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STATE-OF-THE-ART REVIEW

Subtypes of Atrial Functional Mitral Regurgitation

Imaging Insights Into Their Mechanisms and Therapeutic Implications

Nobuyuki Kagiyama, MD, PhD,[a,b] Sergio Mondillo, MD,[c] Kiyoshi Yoshida, MD, PhD,[a] Giulia Elena Mandoli, MD,[c] Matteo Cameli, MD, PhD[c]

ABSTRACT

Functional mitral regurgitation (MR) in patients with atrial fibrillation (AF) without left ventricular dysfunction, namely, atrial functional MR, has been increasingly recognized. Whether mitral annular dilatation causes MR in patients without left ventricular dysfunction has remained controversial; however, recent studies using novel imaging technologies, including 3-dimensional echocardiography, have shown that significant functional MR can sometimes occur in AF patients with significant dilatation of mitral annulus and left atrium. Additional contributors such as atriogenic leaflet tethering, annulus area to leaflet area imbalance resulting from insufficient leaflet remodeling and reduced annular contractility, increased valve stress by flattened saddle shape of the annulus, and left atrial dysfunction may be important triggers of atrial functional MR in the presence of dilated mitral annulus and left atrium. The prevalence of atrial functional MR is reported to be between 3% and 15% in AF patients and those with atrial functional MR are associated with worse clinical outcomes. Because there are few published data regarding therapeutic strategies of atrial functional MR, understanding the principles of therapeutic options and their target mechanisms is important with regards to clinical practice until sufficient evidence is established. In this review, the known mechanisms, clinical implications and, when possible, potential therapeutic options of atrial functional MR are discussed. (J Am Coll Cardiol Img 2020;13:820–35) © 2020 by the American College of Cardiology Foundation.

HISTORICAL BACKGROUND

AF is the most common rhythm disorder observed in 2% of the general population and the prevalence is further increasing as the society is aging (1,2). It is well known that atrial fibrillation (AF) causes left atrial (LA) and mitral annular dilatation without left ventricular (LV) dysfunction (3–5). However, whether AF and succeeding annular dilatation cause significant mitral regurgitation (MR) without LV dysfunction remains controversial.

It had been widely recognized that MR can occur without significant degenerative changes of the mitral leaflets in patients with severe left heart dilatation or LV dysfunction caused either by ischemic heart disease or idiopathic myocardial disease. These types of MR were called functional (secondary) MR in contrast to degenerative (primary) MR caused by the organic change of mitral valve itself (6). Research performed during the early era of 2-dimensional echocardiography (2DE) reported annular dilatation as the primary mechanism related to functional MR

From the [a]Department of Cardiology, The Sakakibara Heart Institute of Okayama, Okayama, Japan; [b]Division of Cardiology, Washington University in St. Louis, St. Louis, Missouri; and the [c]Department of Cardiovascular Diseases, University of Siena, Siena, Italy. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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caused by LV dilatation/dysfunction (7). Then, significant evolution in imaging techniques including 3-dimensional echocardiography (3DE) enabled more detailed and comprehensive observation in mitral valve morphology (8,9), and later studies using 3DE revealed that the primary mechanism of this MR is attributable to tethering of the mitral valve caused by the dilated LV and displaced papillary muscle rather than mitral annular dilatation (10-13). Otsuji et al. compared 25 patients with isolated AF with 24 patients with ischemic MR and showed that, although both groups demonstrated a significantly and similarly dilated mitral annulus, no patient in the AF group presented with significant MR. They concluded that isolated AF and succeeding annular dilatation does not cause MR (14). At that time, the existence of MR in patients with AF and preserved LV function seemed to be disputed by a few papers (14,15).

In approximately 2010, however, several studies once again began reporting the existence of MR in patients with isolated AF (16-19). Gertz et al. studied patients who underwent catheter ablation for AF and reported that patients with significant MR demonstrated an obviously enlarged LA and mitral annulus. Furthermore, they showed that maintaining sinus rhythm by catheter ablation significantly shrank mitral annulus and improved MR. These results strongly suggested that AF and subsequent annular dilatation can cause significant MR. This MR was named "atrial functional MR" in contrast to traditional functional MR resulting from LV dysfunction/dilatation (17). Later studies also supported that there are patients with atrial functional MR with a significantly larger annulus (16,20-26). Now, atrial functional MR is 1 of the hottest topics in the field.

The degree of mitral annular dilatation reported in the Otsuji et al. study was not remarkably small when compared with that reported in the later studies; however, the discrepancy on whether annular dilatation causes MR can be resolved by considering other mechanistic factors of atrial functional MR beyond simple annular dilatation. Although current available evidence is not sufficient, this review will discuss the known mechanisms, clinical implications, and, when possible, the potential therapeutic options of "atrial functional MR," which is defined as MR in patients with isolated AF despite normal LV function and no degenerative change in the mitral valve.

MECHANISMS OF ATRIAL FUNCTIONAL MR

According to a PubMed search, 11 studies have investigated the structural/functional characteristics of mitral apparatus in patients with atrial functional MR. Mitral valve parameters from 10 studies are summarized in **Table 1**. One study was excluded because the study population potentially containing a patient with functional MR by LV dilatation/dysfunction (27).

MITRAL ANNULAR DILATATION AND INSUFFICIENT LEAFLET REMODELING. Anatomically, the mitral leaflets are able to cover the mitral annulus, which is the narrowest portion connecting the LA to LV, with a 1.5 to 2.0 times larger leaflet area than that found in healthy individuals (22,23,25,28,29). Moreover, the mitral leaflets further enlarge when physiologically necessary. Recent studies using animal experiments and 3DE have shown that the mitral leaflet is not of a fixed size and that it enlarges or thickens in response to various stresses ("leaflet remodeling"). Dal-Bianco et al. (29) artificially stretched the papillary muscle down toward the apex to produce functional MR in 50% of 12 sheep that were studied. It was observed 60 days later that the mitral leaflet area expanded by 17 $\pm$ 10% only in the animals that underwent this procedure. Histopathological tests revealed that endothelial-mesenchymal transition played a central role mechanistically in this change (**Figure 1**) (29). A succeeding in vivo study using 3DE performed by the same group demonstrated that patients with functional MR had a smaller mitral leaflet to closure leaflet area ratio (which represents insufficient leaflet remodeling) than was found in healthy individuals and in those without significant MR (28).

The same findings have also been reported in patients without LV dysfunction. Using transesophageal 3DE, we studied the mitral leaflet size in AF patients without LV dysfunction. Although AF patients without MR showed a larger mitral annulus than found in healthy individuals, the mitral leaflet area was also greater and the mitral leaflet to the annulus area ratio was similar to that in healthy individuals (**Figure 2**). In contrast, patients with atrial functional MR showed significantly smaller mitral leaflets compared with the annulus (insufficient leaflet remodeling). These results strongly suggest that leaflet remodeling contributes to the severity of atrial functional MR (22). Kim et al. (23) also reported similar findings of leaflet remodeling in patients with AF using transthoracic 3DE. They further investigated the temporal change in the degree of leaflet remodeling in 7 patients with AF. During a median 4.8-year follow-up period, both the annulus area and leaflet area were enlarged in all the patients; however, significant MR occurred in 4 patients whose leaflet area

ABBREVIATIONS AND ACRONYMS

2DE = 2-dimensional echocardiography

3DE = 3-dimensional echocardiography

AF = atrial fibrillation

LA = left atrium

LV = left ventricle

LVEF = left ventricular ejection fraction

MR = mitral regurgitation

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did not enlarge enough compared with their annulus area. Their leaflet area to annulus area ratio at follow-up was under 1.4, whereas that of the other 3 patients, without significant MR even at follow-up, was more than 1.5 (23).

In both of these studies, as annulus area enlarged, the ratio of mitral leaflet area to the annulus area decreased. Furthermore, all patients with an annulus area >8 cm²/m² (which is about double the normal size) had significant MR, suggesting that leaflet remodeling as a compensatory mechanism has limitations. In contrast, there was a heterogeneity of MR in patients with an annulus area between 5 and 8 cm²/m² (1.3 to 2.0 times larger than that in healthy individuals), and the severity of MR was correlated with the degree of leaflet remodeling. In other words, with this intermediate range of annular dilatation, the significance of atrial functional MR depends on the degree of the leaflet remodeling (**Figure 3**). Measuring mitral leaflet area in vivo requires clear images in diastole, because in systole it is difficult to measure the coaptation area, which is not necessarily symmetric. Since there have been only 2 studies reporting total leaflet area measured in diastole thus far, the prevalence of insufficient leaflet remodeling is unknown; however, the prevalence does not seem to be

TABLE 1 Mitral Valve Parameters in Each Study

First Author, Year (Ref #)	MR Severity in Patients With MR	Modality	Annulus Area (cm²)		
			AFMR	Non-MR	Control
Otsuji et al., 2002 (14)	None	3D TTE		11.6 ± 2.3*	8.0 ± 1.2
Kihara et al., 2009 (16)	12 patient who underwent MV surgery (VC 3.4-6.3)	2D TTE	10.6 ± 2.3*		6.2 ± 1.9
Ring et al., 2013 (25)	33 patients with MR ≥ moderate (ERO 0.23 ± 0.13)	3D TEE	12.9 ± 3.5*		8.8 ± 1.3
van Rosendael et al., 2014 (26)	49 with mild and 7 patients with moderate MR	3D CT	6.7 ± 1.0†‡	5.3 ± 0.7†	
Takahashi et al., 2015 (33)	6 and 4 patients with moderate and severe MR, respectively	2D TEE			
Machino-Ohtsuka et al., 2016 (21)	25 patients with MR ≥ moderate (MR jet/LA area 48 ± 11, VC 3.8 ± 1.4, ERO 0.41 ± 0.14)	3D TEE	12.3 ± 3.2*‡	9.7 ± 1.9	7.8 ± 1.6
Itabashi et al., 2016 (41)	19 and 12 patients with moderate and severe MR, respectively (VC 3.7 ± 0.8)	3D TEE	10.2 ± 2.3b	8.3 ± 2.0	
Ito et al., 2017 (21)	16 patients with MR ≥ moderate	3D TEE			
Kagiyama et al., 2017 (22)	28 patients with MR ≥ moderate (VC 5.1 ± 1.0, ERO 0.26 ± 0.05)	3D TEE	6.5 ± 1.3*†‡	5.7 ± 1.2*†	4.4 ± 1.1†
Kim et al., 2017 (23)	23 patients with MR ≥ moderate (VC 4.1-8.4)	3D TTE	6.3 ± 1.2*†‡	4.6 ± 0.6*†	3.8 ± 0.7†
Cong et al., 2018 (20)	25 patients with MR ≥ moderate (MR jet area 4.4 ± 0.7, ERO 0.47 ± 0.07)	3D TEE	12.7 ± 0.9*‡	9.5 ± 1.4*	8.9 ± 1.0

	MR Severity in Patients With MR	Modality	Total Leaflet Area in Diastole (cm²)		
			AFMR	Non-MR	Control
Otsuji et al., 2002 (14)	None	3D TTE			
Kihara et al., 2009 (16)	12 patient who underwent MV surgery (VC 3.4-6.3)	2D TTE			
Ring et al., 2013 (25)	33 patients with MR ≥ moderate (ERO 0.23 ± 0.13)	3D TEE			
van Rosendael et al., 2014 (26)	49 with mild and 7 patients with moderate MR	3D CT			
Takahashi et al., 2015 (33)	6 and 4 patients with moderate and severe MR, respectively	2D TEE			
Machino-Ohtsuka et al., 2016 (24)	25 patients with MR ≥ moderate (MR jet/LA area 48 ± 11, VC 3.8 ± 1.4, ERO 0.41 ± 0.14)	3D TEE			
Itabashi et al., 2016 (41)	19 and 12 patients with moderate and severe MR, respectively (VC 3.7 ± 0.8)	3D TEE			
Ito et al., 2017 (21)	16 patients with MR ≥ moderate	3D TEE			
Kagiyama et al., 2017 (22)	28 patients with MR ≥ moderate (VC 5.1 ± 1.0, ERO 0.26 ± 0.05)	3D TEE	8.3 ± 1.6*† TLA/AA: 1.29 ± 0.10†‡	9.3 ± 2.0*† 1.65 ± 0.24	7.4 ± 1.7† 1.70 ± 0.29
Kim et al., 2017 (23)	23 patients with MR ≥ moderate (VC 4.1-8.4)	3D TTE	9.6 ± 1.4*†‡ TLA/AA: 1.38 ± 0.10*†	8.6 ± 1.0*† 1.53 ± 0.17	7.5 ± 0.9† 1.53 ± 0.14
Cong et al., 2018 (20)	25 patients with MR ≥ moderate (MR jet area 4.4 ± 0.7, ERO 0.47 ± 0.07)	3D TEE			

Units for severity of MR were; VC, cm; ERO, cm², MR jet/LA area, %; MR jet area, cm². *Significant vs. control. †Significant vs. non-MR group. ‡Value divided by body surface area. §The angle between annular plane and the line connecting the annulus and the posterior leaflet tip.

2D = 2-dimensional; 3D = 3-dimensional; AFMR = atrial functional MR; AHCWR = annulus height-commissure width ratio; CT = computed tomography; ERO = effective regurgitant orifice; LA = left atrium; LVESV = left ventricular end-systolic volume; LVD = left ventricular end-systolic diameter; MR = mitral regurgitation; MV = mitral valve; PML = posterior mitral leaflet; TEE = transesophageal echocardiography; TLA/AA = total leaflet area-to-annulus area ratio; TTE = transthoracic echocardiography; VC = vena contracta width.

Continued on the next page

particularly high because in both studies the number of patients with atrial functional MR is much less than those without MR even in patients with this “intermediate” annuls area.

Several studies have reported determinants of leaflet remodeling in patients with functional MR by LV dysfunction. Debonnaire et al. (30) showed that leaflet size was closely correlated with annulus area and tethering parameters, suggesting that physical extension by annulus dilatation and tethering force might play a role as determinants of leaflet remodeling. Another interesting study on sheep showed that leaflet remodeling, in terms of histological change, can occur by isolated MR without morphological changes of LV/LA (31). However, determinants of leaflet remodeling in patients with AF remain to be investigated.

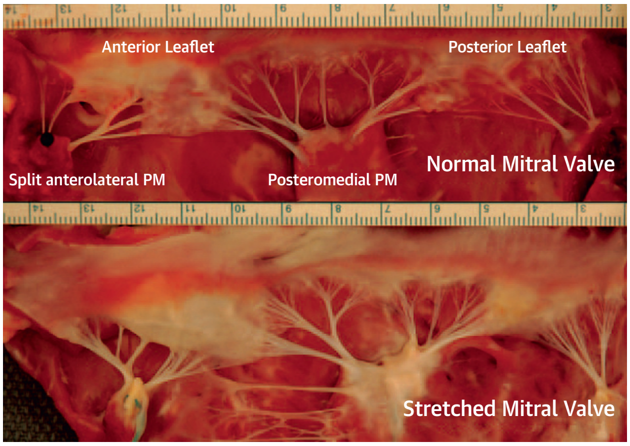
ATRIOGENIC LEAFLET TETHERING: A RARE BUT SIGNIFICANT SUBTYPE. Another possible mechanism of atrial functional MR, known as atriogenic leaflet tethering, has been reported in a few studies (21,24,32,33). The anterior portion of the mitral annulus is attached to the aortic root, a stable fixed position in the heart, whereas the posterior portion is attached to the junction of the LA and free wall of the LV, which is stretched outward when the LA and mitral annulus are observed to enlarge. This posterior attachment is located inside of the crest of the LV

TABLE 1 Continued

Annulus Fractional Change (%)			Nonplanner Angle (°) and AHCWR (%)			PML Angle (°)		
AFMR	Non-MR	Control	AFMR	Non-MR	Control	AFMR	Non-MR	Control
5.1 ± 4.5*		14.6 ± 5.0	AHCWR 14 ± 5		16 ± 4			
						24 ± 10 (48 ± 16)§		
6.9 ± 4.5*,‡	11·0 ± 7·5	22·4 ± 1·0	162 ± 7*,‡	152 ± 11	151 ± 7	52 ± 14*,‡	31 ± 8	29 ± 11
3.7 ± 2.4b	9.9 ± 3.4							
						26 ± 12 (59 ± 13)[+b]	28 ± 10 (44 ± 11)[+a]	35 ± 15 (56 ± 17)[+]
						39 ± 8	37 ± 8	32 ± 16
10.6 ± 7.0*,‡	18.4 ± 8.6*	23·6 ± 8·7	155 ± 7*,‡	150 ± 8*	141 ± 9			
			AHCWR 15 ± 5*,‡	17 ± 4*	19 ± 4			

Tenting Height (cm)			LVESV (ml)			LA Volume (ml)		
AFMR	Non-MR	Control	AFMR	Non-MR	Control	MR	Non-MR	Control
				33 ± 11	35 ± 9			
			30 ± 9		35 ± 10			
3.5 ± 1.5*		4.7 ± 1.1	33 ± 6		31 ± 3	127 ± 61*		40 ± 9
			19 ± 4†‡	17 ± 5†		60 ± 14†‡	45 ± 10	
3.8 ± 1.2			(LVDs) 2.9 ± 0.6			72 ± 26†		
(Volume) 1.72 ± 0.86	2.12 ± 1.08	1.46 ± 0.62	21 ± 7†	21 ± 6†	19 ± 8†	128 ± 105*†‡	51 ± 16*†	28 ± 7†
3.8 ± 1.4	3.8 ± 1.3		37 ± 20	35 ± 19				
4.6 ± 1.6	4.8 ± 2.7	4.6 ± 1.6	(LVDs) 3.5 ± 0.5*†	3.1 ± 0.5	2.8 ± 0.4	95 ± 41*†	38 ± 13*	21 ± 7*
3.8 ± 1.8‡	4.9 ± 1.7	4.5 ± 1.3	(LVDs) 3.3 ± 0.5*	3.0 ± 0.4	2.9 ± 0.4	51 ± 20*†‡	34 ± 16†	24 ± 11†
			23 ± 7†	24 ± 6.5†	21 ± 5†	69 ± 28*†‡	49 ± 19*,†	31 ± 8†
(Volume) 2.67 ± 1.07*†	1.72 ± 0.89	1.72 ± 0.73	31 ± 5	32 ± 5	30 ± 4	98 ± 22*†	81 ± 18†	57 ± 5

FIGURE 1 Mitral Leaflet Remodeling in Sheep With Functional Mitral Regurgitation



The mitral leaflet area significantly expanded in sheep with functional mitral regurgitation caused artificially by stretching the papillary muscle down toward the apex. PM, papillary muscle. Modified with permission from Dal-Bianco (29).

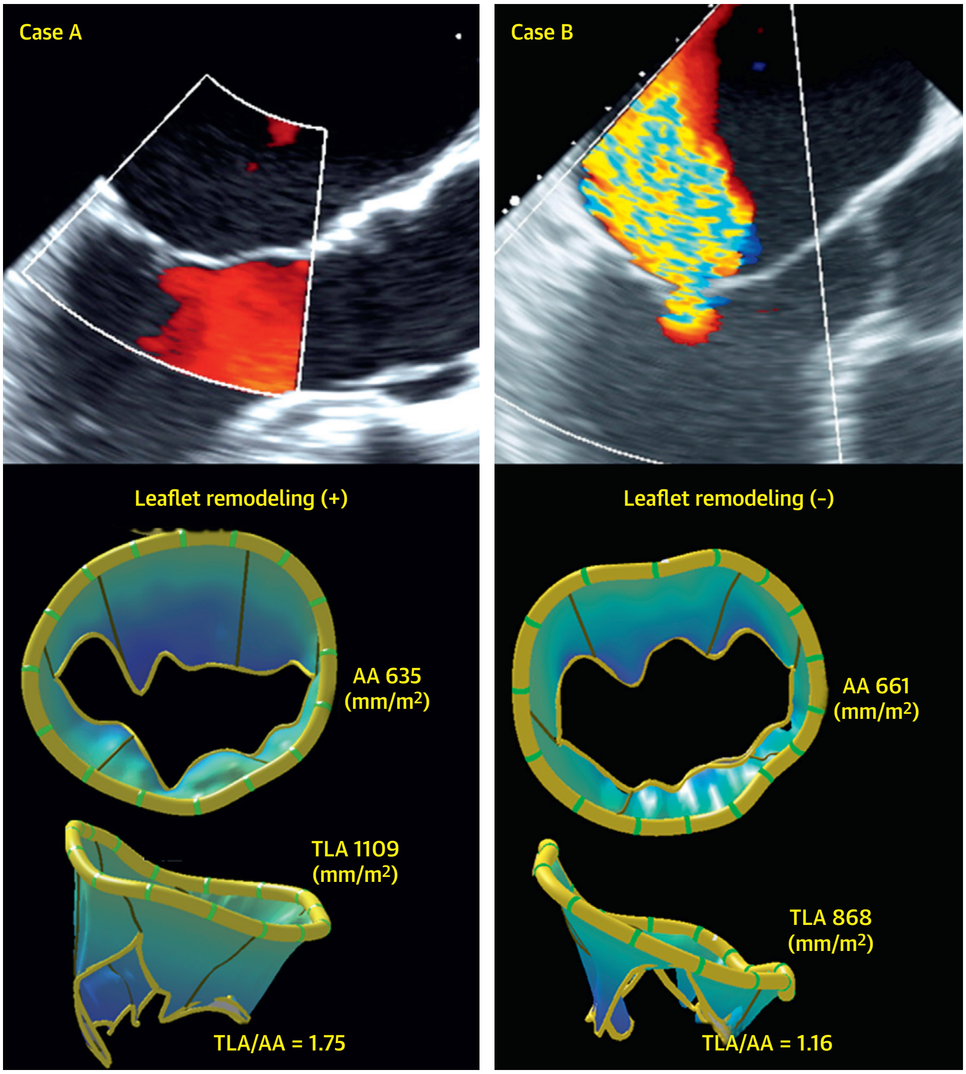
inlet. Because of this anatomical structure, expansion of the LA wall leads to deviation of the posterior annulus toward the outside of the myocardium, causing tethering of the posterior leaflet (**Figure 4**) (32,34). Silbiger (32) proposed this phenomenon of "atriogenic leaflet tethering" as a potential mechanism causing worsening MR in patients with mitral annular dilatation (**Figure 5**). This phenomenon of the development of a steeper posterior leaflet angle has previously been described by a textbook as "hamstringing" in patients with rheumatic mitral stenosis (35) and has recently been verified by a few reports using 2DE and 3DE (21,24). Such patients with a steep-angled posterior leaflet are often encountered in clinical practice. They present with asymmetric posterior tethering, with posterior leaflets "bending" toward the LV, and have posteriorly deviated eccentric MR jets (**Figure 6B**).

The evidence of atriogenic leaflet tethering show discrepancies between studies, however. First, these studies measured different kinds of angles: angle A, which measures between the annular plane and the line connecting the annulus and coaptation point of the anterior and posterior leaflet and angle B, which measures between the annular plane and the line connecting the annulus and the posterior leaflet tip. Because there is redundant leaflet beyond the coaptation point towards the LV, angle B is greater than angle A. In the study by Machino et al. (24), there was a significant difference in angle A between patients with and without MR. In contrast, in the Ito et al. (21) and Takahashi et al. (33) studies, they reported a difference in angle B, and not in angle A, between patients with and without MR. In addition, the values of the reported angles vary widely among studies (**Table 1**); thus, the generality of this mechanism in patients with atrial functional MR is somewhat uncertain, although such cases with posterior leaflet tethering have been encountered in clinical practice. According to our clinical impressions, posterior leaflet tethering is a relatively rare subtype in patients with atrial functional MR and tends to be observed in patients with extremely advanced LA remodeling. In fact, in these studies reporting atriogenic tethering as the main mechanism of atrial functional MR, LA size was notably larger than in other studies (**Table 1**).

ANNULAR CONTRACTILITY AND SADDLE SHAPE: IMPORTANT CO-SUBSTRATES. The mitral annulus is primarily composed of fibrous and adipose tissue. It does not actively contract by itself, but moves passively with contraction of the LA and the more muscular LV. The normal mitral annulus is known to be saddle shaped. In early systole, the area of the mitral annulus decreases 20% to 25% compared with that in diastole (36,37), and the saddle shape increases in depth (24,37). AF rhythm immediately blunts the motion of the mitral annulus (38) and gradually increases the size and flatness of the mitral annulus (24,27). The reduced annular contraction results in a larger systolic mitral annulus area, further boosting the annulus area to leaflet area imbalance. The flattening of the annulus, which results in a loss of the deep saddle shape, causes increased stress on the mitral leaflets and a greater tethering distance (20,39,40).

All 4 studies reporting annulus contractility showed that fractional area change of the annulus was significantly reduced in patients with atrial functional MR compared with those without MR and/or normal subjects (**Table 1**) (23-25,41), suggesting that decreased annulus contractility is common in patients with atrial functional MR. However, the inter-studies variability is significant, and the cutoff value associated with occurrence of MR is unknown. With regard to the saddle shape, 2 studies demonstrated a significantly higher nonplanar angle (more flattened annulus) in patients with atrial functional MR (23,24). Other studies also reported a similar annulus height between those with and without atrial functional MR despite the larger annulus in atrial functional MR, suggesting a more flattened annulus is present in patients with atrial functional MR (20,22,23,25). Thus, flattened annulus seems to be pervasive as well.

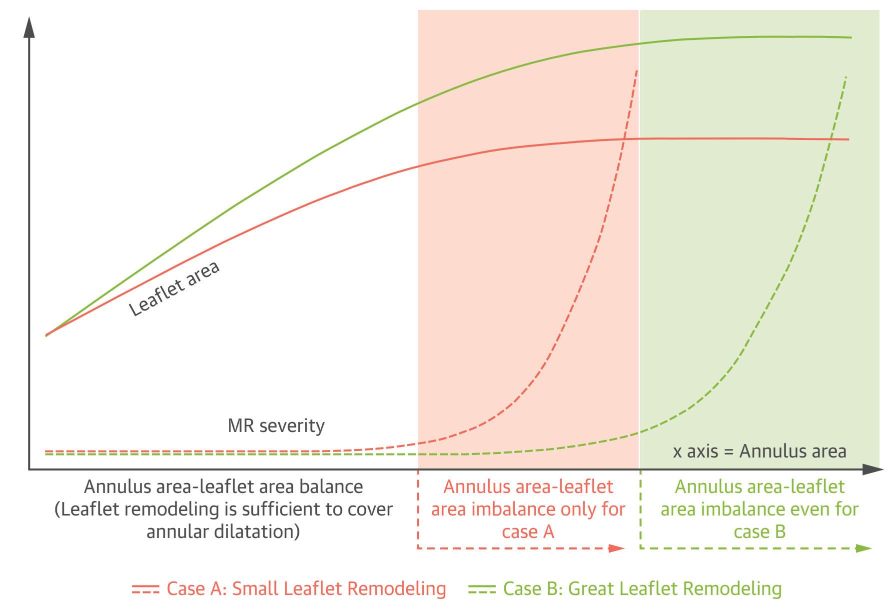
FIGURE 2 **2 Cases With Different Degrees of Mitral Leaflet Remodeling**



Cases A and B had a similarly enlarged mitral annulus area; however, the total leaflet area was different (1,109 vs. 868 mm/m^2). As a result, the total leaflet area to annulus area ratio was 1.75 and 1.16 in cases A and B, respectively, indicating insufficient leaflet remodeling. AA = annulus area; TLA = total leaflet area; TLA/AA = total leaflet area to annulus area ratio.

ATRIAL DYSFUNCTION AND CHANGES IN HEART RATE: FUNCTIONAL ASPECT OF LA REMODELING. It is well established how AF causes, simultaneously to the electrical alteration, a relevant microscopic and macroscopic LA remodeling (42). The interstitial fibrosis, which gradually replaces the contractile atrial myocardium, is responsible for an increase of the LA stiffness together with an altered chamber compliance. Speckle tracking echocardiography is a second level echocardiographic technique that guarantees an angle-independent and objective quantification of myocardial deformation (43). Recent studies have demonstrated the ability of LA strain analysis, especially peak LA strain, to detect fibrosis in LA wall and to stratify the risk of stroke in patients with AF (**Figure 7**) (44). In fact, a strong inverse correlation between the amount of fibrosis assessed by 3D gadolinium late enhancement magnetic resonance and that by peak LA strain has been shown in patients with AF (45); the patients with lower values of peak LA strain have a higher risk of cardioembolic events than those with normal peak LA strain. Additionally, peak LA strain to E/e′ (the most used echocardiographic index for the estimation of LV filling

FIGURE 3 Relationship of Annulus Area to Leaflet Area Imbalance With Mitral Regurgitation



The x-axis indicates the annulus area and the y-axis indicates the leaflet area and MR severity. The upper limit of leaflet remodeling varies; in case A, the leaflet can enlarge more than in case B. When the annulus area increases beyond the upper limit of leaflet remodeling, annulus area to leaflet area imbalance causes significant MR. MR = mitral regurgitation.

pressure) ratio was reported to be useful in the noninvasive assessment of LA stiffness (46). LA strain was also correlated with LA compliance (47), and the amount of fibrosis in LA wall detected by Masson's trichrome staining on tissue samples in patients with MR (48); thus, LA function is impaired by both AF and MR, resulting in further risk of worse clinical outcome.

AF also causes a substantial beat-to-beat variation in cycle lengths and filling time. Although tachycardia generally reduces regurgitant volume per beat (49,50), we sometimes experience improvements in the severity of MR immediately after cardioversion of AF to sinus rhythm. Similar findings were reported in an animal experiment (51). Several old studies suggested that the loss of atrial systole was associated with insufficient mitral valve closure in diastole and early systole (52,53), resulting in atrial functional MR. To date, however, there are few data regarding the direct effect of rapid ventricular response and heart rate variability on atrial functional MR and further studies are needed to investigate the underlying mechanisms.

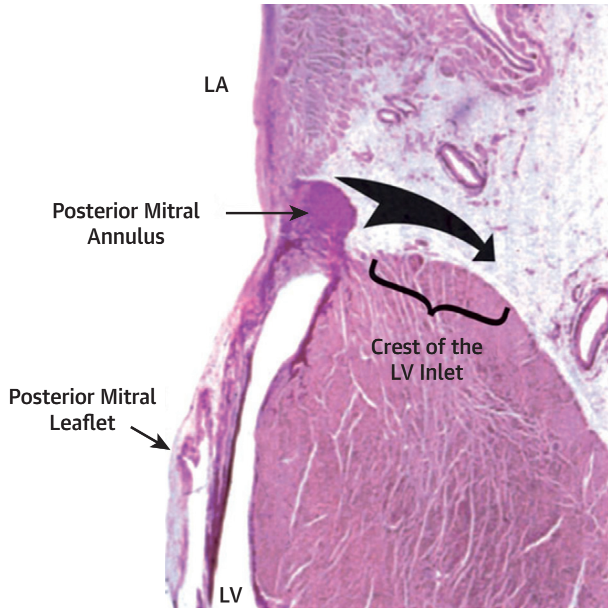
RELATIONSHIP BETWEEN MECHANISMS. Importantly, each of the mechanisms discussed so far relate to 1 aspect of "atrial remodeling" seen in patients with advanced AF. In other words, these various structural and functional changes caused by AF usually progress simultaneously. As shown in the **Central Illustration**, structural changes start with LA and annular dilatation, which are accompanied by flattening of saddle shape of the annulus. Annular dilatation, at least in part, seems to play a role in leaflet remodeling, which attenuates the annulus area to leaflet area imbalance. Functionally, AF reduces annulus contractility, which results in a larger systolic annulus area and worsens the annulus area to leaflet area imbalance. LA dysfunction is further accelerated by MR and is associated with worse clinical outcomes. These changes progress simultaneously in most cases, making it difficult to assess the net influence of each factor. Some studies used a statistical approach to adjust for confounders (**Table 2**); however, unfortunately, there has been no study that considers all the possible mechanisms together with an appropriate statistical approach and a sufficient sample size. It should therefore be acknowledged that this relationship remains theoretical speculation and it is not fully understood whether each factor is just a bystander or an important trigger influencing prognosis. Larger studies focused on the various factors and their relationships with appropriate statistical approaches are obviously warranted to establish the causal relationship between these mechanisms.

CLINICAL IMPLICATIONS OF ATRIAL FUNCTIONAL MR

PREVALENCE AND PROGNOSTIC IMPLICATIONS. In total, 9 studies referring to the prevalence of atrial functional MR in patients with AF and preserved LV function (**Table 3**) were selected. Other studies in which the patient population was uncertain or included patients with LV dysfunction were excluded. Although the prevalence varied widely between studies (between 2.8% and 66.7%), this may be due partly to the difference in methods for MR grading and the study populations. Qualification of functional MR, especially in AF rhythm, is often challenging. Sharma et al. reported a prevalence of 67% (54). They used qualitative grading without quantitative measurements, most of which were not severe but moderate MR. It is a possibility that there were substantial number of patients with "mild-to-moderate" MR. Itabashi et al. reported that 31 of 64 patients with AF who underwent transesophageal echocardiography had significant MR (41). Because the indications for transesophageal echocardiography were not mentioned in this study, it is not guaranteed that their patients reflect a normal population of AF (i.e., they might undergo the examination for evaluation of MR). Last, Saito et al. studied 68 patients with AF and preserved LV ejection fraction (LVEF) and found 44.1% of the patients had atrial functional MR (55). However, their population was patients hospitalized with heart failure, in which the prevalence of atrial functional MR is expected to be higher than in the normal AF population. We may conclude that the prevalence of atrial functional MR in patients with AF and preserved LVEF should be about 3% to 15%. Because the entire AF population is substantial and still growing, this prevalence should not be neglected.

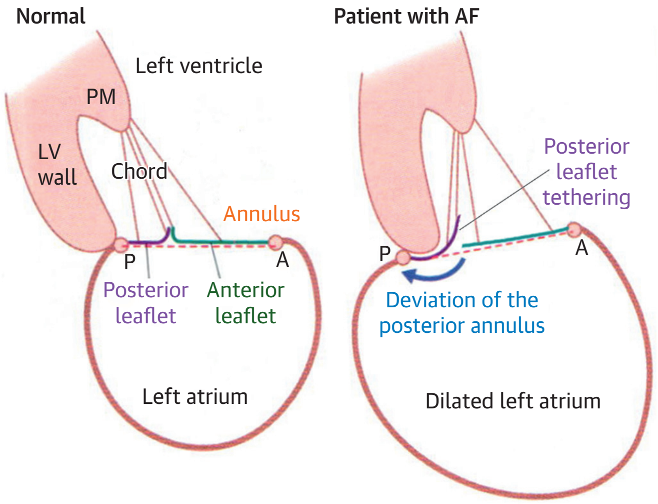
Abe et al. retrospectively studied 11,021 echocardiographic studies and found 298 patients with AF and preserved LVEF (≥50%) after excluding patients with heart failure or other cardiac diseases (56). Using multiparametric MR grading, they reported 24 (8.1%) patients with atrial functional MR. The patients with atrial functional MR had a significantly higher prevalence of adverse events (cardiac death, hospitalization from worsening heart failure, or mitral/tricuspid valve surgery) (**Figure 8**). Multivariate analysis also showed that MR was a significant predictor of worse outcomes (hazard ratio: 4.0; 95% confidence interval:

FIGURE 4 Anatomy of the Posterior Attachment of the Mitral Annulus



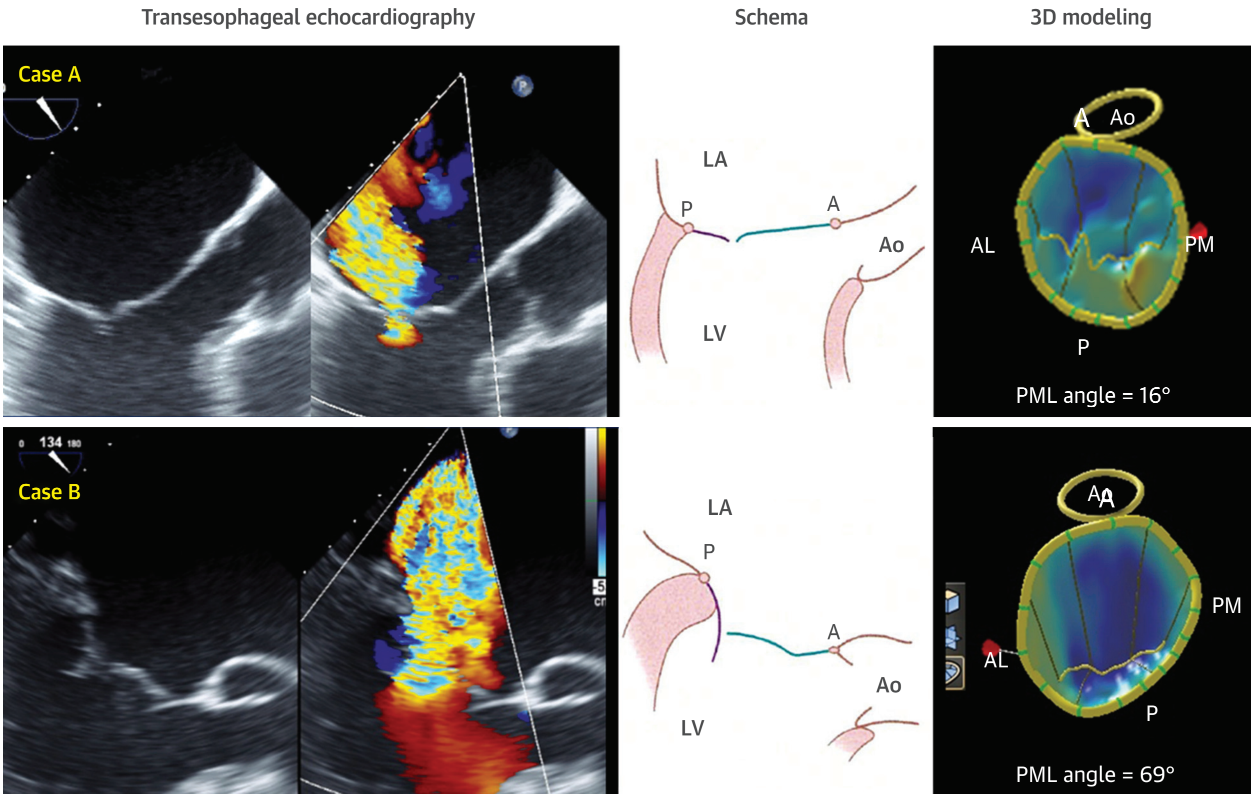
The posterior portion of the mitral annulus is attached to the junction of the left atrium and free wall of the left ventricle. Expansion of the left wall leads to deviation of the posterior annulus toward the outside of the myocardium, causing tethering of the posterior leaflet **(arrow)**. Modified with permission from Silbiger (32). LA = left atrium; LV = left ventricle.

FIGURE 5 Atriogenic Leaflet Tethering



The **left panel** shows normal mitral apparatus. In a patient with significant dilatation of the left atrium and mitral annulus, the P deviates toward the outside of the myocardium, causing tethering of the posterior leaflet as shown in the **right panel**. A = anterior annulus; p = posterior annulus; other abbreviation as in **Figures 1 and 4**.

FIGURE 6 2 Cases With Different Subtypes of Mitral Regurgitation Secondary to Atrial Fibrillation



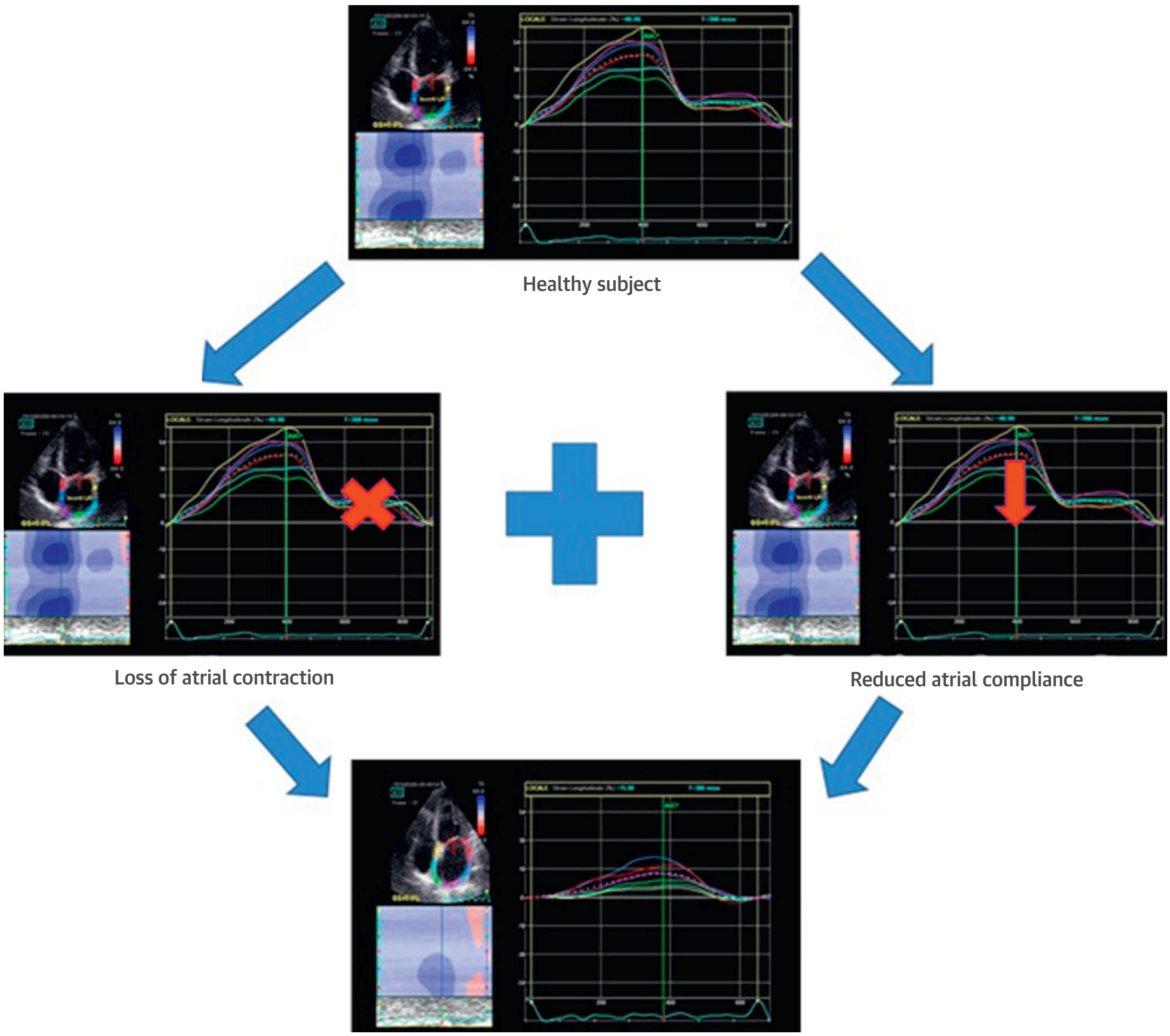
Case A and B represent patients who underwent surgical annuloplasty for mitral regurgitation. In case A, the mitral leaflet to annulus ratio was 1.23 and the primary etiology was considered as insufficient leaflet remodeling. In case B, atriogenic leaflet tethering was considered the primary etiology with a highly steep posterior leaflet angle of 69°. 3D = 3-dimensional; PML = posterior mitral leaflet.

2.3 to 7.0 per 1-grade increase). This was the first study reporting the natural history of patients with atrial functional MR. Because the study was done retrospectively with a relatively small number of patients, further prospective cohort studies are warranted to establish the prognostic implications of atrial functional MR.

SEVERITY OF ATRIAL FUNCTIONAL MR. Quantification of MR severity, especially in functional MR, is challenging. Vena contracta width and effective regurgitant orifice calculated from the proximal isovelocity surface area are the most common and guideline-recommended methods to quantify MR. These methods are often inappropriate for functional MR because of its elliptical regurgitant orifice; therefore, comprehensive multiparametric grading is recommended (6,57). Novel 3D methods including vena contracta area and 3D proximal isovelocity surface area have the potential to overcome these limitations regarding orifice shape (58,59). Transesophageal echocardiography has superior image quality and enables a more detailed morphological assessment of mitral valve apparatus; however, mild anesthesia is often required because of discomfort, which may modify the severity of functional MR (60,61).

Another challenge in the quantification of atrial functional MR is the beat-to-beat variation of cycle lengths, along with variable severity of MR. Although guidelines recommend quantification using the average of 5 or more heart beats for chamber quantification, it is not always easy to implement this recommendation in clinical practice (62). The use of an index beat, whose preceding and pre-preceding beat have the same RR intervals, may be an effective alternative (63).

FIGURE 7 Modifications of the Left Atrial Strain in AF



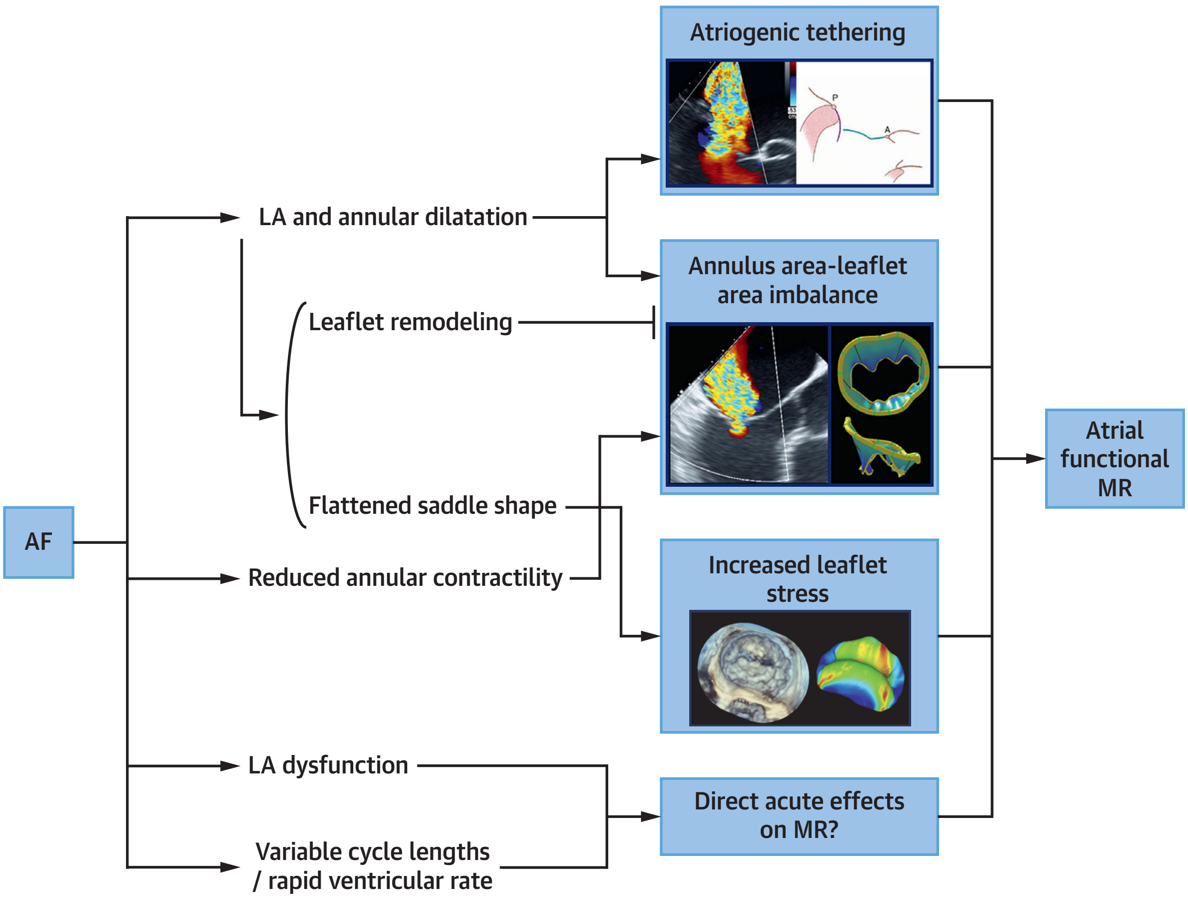
Evolution from a healthy subject to a patient with permanent AF: the figure shows how the loss of atrial systole and the reduction of atrial compliance, resulting from the fibrosis wall, determines an almost flat strain curve. AF = atrial fibrillation.

THERAPEUTIC OPTIONS FOR THE MANAGEMENT OF ATRIAL FUNCTIONAL MR

There is little evidence thus far on therapeutic options for the management of atrial functional MR. Understanding the principles in theoretical approaches is necessary to manage patients at hand and to conduct future studies.

RESTORATION OF SINUS RHYTHM. The study by Gertz et al. (17) suggested that restoring sinus rhythm has a therapeutic effect on atrial functional MR through shrinkage of the enlarged LA. Rhythm control strategies for AF includes pharmacological therapies by antiarrhythmic drugs and catheter or surgical ablation. Pharmacological therapies are easy to start and noninvasive compared with catheter ablation; however, many antiarrhythmic drugs have negative inotropic and paradoxical arrhythmogenic effects and should be carefully used in patients with heart failure. Catheter ablation is a well-established rhythm

CENTRAL ILLUSTRATION Development of MR in Patients With AF



Kagiyama, N. et al. J Am Coll Cardiol Img. 2020;13(3):820-35.

AF causes several structural/functional changes in LA and mitral apparatus. As discussed in the manuscript, these changes result in triggers and boosters of atrial functional MR, including atriogenic tethering, annulus area to leaflet area imbalance, and increased leaflet stress. It might be important to identify these mechanisms using sophisticated imaging techniques for better understanding of the underlying pathology and the appropriate choice of therapeutic options. AF = atrial fibrillation; LA = left atrium; MR = mitral regurgitation.

control therapy for AF, particularly for paroxysmal AF (64), and lately the scope/application of catheter ablation has expanded to treat permanent AF (65). Several studies have shown that catheter ablation is superior to drug therapy to maintain sinus rhythm. Maze procedures, which have better free-from-AF recurrence rates, may be a good choice when other cardiac surgeries are necessary (66). Maintaining a sinus rhythm is more difficult with a larger LA (67), and shrinkage of the LA size following restoration of sinus rhythm is usually limited in patients with a severely remodeled LA (68,69); therefore, the effectiveness of rhythm control by itself might be limited in patients with a particularly markedly dilated LA and mitral annulus.

INTERVENTIONS TO STRUCTURAL CHANGES. Surgical treatment may currently be the most reliable treatment option for MR in atrial functional AF. A few small-sized studies showed that atrial functional MR can be controlled by surgical annuloplasty in most cases (16,33); however, an annuloplasty alone may not always be effective. **Figure 6** shows 2 cases with different anatomical characteristics of the mitral valve. In case A, MR was primarily attributable to insufficient leaflet remodeling with a very small mitral leaflet-to-annulus ratio of 1.23. In contrast, in case B, the mitral leaflet-to-annulus ratio was relatively preserved at 1.47 and atriogenic leaflet tethering was considered the primary etiology. We observed that 3D quantification

TABLE 2 Adjustment for Confounders in Each Study

First Author, Year (Ref. #)	Comparison	Methods for Adjustment for Confounders	Covariates Considered as Confounders	Conclusions
Kihara et al., 2009 (16)	AFMR vs. Control			Annulus dilatation may cause MR in lone AF patients
Ring et al., 2013 (25)	AFMR vs. FMR vs. Control	Multivariate logistic regression	Age, LV diameter, LVEF, LA diameter, annulus area, AP and IC diameter, AHCWR, tenting volume, annulus fractional area change, coaptation index (forward stepwise)	Annulus fractional area change and coaptation index were the strongest predictors of MR (including AFMR and FMR)
van Rosendael et al., 2014 (26)	AFMR vs. AF non-MR	Multivariate logistic regression	Age, LVESV, LVEF, hypertension, type of AF, LA volume	Annulus area, IC and AP diameter, and annulus perimeter were all significantly associated with MR independent of covariates
Machino-Ohtsuka et al., 2016 (24)	AFMR vs. AF non-MR vs. Control	1. Case-control matching 2. Multivariate linear regression (dependent variable = ERO)	1. Sex, age, and body surface area 2. Annulus are, annulus fractional area change, nonplanarity angle, AML angle, PML angle, PML to AML area ratio, Leaflet closure area to annulus area ratio, systolic arterial pressure, and (LA volume or LVEDV + LVEF)	PML angle, annulus area, annulus fractional area change, nonplanarity angle were independent factors. PML angle and annulus area had a higher coefficient than other variables
Itabashi et al., 2016 (41)	AFMR vs. AF non-MR	Multivariate logistic regression	Annulus fractional area change and bending ratio	Small annulus fractional area change and the bending ratio (position of the chordae attached to the AML) were associated with AFMR
Ito et al., 2017 (21)	AFMR vs. AF non-MR	Simple group comparison (no adjustment)		In patients with AFMR, LA and annulus are dilated, AML is flattened and PML is bent toward LV
Kagiyama et al., 2017 (22)	AFMR vs. AF non-MR vs. Control	1. Case-control matching 2. Multivariate logistic regression	1. Sex and age 2. LA volume, type of AF, annulus area, and total leaflet to annulus area ratio	LA volume index and total leaflet to annulus area ratio were the independent predictors of AFMR, while annulus area was not
Kim et al., 2017 (23)	AFMR vs. AF non-MR vs. control	Multivariate logistic regression	Annulus area, posterior to anterior perimeter ratio, and total leaflet to closure area ratio	Annulus area, posterior to anterior perimeter ratio, and total leaflet to closure area ratio were determinants of AFMR
Cong et al., 2018 (20)	AFMR vs. AF non-MR vs. control	1. Case-control matching 2. Multivariate logistic regression	1. Sex, age, and body surface area 2. Annulus area, AHCWR, and tenting volume (selected by a stepwise method from the factors with $p < 0.1$ in univariate analysis)	Annulus area, AHCWR, and tenting volume were independent risk factors

AF = atrial fibrillation; AML = anterior mitral leaflet; AP = anteroposterior; FMR = functional mitral regurgitation resulting from LV dysfunction; IC = inter-commissure; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume. Other abbreviations as in Table 1.

of the leaflet angle showed that the posterior leaflet angle in case A was 15° and that in case B was 69°. Although surgical annuloplasty was performed in both cases for atrial functional MR, postoperative recurrence of MR was reported in case B only. Although to date there is no evidence reported in the published reports, there may be a subtype of patients requiring further intervention in addition to a simple annuloplasty.

Catheter-based interventions may be possible alternatives for atrial functional MR. In addition to MitraClip, which is designed to mimic Alfieri's surgical edge-to-edge technique (70,71), several devices with various unique mechanisms, including mimicking surgical annuloplasty, are being developed (72–75). Theoretically, these annuloplasty devices are expected to be effective for annulus area to leaflet area imbalance. Because patients with AF tend

TABLE 3 Prevalence of Atrial Functional Mitral Regurgitation

First Author, Year (Ref. #)	Prevalence	%	Definition and Population	MR Grading
Gertz et al., 2011 (17)	54/727	7.4	MR ≥ moderate without excessive/restrictive leaflet motion in patients with LVEF ≥50% who underwent catheter ablation	MR jet area/LA area
Sharma et al., 2012 (54)	38/57	66.7	MR ≥ moderate in lone AF patients without heart failure	Qualitative grading by 2 observers
van Rosendael et al., 2014 (26)	7/170	4.1	MR ≥ moderate in AF patients who underwent cardiac CT with LVEF ≥55% and LVEDV <75 ml/m^2	Semiquantitative grading by color and continuous wave Doppler
Machino-Otsuka et al., 2016 (24)	25/907	2.8	MR ≥ moderate in persistent AF patients who underwent TEE with LVEF ≥50% and LVEDV ≤74 ml/m^2	Multiparametric grading including quantitative parameters
Itabashi et al., 2016 (41)	31/64	48.4	MR ≥ moderate in persistent AF patients who underwent TEE with normal LV size, LVEF >50% and no WMA	Multiparametric grading using vena contracta (guideline directed)
Kagiyama et al., 2017 (22)	28/268	10.4	MR ≥ moderate in AF patients who underwent TEE with LVEF >50% and LVDd <55 mm	Multiparametric grading including quantitative parameters
Saito et al., 2018 (55)	30/68	44.1	MR ≥ moderate in AF patients hospitalized with heart failure and LVEF ≥50%	MR jet area/LA area
Abe et al., 2018 (56)	24/298	8.1	MR ≥ moderate in AF patients who underwent TTE with LVEF ≥50% and no WMA, without heart failure	Multiparametric grading including quantitative parameters
Cong et al., 2018 (20)	25/168	14.9	MR ≥ moderate in AF patients who underwent TEE with LVEF ≥50%	Multiparametric grading based on mainly ERO

LVDd = left ventricular diastolic diameter; WMA = wall motion abnormality; other abbreviations as in Tables 1 and 2.

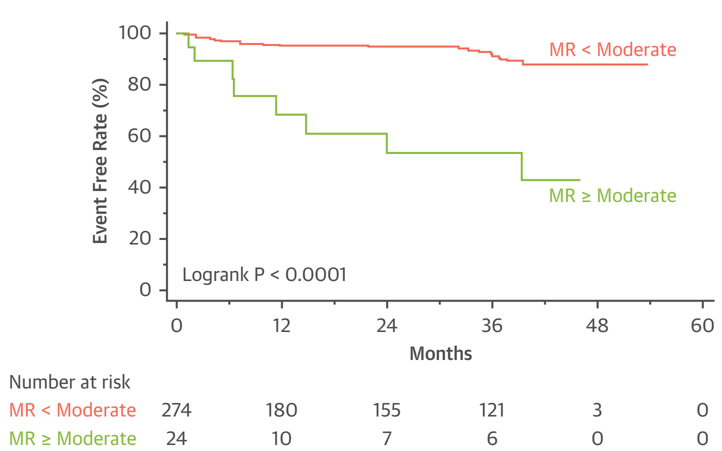
to be old and present with concomitant comorbidities, these catheter-based devices may become a useful treatment choice for atrial functional MR.

ANGIOTENSIN II RECEPTOR BLOCKER. Recently, angiotensin II receptor blockers (ARBs) have been reported to modulate profibrotic changes in the process of mitral valve leaflet remodeling after myocardial infarction, suppressing excess cellular proliferation, valve thickening, and matrix remodeling (76,77). Kim et al. (23) further investigated the effect of ARBs on leaflet remodeling in patients with AF. In patients with atrial functional MR, those taking ARBs or angiotensin-converting enzyme inhibitors had a greater leaflet area to closure area ratio and lower MR severity (23). These results are preliminary and should be considered hypothesis-generating; however, these drugs may have the potential to prompt leaflet enlargement and may have a prophylactic effect on atrial functional MR.

CONCLUSIONS

Significant MR may occur in patients with isolated AF perhaps when a modifying factor (occasionally multiple factors) such as atriogenic leaflet tethering, annulus area to leaflet area imbalance from insufficient leaflet remodeling and reduced annular contractility, and increased valve stress by flattened

FIGURE 8 Kaplan-Meier Curves for Cardiac Death and Heart Failure Hospitalization



In patients with AF and preserved LVEF, patients with atrial functional MR had significantly higher event rates. Modified with permission from Abe et al. (56). LVEF = left ventricular ejection fraction; other abbreviations as in Figures 3 and 7.

HIGHLIGHTS

- AFMR is not rare and may be associated with worse prognosis
- Annulus area to leaflet area imbalance and atriogenic tethering are the 2 key mechanisms
- Understanding subtypes of mechanisms may be important in considering therapeutic options

saddle shape are superimposed on underlying LA and mitral annular dilatation. LA dysfunction may be another factor contributing to further symptoms and worse outcome; however, there are few data on the relationship between these mechanisms, and further studies are clearly needed. Several possible therapeutic options have been proposed; however, to date, no conclusive data are available in the literature and each therapy targets a different mechanism. The subtypes of MR and the appropriate therapeutic options based on evaluation of novel imaging techniques should be considered in the management of MR in patients with AF.

ADDRESS FOR CORRESPONDENCE: Dr. Nobuyuki Kagiyama, West Virginia University Heart and Vascular Institute, 1 Medical Center Drive, Morgantown, West Virginia 26505. E-mail: kgnb_27_hot@yahoo.co.jp.

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