Mitral Annular and Left Ventricular Dynamics in Atrial Functional Mitral Regurgitation: A Three-Dimensional and Speckle-Tracking Echocardiographic Study

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Background: Patients with atrial fibrillation (AF) and left atrial (LA) enlargement may develop functional, normal leaflet motion mitral regurgitation (MR) without left ventricular (LV) remodeling. Mitral annular dynamics and LV mechanics are important for preserving normal mitral valve function. The aim of this study was to assess the annular and LV dynamics in patients with AF and functional MR.

Methods: Twenty-one patients with AF with moderate or more MR (AFMR+ group), 46 matched patients with AF with no or mild MR (AFMR− group), and 19 normal patients were retrospectively studied. Mitral annular dynamics were quantitatively assessed using three-dimensional echocardiography. Systolic LV global longitudinal strain (GLS), global circumferential strain, and LA strain were measured using two-dimensional speckle-tracking echocardiography.

Results: The normal annulus displayed presystolic followed by systolic contraction and increase in saddle shape ($P < .01$ for all). Presystolic annular dynamics were abolished in both groups of patients with AF ($P > .05$ vs normal). In contrast, systolic and total annular dynamics during the cardiac cycle were preserved in AFMR− patients ($P > .10$ vs normal) but impaired in AFMR+ patients ($P < .05$ vs normal and AFMR−). LV GLS ($P < .0001$) and LA strain ($P = .02$), but not LV global circumferential strain ($P = .97$), were impaired in AFMR+ compared with AFMR− patients despite comparable LA and LV volumes. MR severity correlated with systolic annular contraction ($r = 0.64$, $P < .0001$), saddle deepening ($r = 0.53$, $P = .003$), and LV GLS ($r = 0.46$, $P < .0001$). Multivariate analysis identified that impaired systolic contraction (odds ratio, 2.18; $P = .001$) and saddle deepening (odds ratio, 2.68; $P = .04$) were independently associated with MR. Excluding annular dynamics from the model, less negative LV GLS, but not LA strain, became associated with MR (odds ratio, 1.93; $P < .0001$).

Conclusions: In patients with AF and absent LA contraction, the normal predominantly "atriogenic" annular dynamics become "ventriculogenic." Isolated LA enlargement is insufficient to cause important MR without coexisting abnormal LV mechanics and annular dynamics during systole. "Atrial" functional MR may not be purely an atrial disorder. (J Am Soc Echocardiogr 2019;32:503-13.)

Keywords: Mitral regurgitation, Atrial fibrillation, Three-dimensional echocardiography

In patients with atrial fibrillation (AF), secondary, normal leaflet motion mitral regurgitation (MR) may occur in the absence of left ventricular (LV) remodeling.[1,2] This form of MR has been termed "atrial functional MR" (AFMR),[2] implying that it is a disorder of the left atrium. However, the precise mechanisms by which AF causes MR remain incompletely understood. It was postulated that left atrial

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Abbreviations

3D = Three-dimensional

3DE = Three-dimensional echocardiography

AF = Atrial fibrillation

AFMR = Atrial functional mitral regurgitation

AL-PM = Anterolateral-posteromedial

AP = Anteroposterior

EROA = Effective regurgitant orifice area

GCS = Global circumferential strain

GLS = Global longitudinal strain

LA = Left atrial

LAS = Left atrial systolic reservoir strain

LV = Left ventricular

LVEF = Left ventricular ejection fraction

MR = Mitral regurgitation

NPA = Nonplanarity angle

(LA) enlargement associated with persistent AF leads to mitral annular dilation and causes important MR.[1] However, other studies have suggested that isolated annular dilation does not usually cause important MR without LV dilation and dysfunction.[3] Additionally, LA enlargement can be a cause or consequence, or both, of MR, potentially confounding any causality implication. These conflicting results suggest that factors other than atrial and annular dilation may also be important in the pathogenesis of MR.

The mitral annulus is a three-dimensional (3D) structure that undergoes complex conformational change during the cardiac cycle.[4-6] Because the mitral annulus consists of a fibrous tissue plane with no intrinsic contractile elements, annular dynamics are passively determined by extrinsic LA and LV myocardial mechanics.[7] Previous animal models[8,9] and clinical studies[10,11] have revealed presystolic area reduction of the annulus, related to LA contraction, and minimal annular area occurs during LV systole. However, limited data exist on the dynamic effects of AF on the annulus and its relation with the occurrence of MR in patients. Advances in 3D echocardiography (3DE) have allowed quantitative analysis of mitral annular dynamics, whereas speckle-tracking echocardiography can assess LA and LV myocardial mechanics. In the present study, we hypothesize that "atrial" functional MR is associated with abnormal annular dynamics that are functionally linked to atrial and ventricular myocardial function. To test this hypothesis, we used transthoracic 3DE to study the annular dynamics in relation to LA and LV function assessed using speckle-tracking echocardiography. We studied patients with AF with secondary, normal leaflet motion MR without LV enlargement, those without important MR, and normal control subjects. We sought to compare and contrast annular, atrial, and ventricular dynamics throughout the cardiac cycle in these patient populations.

METHODS

Population

We retrospectively screened 1,265 patients with AF who underwent clinically indicated transthoracic echocardiography between March 2013 and June 2015. The definition of AFMR was as follows: MR of at least moderate severity (effective regurgitant orifice area [EROA] $\geq$ 0.2 cm^2) that occurs in AF with normal leaflet motion without LV enlargement or leaflet pathology. Exclusion criteria were primary MR caused by valve prolapse, calcification, or stenosis; LV end-diastolic volume index $>$ 79 mL/m^2 for men and $>$71 mL/m^2 for women by 3DE,[12] LV ejection fraction (LVEF) $\leq$ 50%, and/or regional wall motion abnormality; prior cardiac surgery; and cardiomyopathy or congenital or pericardial disease. Twenty-one subjects with moderate or more "atrial" functional MR (AFMR+ group) were identified and enrolled into this study. The AFMR+ group was compared with 46 AF control subjects (AFMR− group). The AFMR− group was created from a larger group of subjects with AF with LA enlargement but no or mild MR (EROA $<$ 0.2 cm^2) using frequency matching for age, gender, and LA volume index. The process ensured that the two groups had similar mean characteristics of interest, in this case age, gender, and LA volume index, though not necessarily equal numbers. AF was defined as paroxysmal if typical episodes were self-terminating in $<$7 days and persistent if episodes lasted $\geq$7 days. In addition, a group of 19 subjects created by frequency matching for mean age and gender distribution with no history of arrhythmia and normal echocardiography were included as normal control subjects. The study protocol was approved by ethics committee of the institution.

Echocardiography

Transthoracic 3DE was performed using an EPIQ7 system with an X5-1 matrix transducer (Philips Medical Systems, Andover, MA). For all measurements in patients with AF, the index-beat method was used to select the beat with approximately equal preceding and pre-preceding beat intervals for analysis.[13] Quantitative assessment of MR severity was made by measuring EROA using the proximal flow convergence method according to the recommendation of the American Society of Echocardiography.[14] EROA cutoffs for mild, moderate, and severe MR were $>$0 to $<$0.2, $\geq$0.2 to $<$0.4, and $\geq$0.4 cm^2, respectively. Supportive parameters including jet area and continuous-wave Doppler jet profile were examined as an integrative approach to evaluation of MR severity.

Three-dimensional echocardiographic images of the mitral valve were acquired from the apical window. The region of interest was adjusted to the smallest pyramidal volume that encompassed the mitral valve. The high-volume-rate single-beat acquisition protocol was used to avoid stitching artifact as a result of AF while maintaining an adequate volume rate. Volume rates were maximized to $>$15 volume/sec (mean volume rate, 22 $\pm$ 5 volume/sec). All 3D echocardiographic data sets were digitally stored and exported offline to an Image Arena, 4D-MV Assessment, version 2.3 (TomTec Imaging Systems, Munich, Germany) software workstation for image analysis. Mitral annular tracking was initiated at a mid-systolic frame using the semiautomated program. Dynamic models were created by tracking the annulus throughout each frame of the cardiac cycle. Annular measurements were made at seven time points throughout the cardiac cycle: (1) early diastole (the frame after mitral valve opening), (2) mid-diastole (the middle frame between early and late diastole), (3) late diastole (the frame before mitral valve closure), (4) mitral valve closure (the frame with mitral valve closed but before aortic valve opens), (5) early systole (the frame after aortic valve opening), (6) mid-systole (the middle frame between early and late systole), and (7) late systole (the frame before aortic valve closure). At each time point, the following annular parameters were measured: anteroposterior (AP) diameter, anterolateral-

HIGHLIGHTS

- Mechanisms of AFMR are incompletely understood.
- Mitral annular dynamics are linked to LA and LV myocardial contractions.
- Presystolic annular contraction and saddling are absent in AF but LV GLS is normal.
- Systolic annular dynamics and LV GLS are impaired in patients with AFMR.
- The so-called AFMR may not be purely an atrial disorder.

posteromedial (AL-PM) diameter, annular area, circumference, annular height, and nonplanarity angle (NPA), as shown in Figure 1. The presystolic (i.e., before mitral valve closure) and systolic percentage change (Δ) of AP diameter, AL-PM diameter, area, circumference, and NPA were calculated using the following formulas.

$$\text{Presystolic}\Delta = \frac{\text{Late diastolic value} - \text{Maximum diastolic value}}{\text{Maximum diastolic value}} \times 100\%$$

$$\text{Systolic}\Delta = \frac{\text{Minimum systolic value} - \text{Late diastolic value}}{\text{Late diastolic value}} \times 100\%$$

$$\text{Total}\Delta = \frac{\text{Minimum systolic value} - \text{Maximum diastolic value}}{\text{Maximum diastolic value}} \times 100\%$$

Percentage changes of annular height were calculated using the following formulas.

$$\text{Presystolic}\Delta = \frac{\text{Late diastolic height} - \text{Minimum diastolic height}}{\text{Minimum diastolic height}} \times 100\%$$

$$\text{Systolic}\Delta = \frac{\text{Maximum systolic height} - \text{Late diastolic height}}{\text{Late diastolic height}} \times 100\%$$

$$\text{Total}\Delta = \frac{\text{Maximum systolic height} - \text{Minimum diastolic height}}{\text{Minimum diastolic height}} \times 100\%$$

LA and LV Function

LV end-diastolic volume, LV end-systolic volume, and LVEF were determined using 3D echocardiographic volumetric analysis without geometric assumptions (QLAB version 10.8; Philips Medical Systems). LA volume was assessed using the biplane area-length method.[12] Speckle-tracking echocardiography was used to evaluate LA and LV strain. Two-dimensional grayscale harmonic images at the three apical views (four-chamber, two-chamber, and long-axis) and the three parasternal short-axis views (basal, mid, and apical) were analyzed offline on a QLAB version 10.8 workstation. LV global longitudinal strain (GLS) was calculated by averaging the negative peak systolic strains derived from the three apical views and LV global circumferential strain (GCS) from the short-axis views. Peak LA systolic reservoir strain (LAS) was obtained by manually defining the LA wall in the three apical views, using R wave as the initiation of the strain calculation.[15,16] On each view, the region of interest encompassed the LA wall thickness and was divided into six segments by the software. The results of positive peak systolic strain of each segment were averaged to obtain LAS.

Statistical Analysis

Data are reported as mean ± SD or number (percentage) as appropriate. Between-group comparisons of baseline characteristics, summarized measures of mitral annulus, and strains used one-way analysis of variance with post hoc Tukey honestly significantly different comparisons and χ^2 tests as appropriate. Mitral annular dynamics throughout the cardiac cycle were compared between groups using repeated-measures analysis of variance. The Pearson coefficient was used for correlation analysis among EROA, annular dynamics, and strains. To identify independent factors associated with moderate or more MR, univariate analysis was performed for all clinical and echocardiographic variables, including age, gender, rhythm, blood pressures, heart rate, medications, LA and LV volume index, LVEF, annular dynamics, and strains. Among all annular dynamic parameters, Δarea and ΔNPA were tested in the models, as they have been shown to be predictors of MR without testing all related annular parameters to avoid collinearity.[1] Variables with P values ≤ .10 on univariate analysis were tested in the multivariate logistic regression with the forward stepwise method. Intraobserver and interobserver variabilities of EROA and strain measurements were assessed using intraclass correlation coefficients and within-subject coefficients of variation of repeated analysis in 10 randomly selected subjects by the same operator 1 week apart and by a different operator. Reproducibility of annular dynamic 3D echocardiographic analysis was previously reported.[17] Two-tailed P values < .05 were considered to indicate statistical significance. Analyses were performed with JMP version 12.0 (SAS Institute, Cary, NC) and SPSS version 16.0 (IBM, Armonk, NY).

RESULTS

Patient Characteristics

There were no differences in age, gender, body surface area, heart rate, blood pressures, cardiovascular medications, LV volumes index, and LVEF among the three groups (P = NS for all; Table 1). The frequency of persistent AF in the AFMR+ group was higher than in the AFMR− group but did not reach statistical significance (90% vs 75%, P = .20). The LA volume index in the AF groups was matched and was significantly increased compared with normal subjects (P < .0001 for both).

Mitral Annular Structure and Dynamic Function

Annular dimensions averaged over the cardiac cycle are shown in Table 2. Compared with normal subjects, the mitral annulus of both AF groups had increased AP diameter, AL-PM diameter, area, circumference, and NPA and decreased annular height (P < .0001 for all for both AF groups vs normal). Annular AP diameter (P = .005), area (P = .008), and NPA (P = .01) were greater, and height (P = .01) was lower in the AFMR+ than the AFMR− group, with similar AL-PM diameter (P = .31) and circumference (P = .46).

Dynamically, dramatic intergroup differences were observed (Table 2, Figure 2). In normal subjects, AP diameter, AL-PM diameter, area, and circumference decreased in late diastole (P < .01 vs mid-diastole) and further decreased after mitral valve closure. The

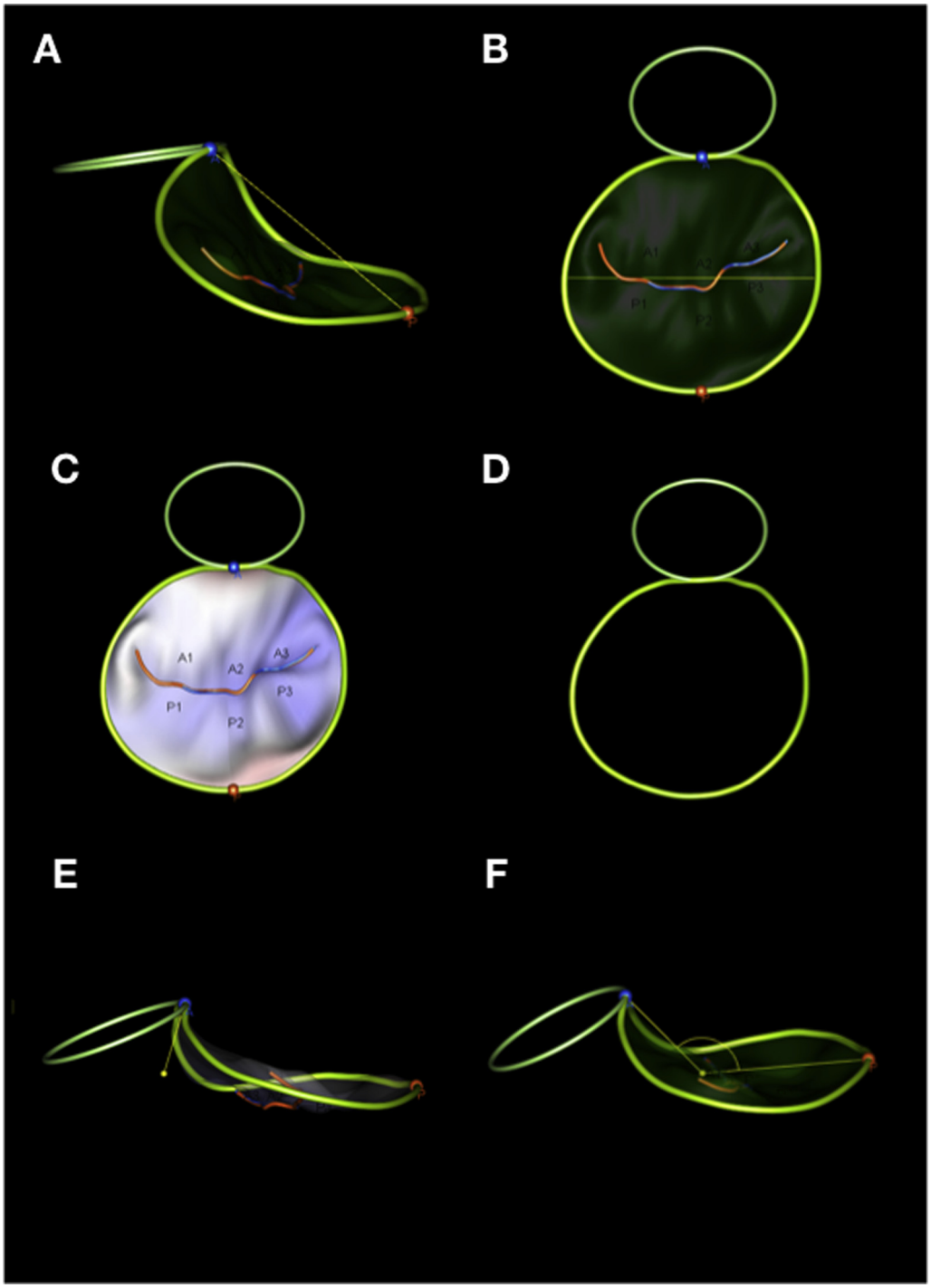

Figure 1 Mitral annular geometry. **(A)** AP diameter (distance between anterior and posterior horns), **(B)** AL-PM diameter (distance between anterolateral and posteromedial annular points), **(C)** area (projected area of the annulus), **(D)** circumference, **(E)** height (vertical distance between the highest and lowest annular points), and **(F)** NPA (angle subtended between anterior and posterior horns at the commissural diameter).

reduction of AP diameter was abrupt, reaching its minimum in early systole, whereas the reductions of AL-PM diameter, area, and circumference were more gradual, reaching their minimums in mid-systole. In late diastole, annular height increased and NPA decreased ($P < .05$ for both vs mid-diastole), indicating a presystolic increase in saddle shape. The saddle shape further increased in systole, with the deepest saddle occurring after mitral valve closure.

In AFMR− patients, no dynamic changes in AP diameter, AL-PM diameter, area, and circumference were detected in late diastole ($P =$ NS for all vs mid-diastole). However, there were dynamic systolic reductions in annular dimensions after mitral valve closure ($P < .05$ for

Table 1 Patient characteristics

Variable	Normal (n = 19)	AFMR− (n = 46)	AFMR+ (n = 21)	P
Age (y)	69 ± 8	70 ± 7	71 ± 11	.73
Men	8 (42)	19 (41)	9 (43)	.80
Body surface area (m^2)	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.1	.98
Persistent AF	NA	35 (76)	19 (90)	.20
Heart rate (beats/min)	68 ± 9	74 ± 13	75 ± 12	.12
Systolic blood pressure (mm Hg)	138 ± 21	137 ± 22	136 ± 24	.96
Diastolic blood pressure (mm Hg)	81 ± 10	79 ± 12	74 ± 13	.31
LA volume (mL)	40 ± 6	82 ± 22*	88 ± 15*	<.0001
LA volume index (mL/m^2)	24 ± 4	48 ± 10*	52 ± 10*	<.0001
LVEDV (mL)	81 ± 14	83 ± 14	81 ± 19	.82
LVEDV index (mL/m^2)	48 ± 7	49 ± 8	48 ± 10	.71
LVESV (mL)	32 ± 6	35 ± 7	34 ± 9	.35
LVESV index (mL/m^2)	19 ± 3	21 ± 4	20 ± 5	.30
LVEF (%)	61 ± 3	58 ± 5	59 ± 4	.13
EROA (cm^2)	NA	0.04 ± 0.07*	0.27 ± 0.06*,†	<.0001
MR grade				<.0001
None		34 (74)	0 (0)	
Mild		12 (26)	0 (0)	
Moderate		0 (0)	20 (95)	
Severe		0 (0)	1 (5)	
Medications				
β-blockers	NA	28 (61)	12 (57)	.79
Diuretics	NA	20 (43)	8 (38)	.79
Digoxin	NA	17 (40)	6 (29)	.59
Angiotensin-converting enzyme inhibitors	NA	22 (48)	9 (43)	.80
Angiotensin receptor blockers	NA	3 (7)	1 (5)	>.99
Calcium channel blockers	NA	24 (52)	7 (33)	.19

LVEDV, LV end-diastolic volume; *LVESV*, LV end-systolic volume; *NA*, not applicable.
Data are expressed as mean ± SD or as number (percentage).
*P < .05 versus normal subjects.
†P < .05 versus AFMR− patients.

all vs late diastole). The timings for annular dimensions reaching their minimums were, nevertheless, delayed to late systole. Presystolic saddle-shape deepening was also absent (P = NS for both vs mid-diastole). Increase in annular height and decrease in NPA occurred after mitral valve closure, with the deepest saddle shape delayed to early systole (i.e., after aortic valve opening).

Similar to AFMR− annulus, AFMR+ annulus demonstrated no presystolic contraction or increase in saddle shape (P = NS for all vs mid diastole). The onset of systolic reductions of annular circumference and AL-PM diameter occurred after mitral valve closure, but those of AP diameter and area were delayed to early or mid-systole. The most striking difference of AFMR+ annulus in contrast to normal and AFMR− annulus was that annular height and NPA remained nondynamic throughout the cardiac cycle (P = NS).

Percentage changes of annular parameters are shown in Table 3. PresystolicΔ of all parameters were abolished in both AF groups compared with normal patients (P < .05 for all). In the AFMR− group, systolic Δarea, Δcircumference, ΔAL-PM diameter, Δheight, and ΔNPA were preserved (P = NS) and systolic ΔAP diameter (P = .007) was augmented compared with normal patients, preserving totalΔ in the annular dynamics. Conversely, systolicΔ of all parameters except circumference were reduced in the AFMR+ group (P < .05 vs AFMR−), resulting in reduced total dynamic changes of all annular parameters (P < .05 vs AFMR− and normal).

LA and LV Strains and Relations with MR and Annular Dynamics

Measurement reproducibility (intraclass correlation coefficient and coefficient of variation) for intraobserver variability of strain and EROA measurements was as follows: LV GLS, 0.96 and 3.9%; LV GCS, 0.94 and 3.4%; LAS, 0.94 and 7.7%; and EROA, 0.98 and 6.3%. Measurement reproducibility (intraclass correlation coefficient and coefficient of variation) for interobserver variability of strain and EROA measurements was as follows: LV GLS, 0.91 and 6.0%; LV GCS, 0.93 and 4.1%; LAS, 0.88 and 8.7%; and EROA, 0.98 and 10.0%. Figure 3 shows the results of speckle-tracking

Table 2 Mitral annular dynamics

	Average	Early diastole	Mid-diastole	Late diastole	Mitral valve closure	Early systole	Mid-systole	Late systole
AP diameter (mm)								
Normal	30.9 ± 1.8	31.0 ± 1.8	31.6 ± 1.9‡	31.0 ± 1.9‡	30.8 ± 1.9‡	30.7 ± 1.9	30.7 ± 1.8	30.9 ± 1.9
AFMR−	35.9 ± 2.7*	35.7 ± 2.8*	36.3 ± 2.7‡	36.4 ± 2.7*	35.9 ± 2.9*,‡	35.8 ± 2.8*,‡	35.6 ± 2.7*,‡	35.5 ± 2.6
AFMR+	38.0 ± 2.7*,†	37.8 ± 2.7*,†	38.1 ± 2.9*,†,‡	38.3 ± 2.7*,†	38.3 ± 2.7*,†	38.1 ± 2.7*,†,‡	37.9 ± 2.8*,†,‡	37.8 ± 2.8*,†
AL-PM diameter (mm)								
Normal	33.2 ± 1.2	33.3 ± 1.3	34.0 ± 1.2‡	33.8 ± 1.2‡	33.4 ± 1.2‡	33.1 ± 1.2‡	32.5 ± 1.3‡	32.5 ± 1.3
AFMR−	37.8 ± 2.7*	37.7 ± 2.7*	38.4 ± 2.7*,‡	38.3 ± 2.8*	38.0 ± 2.8*,‡	37.8 ± 2.8*,‡	37.3 ± 2.8*,‡	37.1 ± 2.7*,‡
AFMR+	38.7 ± 2.3*	38.4 ± 2.3*	39.0 ± 2.3*,‡	39.1 ± 2.3*	39.0 ± 2.3*,‡	38.8 ± 2.4*,‡	38.5 ± 2.3*,‡	38.2 ± 2.4*,‡
Annular area (cm^2)								
Normal	8.4 ± 0.6	8.5 ± 0.6	8.8 ± 0.6‡	8.6 ± 0.6‡	8.4 ± 0.6‡	8.3 ± 0.6‡	8.1 ± 0.6‡	8.2 ± 0.6
AFMR−	10.8 ± 1.5*	10.7 ± 1.5*	11.1 ± 1.5*,‡	11.1 ± 1.5*	10.9 ± 1.5*,‡	10.8 ± 1.5*,‡	10.6 ± 1.5*,‡	10.5 ± 1.4*,‡
AFMR+	11.8 ± 1.1*,†	11.6 ± 1.2*,†	11.9 ± 1.1*,†,‡	11.9 ± 1.1*	11.9 ± 1.1*,†	11.9 ± 1.1*,†	11.8 ± 1.1*,†,‡	11.7 ± 1.0*,†,‡
Circumference (mm)								
Normal	10.7 ± 0.4	10.8 ± 0.4	11.0 ± 0.4‡	10.8 ± 0.4‡	10.8 ± 0.3‡	10.7 ± 0.3‡	10.5 ± 0.4‡	10.5 ± 0.4
AFMR−	12.0 ± 0.8*	12.0 ± 0.7*	12.1 ± 0.8*,‡	12.1 ± 0.8*	12.0 ± 0.8*,‡	11.9 ± 0.8*,‡	11.8 ± 0.8*,‡	11.8 ± 0.7*,‡
AFMR+	12.2 ± 0.7*	12.1 ± 0.8*	12.3 ± 0.8*,‡	12.3 ± 0.7*	12.2 ± 0.7*,‡	12.2 ± 0.8*,‡	12.1 ± 0.8*,‡	12.0 ± 0.7*,‡
Annular height (mm)								
Normal	7.9 ± 0.7	7.6 ± 0.7	7.6 ± 0.6	8.0 ± 0.7‡	8.5 ± 0.8‡	8.3 ± 0.8‡	8.2 ± 0.7‡	8.1 ± 0.7‡
AFMR−	6.1 ± 1.0*	6.1 ± 1.1*	6.0 ± 1.1*	6.1 ± 1.1*	6.2 ± 1.1*,‡	6.3 ± 1.1*,‡	6.2 ± 1.1*,‡	6.0 ± 1.0*,‡
AFMR+	5.4 ± 0.7*,†	5.5 ± 0.8*	5.4 ± 0.6*	5.4 ± 0.7*	5.4 ± 0.7*,†	5.4 ± 0.8*,†	5.4 ± 0.8*,†	5.3 ± 0.7*,†
NPA (deg)								
Normal	138 ± 5	138 ± 5	139 ± 6‡	138 ± 6‡	137 ± 6‡	137 ± 5	138 ± 5‡	139 ± 5‡
AFMR−	159 ± 10*	159 ± 10*	160 ± 10*,‡	159 ± 10*	158 ± 10*,‡	158 ± 10*,‡	158 ± 10*	158 ± 10*,‡
AFMR+	165 ± 7*,†	164 ± 7*,†	164 ± 6*	163 ± 7*	165 ± 8*,†	163 ± 8*,†	163 ± 7*,†	163 ± 7*

Data are expressed as mean ± SD.
*$P < .05$ versus normal subjects.
†$P < .05$ versus AFMR− patients.
‡$P < .05$ versus previous time point.

echocardiography. Compared with normal patients, LV GLS and LV GCS were increased (less negative) and LAS was decreased in both AF groups ($P < .05$ for all). The AFMR+ group showed less negative LV GLS ($P < .0001$) and reduced LAS ($P = .02$) than the AFMR− group, with comparable GCS ($P = 1.00$). Intercorrelations among EROA, LV GLS, and systolic annular dynamics are shown in Figure 4. In patients with MR, EROA correlated moderately with systolic Δannular area ($r = 0.64$, $P < .0001$), ΔNPA ($r = 0.53$, $P = .003$), and LV GLS ($r = 0.46$, $P < .0001$) but not with LAS, LV GCS, and other clinical variables (P = NS). LV GLS also correlated moderately with systolic Δannular area ($r = 0.62$, $P < .0001$) and ΔNPA ($r = 0.59$, $P = .002$), which in turn correlated ($r = 0.46$, $P < .0001$) with each other.

Factors Associated with MR

Table 4 shows the results of multivariate regression analysis for factors associated with at least moderate MR. Of all clinical and echocardiographic variables tested, factors associated with MR on univariate analysis included systolic Δannular area, systolic ΔNPA, LV GLS, and LAS ($P < .10$). In the regression model including both annular dynamics and strain parameters, impaired systolic Δannular area (odds ratio, 2.18; 95% CI, 1.40–3.40) and ΔNPA (odds ratio, 2.68; 95% CI, 1.03–7.01) were independently associated with MR. If annular dynamics were excluded from the model, less negative LV GLS became the only factor independently associated with MR (odds ratio, 1.93; 95% CI, 1.35–2.77).

DISCUSSION

The principal findings of the present study are that (1) normal sinus rhythm is associated with coupled presystolic and systolic annular dynamics with area contraction and increase in a saddle shape, (2) AF is associated with absent presystolic but preserved systolic annular dynamics, albeit with a delayed timing; (3) AFMR is associated with diminished presystolic and additionally systolic annular dynamics; and (4) such abnormal dynamics are associated with impaired LV GLS.

Mitral Annular Dynamics in Sinus Rhythm and AF

The mitral annulus is a fibrous structure central to the fibrous skeleton of the heart with critical valvular physiologic functions. The normal annulus is dynamic, with AP contraction and increased annular height causing accentuated annular saddle shape during systole.[4,18] In normal sinus rhythm, there is also a presystolic component of annular contraction, which is important for preparing the mitral

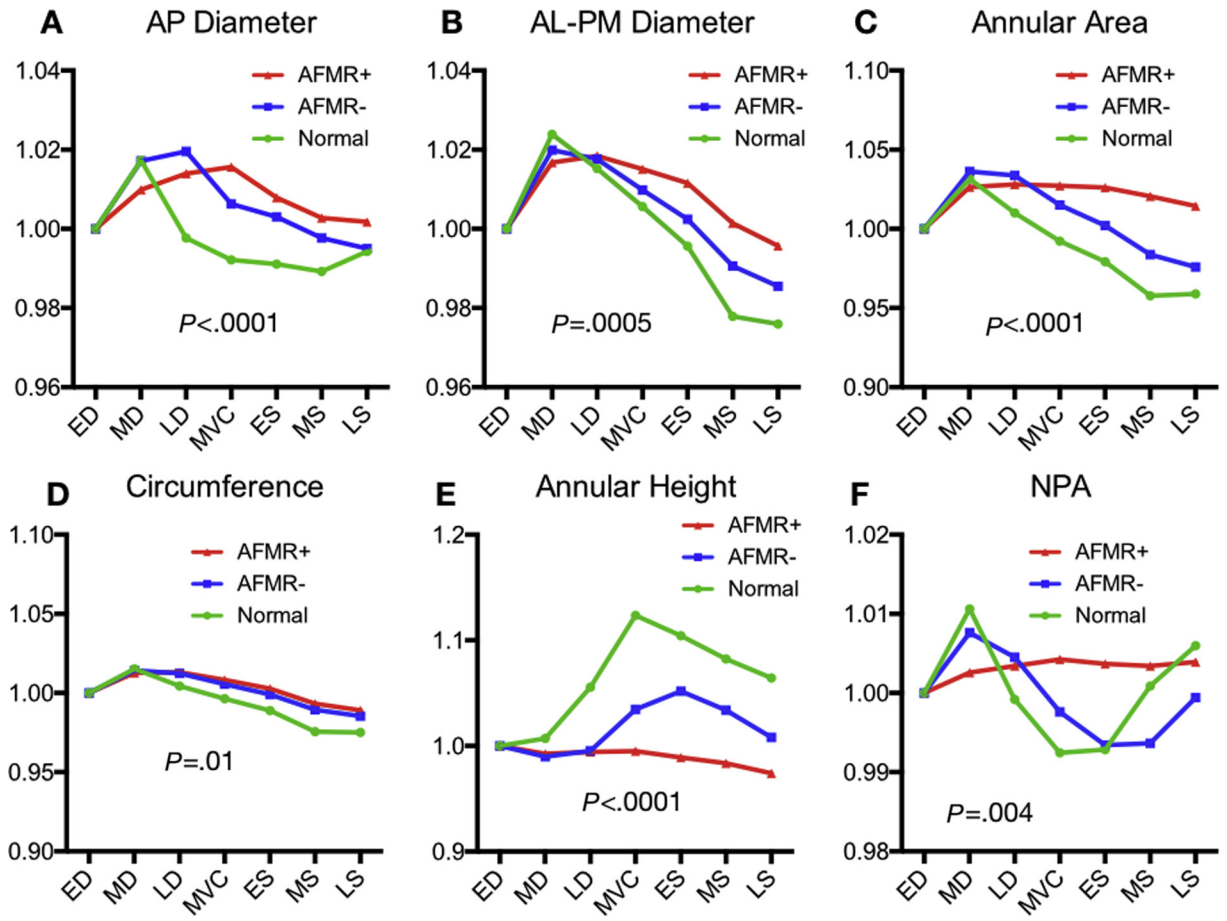

Figure 2 Dynamic changes of mitral annular geometry throughout the cardiac cycle normalized to early diastolic measurement. **(A)** AP diameter, **(B)** AL-PM diameter, **(C)** area, **(D)** circumference, **(E)** height, **(F)** NPA. *P* values of analysis of variance of repeated measures are shown. *ED*, Early diastole; *ES*, early systole; *LD*, late diastole; *LS*, late systole; *MD*, mid-diastole; *MS*, mid-systole; *MVC*, mitral valve closure.

valve for normal closure.[10,19-21] Mihaila *et al.*[10] demonstrated that 61% of total annular area contraction occurs before systole, highlighting the importance of the atrial influence on annular dynamics.[8] The presystolic annular contraction and saddle deepening continue into early systole after the mitral valve closes, reaching the smallest area and the deepest saddle in early or mid-systole.[4,10,19] During that phase, such annular dynamics are crucial to keep the valve "waterproof" and to evenly redistribute the stress imposed on the valve by the rapid rise of LV pressure. These previous experimental and clinical findings are confirmed in our present study. Additionally, by comparing normal subjects with AF patients, we demonstrate that the effects of AF on mitral valve physiology include an alteration of the annular dynamic mechanism from one with closely coupled presystolic and systolic components to one that is predominantly systolic. There is no detectable presystolic annular contraction or deepening in both groups of patients with AF. Importantly, our study reveals striking differences in the systolic component of the annular dynamics between patients with MR and those without. In patients with AF but no MR, the systolic annular dynamics are preserved and capable of contracting the annulus to its minimum size and to maximum height, albeit more slowly, such that the total annular fractional changes are complete. On the contrary, the systolic component of annular contraction in patients with AF who have important MR is diminished in addition to the presystolic diminishment, such that the annulus is larger and flatter throughout systole compared with its no-MR counterpart.

Because the annulus is purely fibrous, its kinetic behavior can only be linked to atrial and ventricular myocardial contraction imposing an annular motion through the tight attachment of annular roots into the atrioventricular junction.[5] Systolic annular deepening has been variably attributed to aortic root expansion and differential translational annular motion caused by apical pulling of longitudinal LV fibers.[6] The latter is supported by our recent observation that LV GLS is normally coupled to annular saddle deepening,[5] which geometrically also reduces annular area in the AP direction. Those mechanisms explain the correlation of LV GLS with systolic ΔNPA, Δarea, and thus MR severity in the present study. Our findings are also consistent with those observed in experimental settings showing that when properly timed LA contraction is abolished by ventricular pacing,[8] ischemia,[9] atrial fiber ablation,[22] or AF,[11] presystolic annular contraction disappears and mitral valve closure delays. Putting into perspective, in normal sinus rhythm presystolic annular dynamics are coupled to atrial contraction, whereas systolic annular motions are linked to ventricular contraction.[10] The dynamic effects of AF on annular dynamics can thus be viewed as an alteration of a predominantly "atriogenic" into a solely "ventriculogenic" annular mechanism.

Table 3 Percentage changes of annular parameters in the cardiac cycle

Variable	Normal (n = 19)	AFMR− (n = 46)	AFMR+ (n = 21)	P
AP diameter				
Presystolic Δ (%)	−2.1 ± 1.5	−0.3 ± 0.6*	−0.6 ± 0.8*	<.0001
Systolic Δ (%)	−1.6 ± 1.4	−3.0 ± 1.8*	−1.7 ± 1.7†	.001
Total Δ (%)	−3.9 ± 1.9	−3.7 ± 1.8	−2.3 ± 2.0*,†	.007
AL-PM diameter				
Presystolic Δ (%)	−0.9 ± 1.0	−0.4 ± 0.5*	−0.2 ± 0.4*	.004
Systolic Δ (%)	−4.0 ± 1.5	−3.3 ± 1.7	−2.3 ± 1.4*,†	.004
Total Δ (%)	−4.8 ± 1.6	−3.8 ± 1.7	−2.5 ± 1.6*,†	<.0001
Annular area				
Presystolic Δ (%)	−2.1 ± 2.0	−0.3 ± 1.6*	−0.1 ± 1.4*	<.0001
Systolic Δ (%)	−5.7 ± 2.3	−5.8 ± 3.0	−1.3 ± 1.4*,†	<.0001
Total Δ (%)	−7.6 ± 2.6	−6.4 ± 2.9	−1.8 ± 1.7*,†	<.0001
Annular circumference				
Presystolic Δ (%)	−1.1 ± 1.4	−0.4 ± 0.6*	−0.3 ± 0.4*	.004
Systolic Δ (%)	−3.1 ± 1.4	−2.8 ± 1.5	−2.4 ± 1.8	NS
Total Δ (%)	−4.2 ± 1.9	−3.2 ± 1.6	−2.9 ± 1.8	NS
Annular height				
Presystolic Δ (%)	5.9 ± 5.1	3.4 ± 2.9*	3.1 ± 3.1*	.02
Systolic Δ (%)	7.1 ± 3.1	7.6 ± 6.6	2.3 ± 5.4*,†	.002
Total Δ (%)	13.5 ± 7.8	11.2 ± 6.8	5.5 ± 6.9*,†	.001
NPA				
Presystolic Δ (%)	−1.5 ± 1.2	−0.8 ± 0.7*	−0.5 ± 0.5*	.0003
Systolic Δ (%)	−1.4 ± 1.1	−1.8 ± 1.3	−0.4 ± 0.9*,†	.0002
Total Δ (%)	−2.7 ± 1.4	−2.6 ± 1.3	−0.9 ± 1.0*,†	<.0001

Data are expressed as mean ± SD.
*P < .05 versus normal subjects.
†P < .05 versus AFMR− patients.

Contraction of basal LV circumferential fibers also reduces annulus area like a sphincter,[7,19] but in our study, LV GCS is relatively preserved in the AFMR+ group. Preservation of LV GCS in these patients probably reflects our inclusion criteria for AFMR+. It is known that circumferential fibers contraction limits outward systolic bulging of the left ventricle like a buttress.[7] Patients with impaired LV GCS in addition to LV GLS tend to already have LV enlargement and/or reduced LVEF,[23] which would not be considered by this study the typical "atrial" functional MR but probably fit into the conventional "ventricular" functional MR category.

The cause of abnormal LV strains in our patients with AF is unclear. Yet it is increasingly recognized that AF is associated with adverse effects on LV myocardium mediated through fibrosis, inflammation, ischemia, oxidative stress, and other mechanisms.[24] LAS reduction in our AFMR+ patients may be a marker of increased LA stiffness associated with fibrosis and increased AF burden[25] or may simply reflect reduced passive stretch by impaired LV GLS.[26] No independent association with MR is found for LAS when adjusted for LV GLS, suggesting LAS does not provide additional information beyond LV strain alone regarding MR pathogenesis. However, one may speculate that LA stiffness could be related to the symptomatic status of patients,[27] which remains to be proved in the setting of AFMR.

Clinical Implications

Our findings support the notion that patients with AF may be at risk for developing secondary, normal leaflet motion MR. Importantly, we provide novel data revealing that the so-called AFMR may be related to subtly impaired ventricular mechanics detectable by strain imaging. An important implication of that finding is that therapeutic measures that restore sinus rhythm, catheter ablation for instance, can potentially reduce MR by restoring the presystolic component of annular dynamics and by improving the systolic component through improving LV strains, in addition to reversing LA remodeling.[2,7,28] Surgical ring annuloplasty[29] and percutaneous MitraClip therapy[30] have been used to correct AFMR with reportedly good short-term outcomes. However, whether such initial favorable outcome conferred by those annulus- and leaflet-targeting interventions can be sustained in longer term without addressing the underlying rhythm and LV problems warrants further investigations.

Study Limitations

This study had several limitations. Our study was retrospective by design. Nevertheless, imaging data were prospectively collected, ensuring data completeness. The small number of subjects meeting our criteria for AFMR limited the number of variables that we could

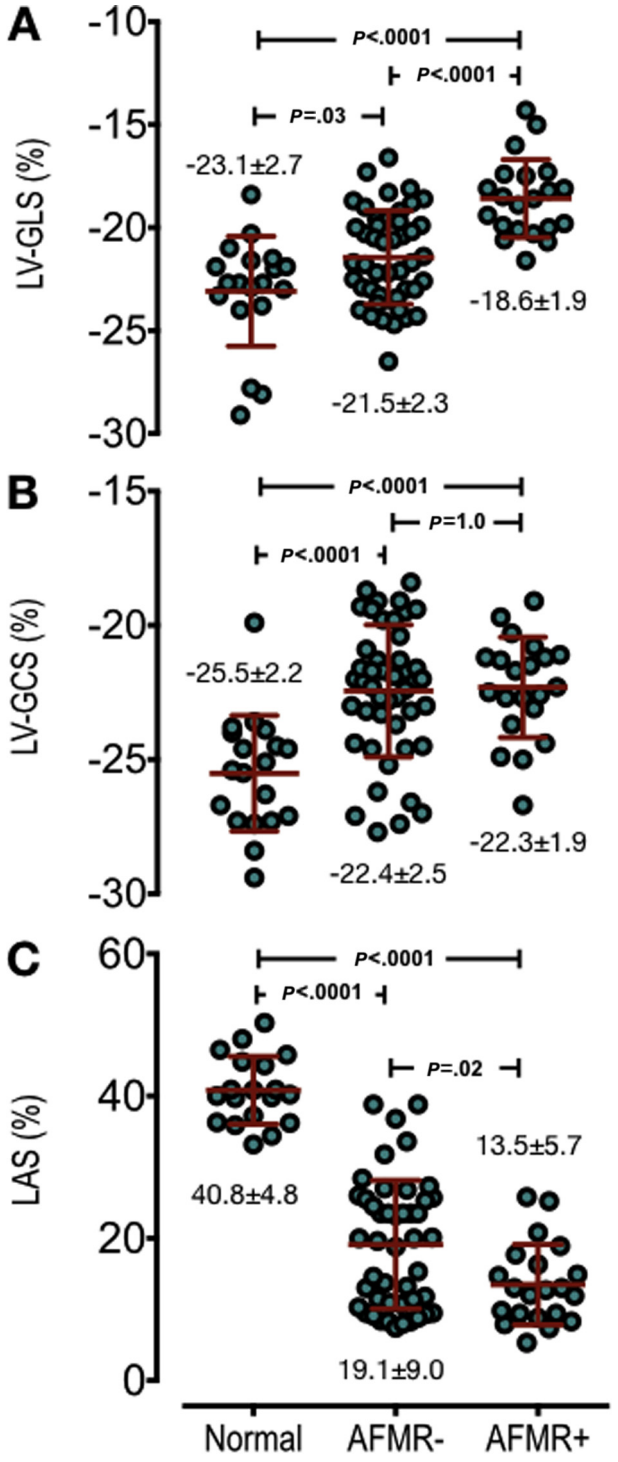

Figure 3 Scatterplots of **(A)** LV GLS, **(B)** GCS, and **(C)** peak LAS of the normal, AFMR−, and AFMR+ groups. LV GLS and LV GCS were increased (less negative) and LAS was decreased in both AF groups compared with normal patients. AFMR+ patients showed increased (less negative) LV GLS and decreased LAS compared with AFMR− patients, with comparable LV GCS. Central and error bars indicate mean and SD, respectively.

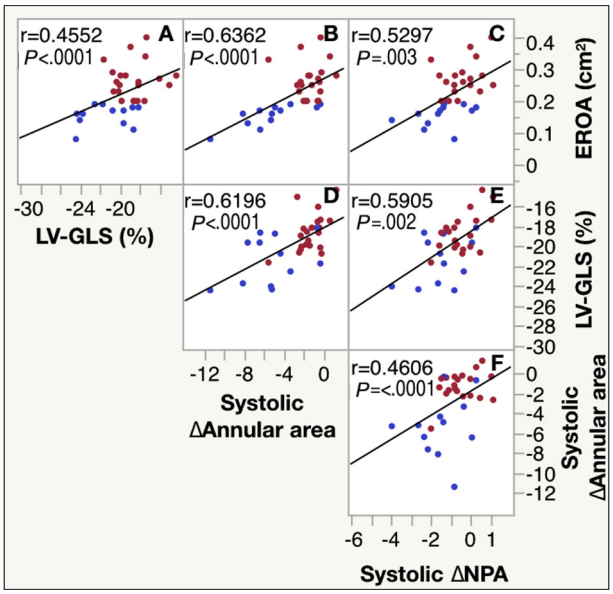

Figure 4 Correlations among EROA, LV GLS, and systolic percentage changes (Δ) of annular area and NPA in patients with at least mild MR. The scatterplots demonstrate significant correlations of EROA with **(A)** LV GLS, **(B)** systolic Δannular area, and **(C)** ΔNPA, correlations of LV GLS with **(D)** systolic Δannular area and **(E)** ΔNPA, and **(F)** between systolic Δannular area and ΔNPA. *Red* and *blue plots* indicate AFMR+ and AFMR− patients, respectively.

explore in the multivariate analysis. This small patient number despite screening 1,265 subjects speaks to the relative rarity of moderate or greater MR in the setting of AF with normal LV volume and LVEF and without a primary MR etiology. The percentage change in annular area over the cardiac cycle observed in our study was less than that reported by others.[31] Use of two-dimensional echocardiography in previous studies may overestimate area change because of out-of-plane motion.[19] Moreover, annular dynamics may decline with aging.[32] Our patient populations are one to two decades older than those studied by others,[4,10,32] potentially contributing to the discrepancy in the magnitude of annular area change. Three-dimensional echocardiography is limited by relatively low temporal resolution, possibly missing time points of maximum or minimum dimensions. Nevertheless, volume rates achieved in this study were >15 volume/sec (mean, 22 volume/sec), higher than the volume rate achieved (8 volume/sec) in a recent study.[1] Limited by sample size, paroxysmal and persistent AF were regarded as equivalent for purposes of statistical analysis. The similar prevalence of AF subtypes between patients with or without MR could be partially explained by our matching of the LA volume, which is related to AF burden. Kim *et al.*[33] recently reported that MR increased with annular dilatation and insufficient adaptive leaflet enlargement, which was not assessed in the present study. Those findings, however, do not refute the concept that MR can result from impaired ventriculogenic annular dynamics during systole, but they do suggest that adaptive leaflet remodeling may counteract annular dysfunction to prevent MR, at least at the early stage of annular remodeling.

Table 4 Multivariate analysis of variables associated with at least moderate MR in patients with AF

Variable	Univariate analysis *P* value	Multivariate analysis: Annular and strain model (systolic Δannular area and ΔNPA included in the regression model) OR (95% CI)	*P*	Multivariate analysis: Strain model (systolic Δannular area and ΔNPA excluded from the regression model) OR (95% CI)	*P*
Systolic Δannular area	<.0001	2.18 (1.40–3.40)	.001	NA	NA
Systolic ΔNPA	.001	2.68 (1.03–7.01)	.04	NA	NA
LV GLS	<.0001	NA	NS	1.93 (1.35–2.77)	<.0001
LAS	.02	NA	NA	NA	NA

NA, Not applicable; *OR*, odds ratio.

CONCLUSIONS

The absence of atrial contraction in patients with AF is associated with altered mechanisms of mitral annular dynamics resulting in a predominant ventricular influence. Isolated LA enlargement and annular dilatation in AF appear to be prerequisite but not sufficient per se to cause important MR without coexisting abnormal LV systolic deformation that impairs the systolic component of annular function. Appreciating the importance of annular and atrioventricular coupling in the integrity of mitral valve may lead us to readdress our approach to normal leaflet motion secondary MR in LA dilatation and to AF in general. The so-called AFMR may not be purely an LA disorder and demands a comprehensive evaluation of ventricular and systemic effects of AF in patients.

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