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Evidence of Atrial Functional Mitral Regurgitation Due to Atrial Fibrillation

Reversal With Arrhythmia Control

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Objectives The purpose of this study was to determine whether atrial fibrillation (AF) might cause significant mitral regurgitation (MR), and to see whether this MR improves with restoration of sinus rhythm.

Background MR can be classified by leaflet pathology (organic/primary and functional/secondary) and by leaflet motion (normal, excessive, restrictive). The existence of secondary, normal leaflet motion MR remains controversial.

Methods We performed a retrospective cohort study. Patients undergoing first AF ablation at our institution (n = 828) were screened. Included patients had echocardiograms at the time of ablation and at 1-year clinical follow-up. The MR cohort (n = 53) had at least moderate MR. A reference cohort (n = 53) was randomly selected from those patients (n = 660) with mild or less MR. Baseline echocardiographic and clinical characteristics were compared, and the effect of restoration of sinus rhythm was assessed by follow-up echocardiograms.

Results MR patients were older than controls and more often had persistent AF (62% vs. 23%, $p < 0.0001$). MR patients had larger left atria (volume index: 32 cm^3/m^2 vs. 26 cm^3/m^2, $p = 0.008$) and annular size (3.49 cm vs. 3.23 cm, $p = 0.001$), but similar left ventricular size and ejection fraction. Annular size, age and persistent AF were independently associated with MR. On follow-up echocardiogram, patients in continuous sinus rhythm had greater reductions in left atrial size and annular dimension, and lower rates of significant MR (24% vs. 82%, $p = 0.005$) compared with those in whom sinus rhythm was not restored.

Conclusions AF can result in "atrial functional MR" that improves if sinus rhythm is restored. (J Am Coll Cardiol 2011;58:1474–81) © 2011 by the American College of Cardiology Foundation

The mitral valve is an intricate structure, whose normal function depends on a complex interplay between the mitral leaflets, chordae tendinae, papillary muscles, left ventricle, and the mitral annulus to maintain normal function. Mitral regurgitation (MR) may occur when any part of this interplay is disrupted. MR can be categorized according to mitral leaflet motion using Carpentier's classification as normal (Type I), excessive (Type II), or restrictive (Type III) (1). A complimentary method of classifying MR is by the presence of mitral leaflet disease (primary or organic MR) versus only secondary involvement of the leaflets (functional MR) (2). Etiologies associated with organic and secondary Type II MR include myxomatous degeneration and ruptured chordae or papillary muscles, respectively. Examples of organic and secondary Type III MR include rheumatic valve disease and functional MR from dilated cardiomyopathy.

See page 1482

Normal leaflet motion MR is less common than the other types, and almost exclusively results from organic leaflet disease leading to annular dilation (2). In Carpentier's analysis of 551 cases of surgical MR, over 98% of the Type I patients had annular dilation causing valvular dysfunction, nearly all from rheumatic disease (1). Organic Type I MR may also occur, although rarely, from extensive mitral annular calcification (3), perforation secondary to endocarditis, or from a congenitally cleft mitral leaflet. Functional Type I MR is less well described.

One disease process that might give rise to functional Type I MR, through a mechanism of atrial remodeling leading to mitral annular dilation, is atrial fibrillation (AF).

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This has been described in 2 small series, neither of which was able to demonstrate a causal link between AF and MR (4,5). Other studies have suggested that the mitral annular dilation associated with AF is not sufficient to cause significant MR (6,7). We have identified a number of patients with functional Type I MR undergoing AF ablation at our institution (8). We undertook the current study to evaluate the hypothesis that AF may be associated with what we call "atrial functional MR," and that it may be of at least moderate severity. By assessing mitral valve function before and after AF ablation, we sought to detect what contribution AF may make to valve dysfunction, and whether it is reversible.

Methods

We performed a retrospective cohort study to determine whether AF is associated with significant atrial functional MR. The institutional review board at the University of Pennsylvania approved the study.

Patient selection. All patients referred to the University of Pennsylvania Health System for catheter ablation of drug-refractory AF between June 2003 and December 2008 were eligible for inclusion. Reports from transthoracic echocardiograms performed within 3 days of catheter ablation of AF were screened, and an experienced research echocardiographer analyzed the images of those with greater than mild MR. All patients with secondary Type I MR of at least moderate severity (as described in the following text) and who also had complete 1-year clinical follow-up after ablation were included in the MR cohort. The reference cohort was randomly selected in a 1-to-1 fashion from those patients with mild or less MR on initial report screening and subsequent image analysis and who also had complete 1-year clinical follow-up. Patients with an ejection fraction <50% were excluded to avoid including patients whose MR might be due to ventricular dysfunction. Demographic and clinical information were prospectively obtained in all patients. The clinical AF syndrome was determined based on the predominant arrhythmia presentation at the time of admission and was defined as paroxysmal if AF episodes were self-terminating in <7 days and persistent if typical AF episodes lasted ≥7 days and/or required intervention for termination.

Ablation procedure. All patients underwent proximal antral pulmonary vein (PV) isolation guided by intracardiac echocardiogram and circular multipolar electrode catheter recordings and elimination of all provocable PV triggers and all non-PV triggers resulting in AF, as previously described (9). All 4 PVs were isolated routinely in patients with a history of persistent AF, those without provocable AF triggers, and those patients with significant risk factors for AF including a history of hypertension, left atrium (LA) enlargement, and those over the age of 50 years. In the remaining selected patients, we isolated arrhythmogenic PVs only. Patients with a clinical history of typical right atrial flutter or induced typical atrial flutter during the ablation procedure also underwent cavotricuspid isthmus ablation. The ablation endpoint was both persistent PV isolation and no AF with repeat incremental infusion of up to 20 μg/min of isoproterenol. Patients with identified macro–re-entrant atrial tachycardias had the circuit defined using activation and/or entrainment mapping to guide appropriate linear ablation strategy with an endpoint of bidirectional block.

Abbreviations and Acronyms

AF = atrial fibrillation

LA = left atrium

MR = mitral regurgitation

PV = pulmonary vein

TTM = transtelephonic monitor

Patient follow-up. Patients were routinely treated with previously ineffective antiarrhythmic medications (usually a class 1C agent or sotalol) prior to discharge. The patients were clinically evaluated as outpatients at 6 to 12 weeks, 6 months, and 1 year, at which time they were queried for symptoms and 12-lead electrocardiograms were obtained. Echocardiograms were performed at the first visit and at the second or third visits, at the treating physician's discretion. Antiarrhythmic medications were typically discontinued at 6 to 12 weeks if patients had paroxysmal AF and at 6 months if they had persistent AF, but were continued beyond this point in selected patients based on doctor and/or patient preference even in the absence of an arrhythmia event. The patients were provided with a transtelephonic monitor (TTM) and instructed to transmit 2 times daily and with symptoms during the first 4 weeks after ablation. They were then instructed to transmit once at 6 to 12 weeks, then once at 6 months and 1 year. Patients also made additional TTM transmission if they had any arrhythmia symptoms at any time during follow-up and/or when antiarrhythmic medications were discontinued. Source documentation of arrhythmia recurrence was sought. The first 3 months after ablation were censored from follow-up for judging recurrence. One-year AF recurrence was defined according to consensus guidelines as any documented electrocardiographic episode of atrial arrhythmia lasting 30 s or longer with or without symptoms (10). Recurrence at the time of follow-up echocardiography was defined as any electrocardiographic recurrence during the 6 months preceding the echocardiogram.

Echocardiography. Standard 2-dimensional and Doppler echocardiography with color flow mapping was performed according to the standard clinical protocol at the University of Pennsylvania Health System. Echocardiograms were then analyzed offline using digital analysis software (KinetDx, Siemens, Mountain View, California) by a single research echocardiographer, blinded to patient outcomes and to the relative timing of the echocardiogram. LA anterior–posterior systolic diameter was measured in the parasternal long-axis view, and the major axis of the LA was measured in the apical 4-chamber view. LA area at end-systole was measured in the apical 2- and 4-chamber views. Similarly, LA volumes at end-systole were measured in the apical 2- and 4-chamber views using a single-plane modified Simpson's method of discs, and values averaged. Mitral annular dimensions were measured in parasternal long-axis, apical 2-chamber, and apical long-axis views.

MR color jet area was measured in the apical 4-chamber, apical 2-chamber, and apical long-axis views. Color Doppler scale and, therefore, Nyquist limit were determined by the clinical ultrasonographer and in general were set to 50 to 70 cm/s. The ratio of MR color jet area to LA area (MR/LA ratio) was then calculated, using the largest measured values for both. Mild MR was defined as a MR/LA ratio of ≥0.1 to <0.2, moderate MR as ≥0.2 to <0.4, and severe as ≥0.4. Only patients with moderate or greater MR were included in the MR cohort. Leaflet motion was characterized as normal, excessive, or restrictive. Only patients with normal mitral leaflet motion (Carpentier Type I) were included in the MR cohort. Patients with any evidence of primary leaflet involvement, such as from prior endocarditis, rheumatic valve disease, congenital anomaly, or significant mitral annular calcification, were excluded.

Statistical analysis. This study had 2 primary analyses. The first was to define the clinical and echocardiographic characteristics associated with significant atrial functional MR. The second primary analysis was the change in MR severity associated with restoration of sinus rhythm. All continuous variables are presented as mean ± SD, categorical values are presented as percentages, and odds ratios are presented with 95% confidence intervals (CIs). For comparisons between the MR and reference cohorts, continuous variables were compared with a *t* test, and categorical values were compared using a chi-square test. For paired samples within groups, continuous variables were compared using a paired *t* test. We performed binary logistic regression in order to detect the variables that were independently associated with significant MR. All models were constructed using those variables whose univariate correlation with significant MR had $p \leq 0.1$. In order to avoid colinearity, we created 3 iterations of each model, each including only 1 measure of LA size (dimension, area, volume, or volume index). The omnibus chi-square test was used to determine the strength of each model. For the between-group comparisons of MR grade by category, we used a Wilcoxon rank sum test. All significance tests were 2-tailed, and $p < 0.05$ was considered significant.

Results

Patients. The entry of patients into the study is illustrated in Figure 1. There were 828 patients who underwent a first AF ablation at our institution between June 2003 and December 2008. There were 97 patients who met our criteria for significant MR after study review. Of these, 54 had normal leaflet motion with no apparent primary leaflet pathology (6.5% of all patients undergoing first ablation), 53 of whom had 1-year clinical follow-up and were included as the MR cohort. One patient required mitral valve surgery in the first year after ablation, but after her 6-month echocardiogram, and was included in the analyses. Of the 660 patients with mild or less MR and 1-year clinical follow-up, 53 patients were randomly selected as the reference cohort.

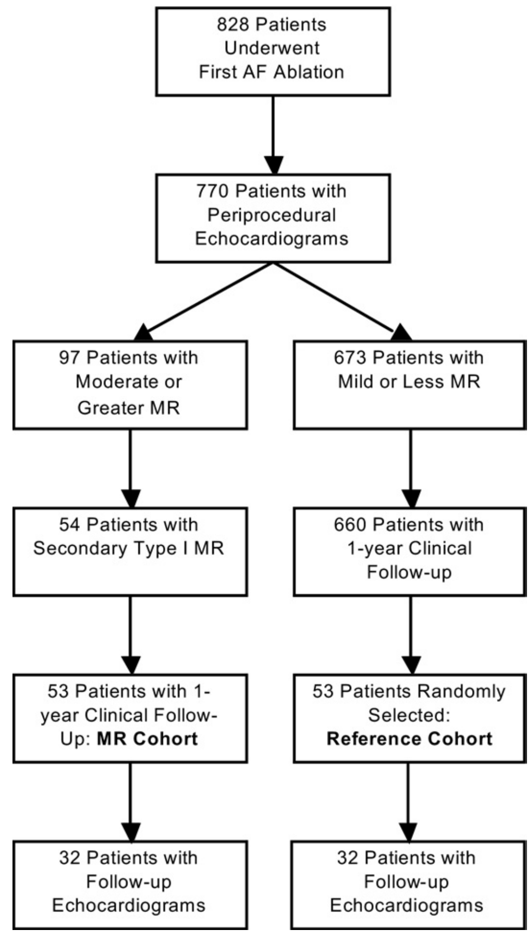

Figure 1 **Flow Diagram Illustrating Selection of the MR and Reference Cohorts for the Study**

The 32 patients with secondary Type I mitral regurgitation (MR) and follow-up echocardiograms were evaluated to determine the response of mitral regurgitation to termination of atrial fibrillation (AF).

Procedural outcomes. We observed no significant differences in procedural outcomes between the MR and reference cohorts. In both cohorts, 98% of veins targeted for ablation demonstrated entrance and exit block ($p = 1.00$) at the conclusion of the procedure.

Univariate and multivariate associations with MR. Clinical characteristics of the MR and reference cohorts are shown in Table 1. Patients with MR were older, more likely to have persistent AF, and more frequently had hypertension. Ninety-seven percent of patients were in sinus rhythm at the time of their baseline echocardiogram. Echocardiographic characteristics of the MR and reference cohorts are shown in Table 2. Patients with MR had significantly larger LA size by several measures

Table 1 Clinical Characteristics of the MR and Reference Cohorts

	MR Cohort (n = 53)	Reference Cohort (n = 53)	p Value
Age, yrs	61.6 ± 8.4	55.4 ± 12.4	0.003
Male	70% (37)	66% (35)	0.68
Hypertension	62% (33)	43% (23)	0.052
Diabetes	6% (3)	11% (6)	0.30
Prior stroke or TIA	6% (3)	2% (1)	0.31
CHADS-2 score	0.9 ± 0.7	0.6 ± 0.7	0.052
Persistent AF	62% (33)	23% (12)	<0.0001

Values are mean ± SD or % (n).
AF = atrial fibrillation; MR = mitral regurgitation; TIA = transient ischemic attack.

and larger mitral annular dimensions, but no difference in any measure of left ventricular size or function. Among the reference cohort, 60% had trace or no MR and 40% had mild MR. In the MR cohort, 72% had moderate MR and 28% had severe MR.

Binary logistic regression models were constructed to determine the variables that were independently associated with significant MR. One model included only echocardiographic characteristics (1 measure of LA size in each iteration, as well as mitral annular dimension). The strongest predictive model included LA volume index and mitral annular dimension (omnibus chi-square = 17.7, $p < 0.0001$). The odds ratio for mitral annular dimension was 5.80 per cm (95% CI: 1.72 to 19.49 per cm, p = 0.005) and for LA volume index was 1.34 per 5 cm^3/m^2 (95% CI: 1.00 to 1.79 per 5 cm^3/m^2, p = 0.051). When significant clinical associations were added to the regression equation, the strength of the model improved (omnibus chi-square = 22.1, $p < 0.0001$), but LA volume index was no longer a significant independent predictor (Fig. 2). Mitral annular dimension had the largest odds ratio in the final model (8.39 per cm, 95% CI: 1.94 to 36.35 per cm, p = 0.004).

Follow-up echocardiography. Follow-up echocardiograms were available in 32 of the 53 patients in the MR cohort, an average of 277 days after ablation. There were no statistically significant differences in any clinical or echocardiographic characteristics between the patients with and without follow-up echocardiograms, nor was there a difference in 1-year clinical outcome. Rhythm status at follow-up was defined as described above, applied only to the 6 months preceding echocardiography. By this definition, 21 patients were free of recurrence and 11 patients had recurrence of AF. Ninety-four percent of patients were in sinus rhythm at the time of follow-up echocardiography. At the time of ablation, patients with eventual recurrence had larger measures of LA size (LA volume index: 41.3 cm^3/m^2 vs. 28.2 cm^3/m^2, p = 0.02), with nonsignificant trends towards larger regurgitant jet area and mitral annular dimension (Table 3). Other echocardiographic measures were not significantly different between the 2 groups at baseline.

At follow-up, both groups had reductions in LA size, but only the group in sinus rhythm had a significant decrease in mitral annular dimension (3.41 cm at baseline to 3.24 cm at follow-up, p = 0.02). Both groups experienced some decrease in MR, but at follow-up, the patients in sinus rhythm had significantly less MR than patients with AF recurrence (MR/LA ratio: 0.16 vs. 0.28, p = 0.005) (Table 3), despite being similar at baseline. Measures of left ventricular size and function remained similar between both groups at follow-up.

At baseline both groups had similar percentages of patients with moderate and severe MR (p = 0.72) (Fig. 3). At follow-up, 19% of the patients in sinus rhythm had trace or no MR, compared with 0% in the recurrence group, and 57% in the sinus rhythm group had mild MR compared with 18% in the recurrence group. Only 24% of the sinus rhythm patients still had significant MR at follow-up, compared with 82% in the recurrence group (p = 0.005 for entire trend) (Fig. 3).

Follow-up echocardiograms were available in 32 of the 53 patients in the reference cohort, an average 300 days after ablation. There were no statistically significant differences in any clinical or echocardiographic characteristics between the patients with and without follow-up echocardiograms, nor was there a difference in 1-year clinical outcome. Using the definition of rhythm status described above, 17 patients were in sinus rhythm and 15 had a recurrence at the time of echocardiography. There were no significant echocardiographic differences between the groups at baseline (Table 4). Patients in whom sinus rhythm was maintained after ablation experienced a significant decline in LA size (LA volume index: 27.4 to 23.7 cm^3/m^2, p = 0.02). There was a small, but significant, increase in the degree of MR in the patients with recurrence (MR/LA ratio: 0.09 to 0.11, p = 0.01). In those patients without recurrence, the degree of MR did not change (MR/LA ratio: 0.09 to 0.10, p = 0.62).

Table 2 Echocardiographic Characteristics of the MR and Reference Cohorts

	MR Cohort (n = 53)	Reference Cohort (n = 53)	p Value
LA dimension, cm	4.38 ± 0.56	4.03 ± 0.52	0.001
LAA, cm^2	21.8 ± 5.2	19.2 ± 3.3	0.003
LA volume, cm^3	68.5 ± 29.3	55.2 ± 14.1	0.004
LA volume index, cm^3/m^2	31.8 ± 12.9	26.4 ± 6.6	0.008
Mitral annulus dimension, cm	3.49 ± 0.31	3.23 ± 0.42	0.001
MRJA, cm^2	6.0 ± 2.7	1.2 ± 0.7	<0.0001
MRJA/LAA ratio	0.35 ± 0.11	0.09 ± 0.04	<0.0001
Ejection fraction, %	61.5 ± 7.1	62.2 ± 7.1	0.63
LV end-diastolic dimension, cm	5.01 ± 0.57	4.92 ± 0.49	0.39
LV end-systolic dimension, cm	3.41 ± 0.58	3.25 ± 0.62	0.17
Septal thickness, cm	1.14 ± 0.21	1.09 ± 0.19	0.21
Posterior wall thickness, cm	1.10 ± 0.17	1.06 ± 0.17	0.31

Values are mean ± SD.
LA = left atrium; LAA = left atrium area; LV = left ventricle; MR = mitral regurgitation; MRJA = mitral regurgitation jet area.

JACC Vol. 58, No. 14, 2011
September 27, 2011:1474–81

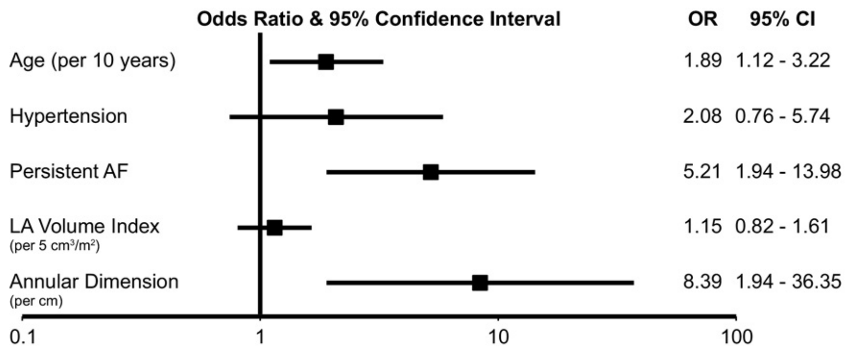

Figure 2 Forest Plot Illustrating the Independent Predictors of Atrial Functional MR

All univariate predictors with $p \leq 0.1$ were included in the model. The x-axis is on a logarithmic scale. CI = confidence interval; LA = left atrium; OR = odds ratio; other abbreviations as in Figure 1.

No patient in the reference cohort developed moderate or worse MR during the follow-up period.

Discussion

Although 2 smaller studies have examined the association between AF and secondary, normal leaflet motion MR (4,5), our study is, to our knowledge, the largest and the first to provide evidence that AF may be a cause of significant MR. By demonstrating the quick and nearly complete resolution of MR 6 to 12 months after the restoration of sinus rhythm, we believe we have shown that AF itself may be the precipitant of significant MR, rather than simply a

Table 3 Follow-Up Echocardiographic Characteristics of MR Cohort Patients With Recurrence Versus Sinus Rhythm

	Rhythm at Follow-Up Echocardiogram (Recurrence n = 11, Sinus n = 21)*	Initial	Follow-Up	p Value (Initial vs. Follow-Up)	p Value (Recurrence vs. Sinus at Follow-Up)
LA dimension, cm	Recurrence	4.72 ± 0.62	4.58 ± 0.64	0.15	0.05
	Sinus	4.31 ± 0.54†	4.16 ± 0.53	0.09	
LAA, cm^2	Recurrence	25.5 ± 8.0	21.9 ± 4.0	0.04	0.01
	Sinus	20.7 ± 3.6†	18.5 ± 3.0	0.01	
LA volume, cm^3	Recurrence	88.1 ± 50.4	66.4 ± 18.4	0.07	0.02
	Sinus	62.3 ± 17.8†	52.4 ± 12.7	0.02	
LA volume index, cm^3/m^2	Recurrence	41.3 ± 22.0	31.2 ± 8.0	0.06	0.007
	Sinus	28.2 ± 7.6†	23.9 ± 6.0	0.02	
Mitral annulus dimension, cm	Recurrence	3.59 ± 0.27	3.48 ± 0.34	0.29	0.06
	Sinus	3.41 ± 0.29	3.24 ± 0.31	0.02	
MRJA, cm^2	Recurrence	7.2 ± 3.0	5.4 ± 3.7	0.11	0.001
	Sinus	5.8 ± 2.5	2.2 ± 1.5	<0.0001	
MRJA/LAA ratio	Recurrence	0.37 ± 0.10	0.28 ± 0.14	0.04	0.005
	Sinus	0.34 ± 0.09	0.16 ± 0.09	<0.0001	
Ejection fraction, %	Recurrence	63 ± 11	62 ± 11	0.73	0.58
	Sinus	61 ± 7	63 ± 5	0.17	
LV end-diastolic dimension, cm	Recurrence	5.10 ± 0.28	5.01 ± 0.32	0.06	0.83
	Sinus	5.06 ± 0.66	5.05 ± 0.53	0.89	
LV end-systolic dimension, cm	Recurrence	3.30 ± 0.41	3.20 ± 0.59	0.52	0.88
	Sinus	3.50 ± 0.65	3.23 ± 0.57	0.02	
Septal thickness, cm	Recurrence	1.22 ± 0.19	1.15 ± 0.17	0.35	0.36
	Sinus	1.14 ± 0.16	1.10 ± 0.13	0.42	
Posterior wall thickness, cm	Recurrence	1.17 ± 0.18	1.11 ± 0.13	0.27	0.36
	Sinus	1.07 ± 0.12	1.06 ± 0.14	0.80	

Values are mean ± SD. Echocardiographic characteristics of the patients with significant MR and follow-up echocardiograms are shown. Patients are grouped according to their rhythm status at the time of follow-up echocardiography as recurrence of atrial fibrillation (AF) or sinus rhythm. The p values in the second column from the right represent comparisons between baseline and follow-up within each group. The p values in the final column are for comparisons of follow-up values between the recurrence and sinus rhythm groups. *These numbers are different from 1-year recurrence because status was assessed at time of follow-up echocardiography and only took into account the preceding 6 months. †Baseline comparison between recurrence and sinus groups had significant or near-significant p values for LA dimension ($p = 0.06$), LA area ($p = 0.02$), LA volume ($p = 0.04$), and LA volume index ($p = 0.02$). The remaining baseline comparisons were not significantly different.

Abbreviations as in Table 2.

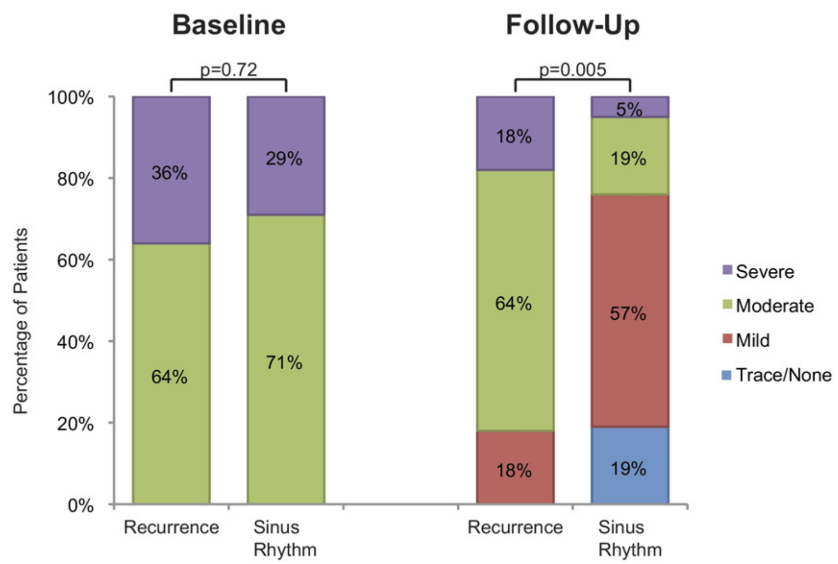

Figure 3 **MR Severity at Baseline and Follow-Up**

Patients are categorized by the rhythm at the time of follow-up as recurrence of atrial fibrillation or sinus rhythm. All patients had moderate or severe mitral regurgitation (MR) at initial echocardiogram. In patients in sinus rhythm at follow-up, only 24% still had moderate or severe MR.

concurrent finding. We refer to this as atrial functional MR, to distinguish it from the secondary, leaflet restriction MR associated with left ventricular dysfunction, which has often been referred to simply as functional MR.

The clinical characteristics associated with atrial functional MR were older age, hypertension, and most powerfully, persistent rather than paroxysmal AF. By echocardiography, MR was associated with increased LA size and mitral annular dilation, although there was no relation to left ventricular size or function, as previously noted (5). After multivariate regression, we found that only age, persistent AF, and mitral annular dilation were linked to MR. This suggests that LA size, notably not independently correlated with MR, may mediate its impact via its effect on the mitral annulus.

Pathophysiology of atrial functional MR. By studying follow-up echocardiograms after AF ablation, we were able to evaluate possible pathophysiological mechanisms underlying atrial functional MR. Patients with successful ablations experienced significant reductions in LA size and mitral annular dimension, and less than a third still had significant MR at follow-up. In contrast, among patients who had recurrence of AF, there was no significant change in annular dimension despite near-significant reductions in LA size. Over 80% of the patients with recurrence still had significant MR at follow-up. These findings, combined with those from our regression model, which showed that mitral annular dimension was the only independent echocardiographic predictor of MR, strongly suggest that atrial functional MR is mediated through a process of annular dilation.

Several studies have previously shown that an enlarged LA, particularly as the result of AF, is associated with significant mitral annular dilation (4,6,7). Whether a stretched mitral annulus is sufficient to cause significant MR remains controversial. Tanimoto and Pai (4) found that atrial enlargement and subsequent mitral annular dilation correlated with mitral regurgitation, but other studies have shown the opposite. Otsuji et al. (6) compared patients with isolated AF or cardiomyopathy to controls. Although both AF and cardiomyopathy patients had significant mitral annular dilation, only the patients with cardiomyopathy had any instances of significant MR. Their findings can likely be explained by the addition of left ventricular dilation in the cardiomyopathy group, leading to MR from restricted leaflet motion. Zhou et al. (7) found that AF caused more dilation of the tricuspid annulus than the mitral annulus, leading to moderate or greater tricuspid regurgitation in over one-third of patients studied. None of the patients had significant MR, which the authors attributed to a better-developed mitral annular fibrous skeleton compared with the tricuspid annulus.

These findings do not refute the concept that significant MR can result from AF and annular dilation, but they do suggest that it may be less common than other types of MR. Kihara et al. (5) found only 12 instances of patients with atrial functional MR requiring surgery in a database of over 18,000 procedures. Nevertheless, these patients were successfully treated with annuloplasty and surgical AF ablation, with no more than mild residual MR 1 year later. Our study of 53 patients with significant atrial functional MR represents over 6% of all patients referred for AF ablation at our

Table 4 Follow-Up Echocardiographic Characteristics of Reference Cohort Patients With Recurrence Versus Sinus Rhythm

	Rhythm at Follow-Up Echocardiogram (Recurrence n = 15, Sinus n = 17)*	Initial	Follow-Up	p Value (Initial vs. Follow-Up)	p Value (Recurrence vs. Sinus at Follow-Up)
LA dimension, cm	Recurrence	4.15 ± 0.43	3.95 ± 0.56	0.13	0.66
	Sinus	3.98 ± 0.60	3.85 ± 0.64	0.06	
LAA, cm^2	Recurrence	19.2 ± 2.7	18.2 ± 3.9	0.16	0.99
	Sinus	19.8 ± 3.9	18.2 ± 3.6	0.049	
LA volume, cm^3	Recurrence	54.8 ± 11.3	50.1 ± 15.0	0.07	0.89
	Sinus	57.3 ± 17.0	49.4 ± 14.6	0.03	
LA volume index, cm^3/m^2	Recurrence	25.0 ± 3.5	22.7 ± 5.2	0.06	0.62
	Sinus	27.4 ± 7.1	23.7 ± 6.6	0.02	
Mitral annulus dimension, cm	Recurrence	3.37 ± 0.40	3.23 ± 0.47	0.25	0.46
	Sinus	3.19 ± 0.40	3.11 ± 0.41	0.42	
MRJA, cm^2	Recurrence	1.1 ± 0.3	1.7 ± 0.9	0.02	0.10
	Sinus	1.4 ± 1.0	1.2 ± 0.8	0.47	
MRJA/LAA ratio	Recurrence	0.09 ± 0.03	0.11 ± 0.03	0.01	0.33
	Sinus	0.09 ± 0.05	0.10 ± 0.05	0.62	
Ejection fraction, %	Recurrence	62 ± 5	63 ± 5	0.43	0.78
	Sinus	64 ± 9	62 ± 7	0.49	
LV end-diastolic dimension, cm	Recurrence	5.04 ± 0.45	5.10 ± 0.40	0.54	0.35
	Sinus	4.90 ± 0.54	4.91 ± 0.66	0.91	
LV end-systolic dimension, cm	Recurrence	3.37 ± 0.64	3.05 ± 0.34	0.01	0.27
	Sinus	3.17 ± 0.63	2.88 ± 0.50	0.006	
Septal thickness, cm	Recurrence	1.14 ± 0.17	1.08 ± 0.26	0.45	0.30
	Sinus	1.11 ± 0.22	1.17 ± 0.22	0.11	
Posterior wall thickness, cm	Recurrence	1.05 ± 0.16	1.11 ± 0.12	0.13	0.67
	Sinus	1.12 ± 0.19	1.08 ± 0.22	0.30	

Values are mean ± SD. Echocardiographic characteristics of the patients in the reference cohort with follow-up echocardiograms are shown. Patients are grouped according to their rhythm status at the time of follow-up echocardiography as recurrence of atrial fibrillation (AF) or sinus rhythm. The p values in the second column from the right represent comparisons between baseline and follow-up within each group. The p values in the final column are for comparisons of follow-up values between the recurrence and sinus rhythm groups. There were no significant differences between the groups in any characteristic at baseline. *These numbers are different from 1-year recurrence because status was assessed at time of follow-up echocardiography and only took into account the preceding 6 months. Abbreviations as in Table 2.

institution and adds significantly to the case literature of this entity.

The precise mechanism by which atrial dysfunction leads to MR merits further exploration. Our findings suggest a crucial role of the mitral annulus, and further studies of the mitral annulus after AF ablation, such as with 3-dimensional echocardiography (11), might be useful. The function of the LA likely plays a role. Well-timed atrial contraction is important for appropriate mitral valve closing (12), and the strength and timing of atrial contraction may contribute to normal mitral valve function as well (13).

Significance of atrial functional MR. The prognostic importance of atrial functional MR in the setting of AF is unclear, but potentially significant if one considers parallels in similar disease entities. Significant ventricular functional MR predicts poorer survival compared with patients with heart failure and normal mitral valve function (14). Worsening severity of organic MR increases mortality risk as well, even in asymptomatic patients (15). LA enlargement itself is a poor prognostic sign. An enlarged LA independently predicts adverse events in patients with lone AF (16) and portends worse survival in patients with organic MR (17). It is generally believed that MR, in a vicious cycle whereby MR instigates atrial and annular remodeling leading to worsening MR, progresses over time (2). However, this may vary depending on the etiology (18), and long-term studies of the clinical importance of atrial functional MR are warranted.

Treatment of atrial functional MR. The most important finding of our study may be that atrial functional MR could potentially be treated without cardiac surgery. Over 80% of patients in the MR cohort had no more than mild residual MR at follow-up with successful restoration of sinus rhythm. Improvement in MR, even without surgery, is not unprecedented in functional MR. Medical therapy for heart failure can improve MR severity and functional class (19,20). The question then is whether all patients with significant atrial functional MR would benefit from a rhythm control approach to treatment of AF. Although rhythm control is typically not recommended over rate control as an initial strategy (21), patients who develop atrial functional MR may represent a subgroup that derives significant clinical benefit from restoration of sinus rhythm. This question would best be answered in a prospective study.

Study limitations. Although clinical variables and rhythm assessments were prospectively collected in our study, the primary exposure, MR, was retrospectively detected, and therefore, our study has the typical limitations of retrospective analysis. Patient follow-up at 1 year was available in nearly all patients, but the method of follow-up was physician dependent, and not all patients with MR had follow-up echocardiography. Therefore, our findings should be considered hypothesis-generating only.

Because we used a clinical echocardiographic protocol, most echocardiograms did not include sufficient data to utilize additional commonly used methods of quantifying mitral regurgitation such as proximal isovelocity surface area–derived effective regurgitant orifice or regurgitant volume. The measure we chose to assess MR severity, MR/LA ratio, can be impacted by LA size and compliance, blood pressure, volume status, and the color Doppler scale set by the ultrasonographer. Yet, MR/LA ratio has been used in several prior studies that have assessed MR in the setting of AF (4,5,7,13).

Conclusions

Our findings suggest that patients with AF and an enlarged mitral annulus may be at risk of developing secondary, normal leaflet motion MR (atrial functional MR). Despite having a moderate or greater degree of MR, patients with atrial functional MR showed significant improvement in valve function with restoration of sinus rhythm. Since our study is retrospective and therefore only hypothesis-generating, the question of whether all patients with AF and atrial functional MR should be treated with a rhythm control strategy should be addressed in a prospective study.

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