).

We then tested the prognostic value of LA remodeling staging. There was a progressive and significant increase

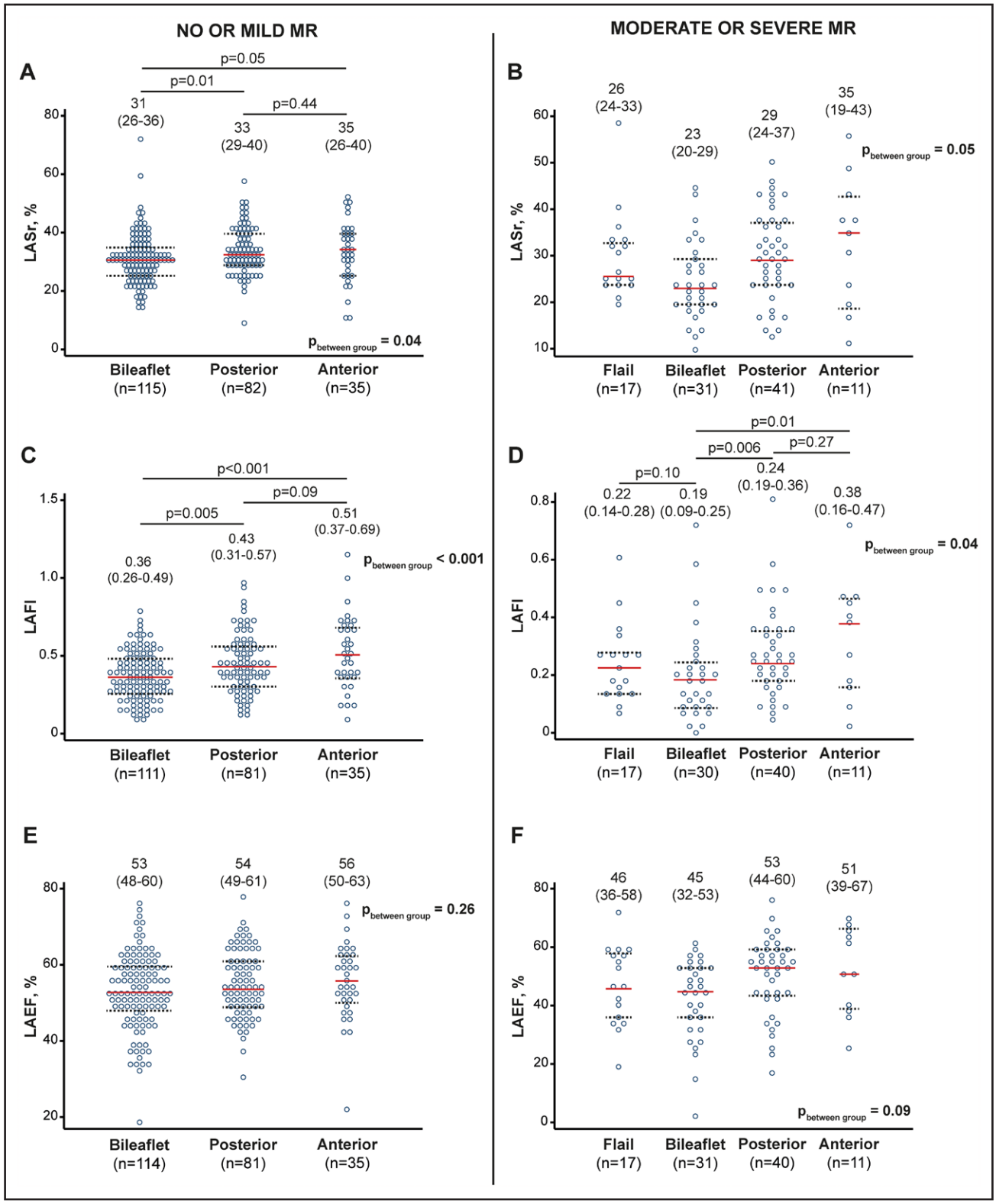

Figure 2. Distribution of LA function parameters according to MVP subtypes and MR severity.
Comparison of LASr, LAFI, and LAEF according to MVP subtypes in no or mild (**A**, **C**, **E**) and moderate or severe (**B**, **D**, **F**) MR subgroups. The dot plot shows the median value (red line), and the error bars (dotted black line) represent the interquartile range (IQR). Numbers on top of the plot indicate the median with IQR between brackets. Numbers between brackets below the graph are number of patients. LA indicates left atrium; LAEF, left atrial emptying fraction; LAFI, left atrial function index; LASr, left atrial reservoir strain; MR, mitral regurgitation; and MVP, mitral valve prolapse.

Table 2. Factors Associated With Parameters of LA Function

	Univariable analysis		Multivariable analysis*	
	β±SE	*P* value	β±SE	*P* value
LA reservoir strain				
Ventricular arrhythmias	−0.06±1.58	0.26	…	…
MVP-bileaflet	−0.14±1.02	0.008	−0.18±0.99	0.001
Moderate or severe MR	−0.19±1.10	<0.001	−0.05±1.13	0.31
Presence of MAD	−0.15±1.03	0.005	−0.11±1.02	0.04
LV-GLS	−0.36±0.14	<0.001	−0.28±0.15	<0.001
LA function index				
Ventricular arrhythmias	−0.06±0.03	0.32	…	…
MVP-bileaflet	−0.16±0.02	0.005	−0.21±0.02	<0.001
Moderate or severe MR	−0.40±0.02	<0.001	−0.28±0.03	<0.001
Presence of MAD	−0.11±0.02	0.08	−0.07±0.02	0.20
LV-GLS	−0.09±0.003	0.08	−0.01±0.003	0.81
LA emptying fraction				
Ventricular arrhythmias	0.04±1.94	0.52	…	…
MVP-bileaflet	−0.11±1.27	0.06	−0.21±1.28	<0.001
Moderate or severe MR	−0.28±1.33	<0.001	−0.22±1.46	<0.001
Presence of MAD	−0.03±1.40	0.60	0.05±1.32	0.43
LV-GLS	−0.26±0.17	<0.001	−0.30±0.19	<0.001

Values are beta standardized coefficient (β)±SE. LA indicates left atrial; LV-GLS, left ventricular global longitudinal strain; MAD, mitral annular disjunction; MR, mitral regurgitation; and MVP, mitral valve prolapse.

*Multivariable model including age, sex, hypertension, diabetes, coronary artery disease; left ventricular end-systolic volume, E/e' ratio, and right ventricular systolic function.

in the risk of events with the increase in LA remodeling staging ($P<0.001$; Figure 3D). The prognostic significance of LA remodeling staging was further tested according to MAD (Figure S2). There was a significant increase in the risk of events with the increase in LA remodeling staging, irrespective of MAD ($P_{interaction}=0.99$; Figure S2).

In multivariable adjustment including MR and MV intervention and/or implantable cardioverter defibrillator placement, stage 4 of LA remodeling remained significantly associated with a higher risk of events compared with stage 1 (hazard ratio, 6.09 [95% CI, 1.69–21.9]; $P=0.006$; Table 3).

Incremental Prognostic Value of LA Parameters

The addition of LASr, LAFI, and LA remodeling staging in the multivariable base model significantly improved the 5-year risk prediction of events (Table S4).

DISCUSSION

The main findings of the present study are as follows: (1) bileaflet MVP is an independent predictor of reduced atrial function as assessed by LASr, LAFI, and LAEF; (2) reduced LA function is significantly associated with a higher risk of composite cardiac death, heart failure hospitalization, or new onset of AF, regardless of significant MR; and (3) staging of LA remodeling based on LASr and LA enlargement provides incremental value beyond significant MR to prediction of cardiovascular risk.

Evidence of a Primary Atriopathy in MVP

In our study, inclusive of different MVP subtypes and various degrees of MR severity, we provide a comprehensive assessment of LA function using LASr, LAFI, and LAEF. We demonstrate that LA function can be significantly altered in MVP patients even without significant MR, suggesting the existence of a primary atriopathy. Recently, Yang et al[21] found that MVP with less than moderate MR was associated with LA remodeling but focused on LA volume and did not investigate MVP-related differences in LA function. We found that bileaflet MVP is independently associated with lower LA function, and this observation was consistent for each parameter of LA function and after comprehensive multivariable adjustment. LV filling pressures by E/e' were overall normal and did not affect this association, suggesting that the observed atriopathy is not a consequence of diastolic dysfunction. Among LA function parameters, LASr, less influenced by moderate-severe MR compared with LAFI and LAEF (both derived from LA volumes), may represent the ideal diagnostic tool for detection of this MVP-related primary atriopathy.

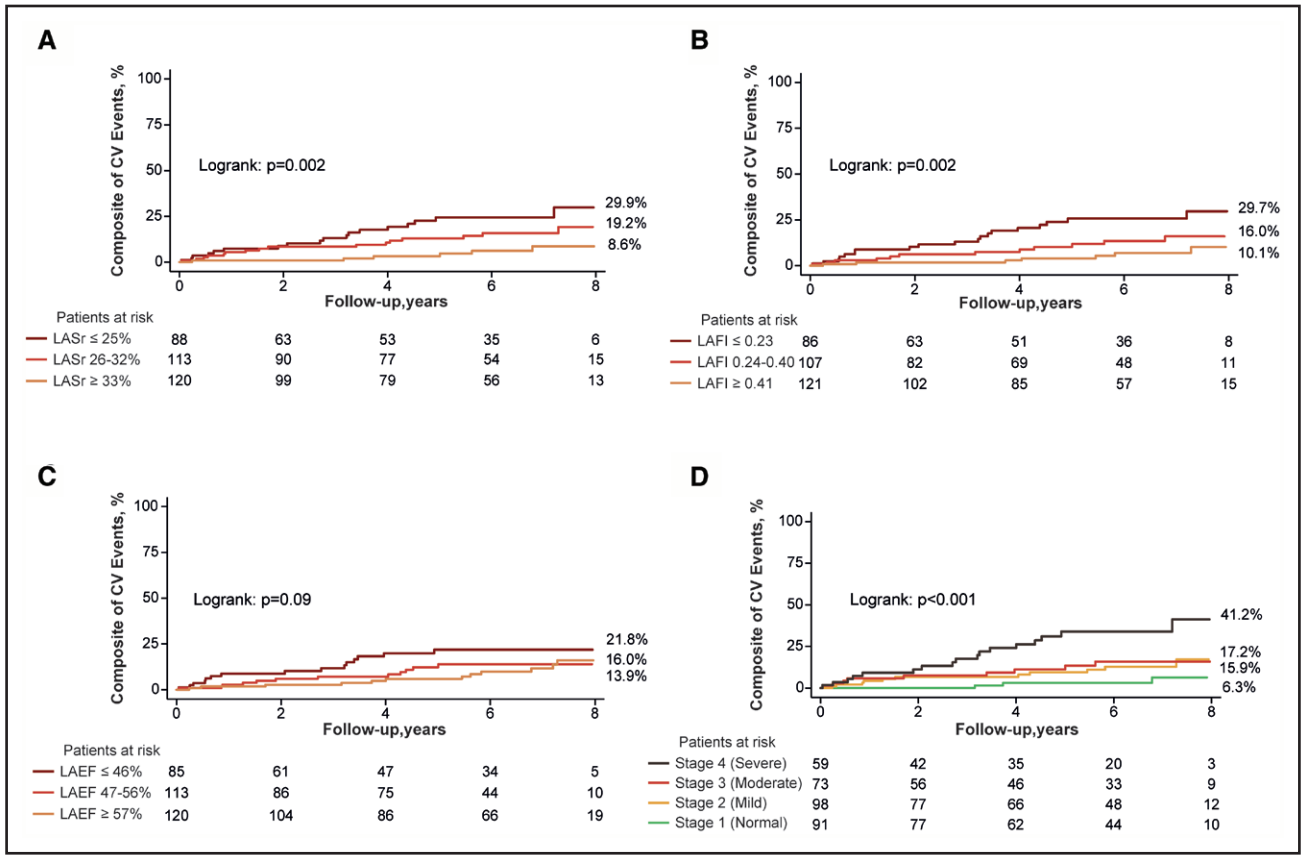

Figure 3. Risk of clinical events according to LA function.
Survival curves with risk of cardiac death, heart failure hospitalization, or new onset of atrial fibrillation according to tertiles of LASr (**A**), LAFI (**B**), and the stage of LA remodeling (**C**). Patients were classified as follows: stage 1 (no remodeling); stage 2 (mild remodeling); stage 3 (moderate remodeling); and stage 4 (severe remodeling). Next to each curve is the percentage of patients with increased risk of events at 8 years of follow-up. Bottom numbers refer to patients at risk at each time interval. CV indicates cardiovascular; LA, left atrium; LAEF, left atrial emptying fraction; LAFI, left atrial function index; and LASr, left atrial reservoir strain.

The underlying mechanism for lower atrial function in bileaflet MVP without severe MR remains to be elucidated. We hypothesize that LA function may be affected by complex valvular-ventricular mechanics commonly associated with this MVP phenotype, with atrialization of mitral leaflets. As hypothesized for the LV, it is possible that the repetitive traction of billowing MV leaflets alongside abnormal mitral annular motion could increase mechanical stretch on the LA.[6] Therefore, increased mechanical traction of the LA walls could contribute to LA remodeling, wall thickening and fibrosis, and ultimately impairment. Conversely, a larger prolapse volume, typically associated with bileaflet MVP,[22] could impair LA filling and reduce the available LA volume during the filling phase, thereby contributing to the deterioration of LA function. Interestingly, the prolapse volume has been related to both LV and LA remodeling, namely increased LA volume, in prior literature.[22] Nevertheless, whether it may directly contribute to impaired LA function remains to be determined.

Beyond the hypothesis of abnormal valvular-atrial mechanics, a primary atriomyopathy could be linked to a genetically determined extracellular matrix dysregulation similar to what is observed at the valvular level.[23,24] Hence, a genetic atriopathy could be contributing to LA remodeling and fibrosis in bileaflet MVP.[1] Further studies are needed to test this hypothesis.

LA Function in MVP: A Complex Interplay With MAD

MAD can augment abnormal valvular-myocardial mechanics with papillary muscle traction by prolapsing leaflets and curling of the inferolateral basal LV.[25] However, the impact of MAD on LA function in MVP has received less attention.

In our study, MAD was associated with lower LA function, namely LASr, but not LAFI and LAEF, which are derived from LA volumes. Prior studies have reported no significant association between MAD and LA function as assessed by LA volumes in MVP.[21,26] However, LA volumes are intimately influenced by MR severity and could have masked the potential impact of MAD. Indeed, in our study, MAD was not a significant

Table 3. LA Function and Risk of Cardiovascular Events

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Model including				
LA reservoir strain				
Upper tertile (≥33%)	Ref.		Ref.	
Mid tertile (low: 32%–26%)	3.20 (1.28–8.02)	0.01	2.65 (1.05–6.69)	0.04
Lower tertile (very low: ≤25%)	4.64 (1.84–11.7)	0.001	2.76 (1.05–7.29)	0.04
Model including				
LA function index				
Upper tertile (≥0.41)	Ref.		Ref.	
Mid tertile (low: 0.40–0.24)	2.02 (0.84–4.89)	0.12	1.90 (0.78–4.64)	0.16
Lower tertile (very low: ≤0.23)	3.99 (1.76–9.06)	0.001	2.39 (0.95–5.99)	0.06
Model including				
LA emptying fraction				
Upper tertile (≥57%)	Ref.		Ref.	
Mid tertile (low: 56%–47%)	1.57 (0.73–3.35)	0.25	1.21 (0.55–2.67)	0.64
Lower tertile (very low: ≤46%)	2.30 (1.07–4.92)	0.03	1.31 (0.57–2.99)	0.52
Model including				
Stages of LA remodeling				
Stage 1 (no remodeling)	Ref.		Ref.	
Stage 2 (mild remodeling)	3.64 (1.03–12.9)	0.04	3.18 (0.88–11.5)	0.08
Stage 3 (moderate remodeling)	4.77 (1.33–17.1)	0.02	3.49 (0.95–12.8)	0.06
Stage 4 (severe remodeling)	10.6 (3.10–36.2)	<0.001	6.09 (1.69–21.9)	0.006

Values are hazard ratio (HR) with 95% CI.

Multivariable model adjusted for age, sex, moderate or severe mitral regurgitation, left ventricular ejection fraction <50%, and mitral valve intervention or implantable cardioverter defibrillator implantation (time-dependent variable). LA indicates left atrial.

predictor of LAFI or LAEF after multivariable adjustment, including MR severity. However, unlike LAFI and LAEF, LA strain as quantified by STE (ie, LA reservoir function) is less load-dependent when assessing the extent of contraction of LA myocardium.[27] Previous findings have also demonstrated that LA strain by STE may be used as a surrogate marker for atrial fibrosis.[28] Consequently, while LA volume and the parameters derived from LA volume are reliable indices of LA function, they may not be able to capture the entirety of LA mechanics.[13]

The interdependency of LA and LV strains observed in our study has been previously reported.[29] Our results suggest that the contribution of MAD to LA strain is independent of LV longitudinal function. Nevertheless, the complex interplay between LV and LA functions in the presence of MAD warrants further investigation. Altogether, these findings emphasize the importance of LA strain as a useful noninvasive imaging biomarker for characterizing the morphofunctional impact of MAD on atrial function in MVP.

Finally, beyond the presence of MAD, whether the type and severity (ie, length) of MAD are causally linked to LA impairment or serve as markers for LA remodeling and dysfunction merits further investigation.

LA Function and Risk of Cardiac Events in MVP

Prior studies support the prognostic role of LA functional assessment in MVP.[12,13] However, our study is unique in that it evaluates the outcome related to LA function based on LA strain assessment. Moreover, prior studies predicted overall mortality rather than focusing on cardiovascular outcomes, including atrial arrhythmic events and cardiac death, that are more closely related to a malignant MVP phenotype. A prior study also tested the prognostic utility of LA function as assessed by STE; however, this study only assessed the risk of MV surgery in a population with moderate or severe MR.[30] In the present study, using a multiparametric assessment of LA function, including for the first time STE, we demonstrate that lower LA function as quantified by LASr and LAFI is associated with a higher risk of composite clinical events including cardiac death, heart failure hospitalization, or the new onset of AF, irrespective of MR severity. Notably, the composite of clinical events was primarily influenced by the occurrence of AF. In addition to impacting individual quality of life, AF is a trigger for subsequent major clinical outcomes, including heart failure and increased morbidity and mortality.

The lack of association between LAEF and cardiovascular events could be related to the confounding effect of LA volume and MR severity. Therefore, LAEF may have lesser clinical significance for risk stratification in patients with MVP as it may not capture the primary fibrotic atriopathy better identified by LASr. Hence, we propose a classification of the extent of LA remodeling based on LA volume and LASr alone. Based on this classification, we demonstrate a gradual increase in the risk of cardiovascular events with the increase in LA remodeling stage, irrespective of significant MR. Consequently, a comprehensive assessment of LA function may help identify patients with MVP and a primary atriopathy who may benefit from closer clinical and imaging follow-up.

Study Limitations

The present study was a retrospective analysis and thus has inherent limitations related to such a design. The characterization of LA fibrosis using imaging modalities and/or histology was not available in the present analysis. Therefore, additional studies are needed to test the hypothesis of atrial myopathy driven by fibrosis, potentially leading to the onset of atrial arrhythmia.

Conclusions

Bileaflet MVP is associated with lower LA function regardless of MR severity, suggesting a primary atriopathy in this MVP subtype. A novel STE-based staging of LA remodeling is linked to a higher risk of cardiovascular events in MVP and provides incremental prognostic value beyond standard risk factors, including severe MR. Hence, a multiparametric assessment of LA function by echocardiography may improve risk stratification in MVP and could represent a useful tool in clinical practice.

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Disclosures

None.

Supplemental Material

Supplemental Methods
Figures S1 and S2
Tables S1–S4

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