Looking into the Mechanistic Link Between Mitral Regurgitation and Atrial Fibrillation

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KEYWORDS

• Atrial fibrillation • Atrial functional mitral regurgitation • Echocardiography • Heart failure • Valvular heart disease

KEY POINTS

- Atrial functional mitral regurgitation can occur in patients with atrial fibrillation despite a preserved left ventricular systolic function.
- Atrial functional mitral regurgitation is an important cause of heart failure and a considerable therapeutic target in patients with heart failure with atrial fibrillation.
- Mitral annular dilatation owing to atrial fibrillation-induced left atrial dilatation is primarily necessary for the generation of atrial functional mitral regurgitation.
- Hamstringing of the posterior mitral leaflet also relates to the generation of atrial functional mitral regurgitation.
- Further mitral annular dilatation owing to progressive dilatations of the left atrium and left ventricle, with mitral regurgitation-induced volume overload, worsens atrial functional mitral regurgitation.

INTRODUCTION

Primary mitral regurgitation (MR), when significant, can lead to the occurrence of atrial fibrillation (AF) owing to the left atrial (LA) volume/pressure overload. Therefore, atrial fibrillation can be viewed as evidence of the pathologic significance of primary MR, and the presence of concomitant severe primary MR and new-onset atrial fibrillation is considered a sign of a surgical indication for MR.[1,2] Conversely, MR can also occur as a consequence of LA dilatation in patients with atrial fibrillation. This type of secondary MR and its mechanistic link with atrial fibrillation are the topic of discussion in the present review article.

DEFINITION OF ATRIAL FUNCTIONAL MITRAL REGURGITATION

Secondary MR (ie, functional MR) was originally identified as resulting from mitral leaflet tethering–tenting owing to left ventricular (LV) systolic dysfunction and remodeling in patients with ischemic heart disease or dilated cardiomyopathy.[3–5] One long-held belief is that atrial fibrillation, on its own, sometimes causes significant functional tricuspid regurgitation (TR), but does not usually cause significant functional MR.[6,7] By contrast, several studies have recently shown that functional MR can occur in patients with atrial fibrillation and an enlarged LA, despite a lack of

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Cardiol Clin 39 (2021) 281–288
https://doi.org/10.1016/j.ccl.2021.01.010

LV systolic dysfunction.[8–22] This occurrence can be termed atrial functional MR (AFMR) and has received much attention as an important cause of heart failure. It is also a considerable therapeutic target in patients with heart failure with persistent atrial fibrillation and preserved LV ejection fraction (LVEF). The traditional functional MR occurring in patients with LV dilatation and/or systolic dysfunction has sometimes been termed ventricular functional MR (VFMR) to distinguish it from AFMR.[15,21]

AFMR can be defined as MR with:

- LA dilatation, mainly seen in patients with atrial fibrillation;
- No significant degenerative change in the mitral valve complex; and
- No significant LV systolic dysfunction or dilatation.

However, no cut-off values for LVEF and LV size have yet been established to rule in/out AFMR. Most previous studies that have examined AFMR have used 50% as the cut-off value for LVEF. Some studies have also used the cut-off value of the LV diastolic diameter or volume using various references that established the normal values to study pure AFMR.[10,11,13] In real-world clinical settings, however, patients with AFMR can have a dilated LV owing to the volume overload resulting from chronic MR. Patients with AFMR can also have a decreased LVEF in the advanced stage. Therefore, patients with mild LV dilatation or mild LV systolic dysfunction should also be recognized as having AFMR if they have functional MR that originates from LA dilatation rather than from LV dilatation or systolic dysfunction.[20,21]

Patients with sinus rhythm can also have AFMR owing to LA dilatation resulting from LV diastolic dysfunction rather than from atrial fibrillation, whereas significant AFMR is thought to be less prevalent in patients with sinus rhythm than in patients with atrial fibrillation. Tamargo and colleagues[23] studied 280 patients with heart failure with a preserved LVEF and showed that patients with mild to moderate functional MR had a higher prevalence of atrial fibrillation than did patients with no to trivial functional MR (38% vs 13%; $P<.0001$). Surprisingly, the remaining 62% of the patients with heart failure with a preserved LVEF and mild to moderate functional MR had a sinus rhythm. The true distribution of the sinus rhythm and atrial fibrillation in patients with AFMR remains unknown because patients with more than moderate MR were excluded from the study.

PREVALENCE AND PROGNOSIS OF PATIENTS WITH ATRIAL FUNCTIONAL MITRAL REGURGITATION

We found that the prevalence of significant AFMR was 8.1% in patients with atrial fibrillation who underwent transthoracic echocardiography but were without other underlying heart diseases or reduced LVEF, whereas the prevalence was 28% for patients with longstanding persistent atrial fibrillation (duration >10 years) (**Fig. 1**).[14] This difference was greater than expected. The event-free rate for cardiac death or hospitalization for worsening heart failure was not high (53%), even at a follow-up of only 24 months, in patients with significant AFMR (**Fig. 2**A). Patients with significant AFMR in conjunction with secondary TR had the poorest prognosis, with an event-free rate of 27% at 24 months (**Fig. 2**B).

TR owing to right atrial dilatation and tricuspid annular dilatation is also referred to as atrial functional TR (AFTR). The combination of AFMR and AFTR, which had the poorest prognosis, should therefore receive greater therapeutic attention. Some other studies have reported that patients with persistent atrial fibrillation who were hospitalized owing to heart failure with preserved EF had significant AFMR more frequently (37%–44%), even at discharge after medical therapies, and their AFMR was associated with readmission owing to heart failure during the postdischarge follow-up.[15,16] Dziadzko and colleagues,[20] in a study of 727 residents living in a community,

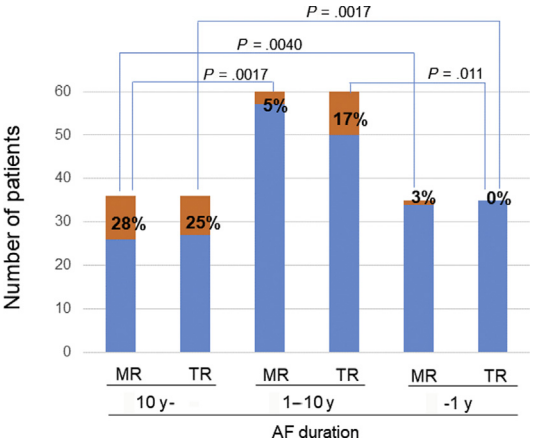

Fig. 1. Prevalence of significant (ie, moderate or greater) MR or TR versus duration of AF. *Blue*, not significant; *orange*, significant. (*From* Abe Y, Akamatsu K, Ito K, et al. Prevalence and prognostic significance of functional mitral and tricuspid regurgitation despite preserved left ventricular ejection fraction in atrial fibrillation patients. Circ J. 2018;82:1451–8; with permission.)

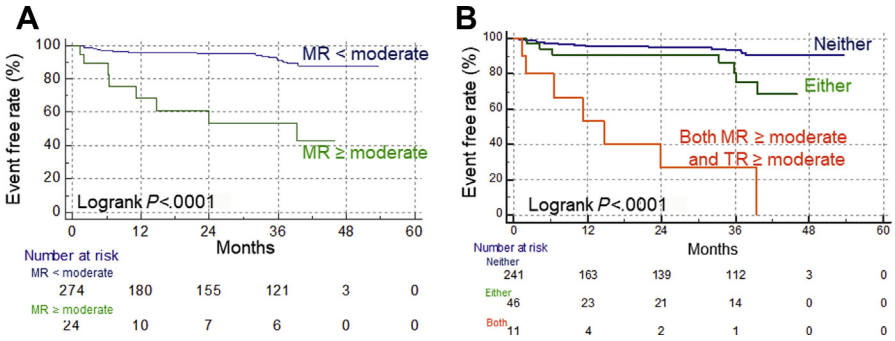

Fig. 2. Kaplan–Meier event-free rates of cardiac death, hospitalization owing to worsening heart failure (*A*) by the status of significant (ie, moderate or greater) mitral regurgitation (MR); and (*B*) by the status of significant MR or TR. (*From* Abe Y, Akamatsu K, Ito K, et al. Prevalence and prognostic significance of functional mitral and tricuspid regurgitation despite preserved left ventricular ejection fraction in atrial fibrillation patients. Circ J. 2018;82:1451–8; with permission.)

reported that 32%, 38%, and 27% of the residents with a first diagnosis of isolated moderate or severe MR (determined by clinically indicated echocardiography) had organic MR, VFMR, and AFMR, respectively. The study also revealed a significantly increased prevalence of AFMR with patient age, and the AFMR was related to mortality or the incidence of heart failure. Kim and colleagues[24] recently reported better outcomes for medically treated patients with AFMR than with VFMR with LV dysfunction, but worse outcomes than patients with primary MR. Consequently, the appropriate diagnosis and treatment of AFMR will become more important in preventing cardiac death and heart failure in patients with atrial fibrillation in our aging societies.

ETIOLOGY OF ATRIAL FUNCTIONAL MITRAL REGURGITATION

The etiology of AFMR is the most important issue covered in this review article. Several recent studies have shown that LA dilatation and the subsequent mitral annular (MA) dilatation are both main etiologies of AFMR.[8–14,17–22] The fact that MA dilatation is not mainly induced by LV dilatation but by LA dilatation is not fully unknown.[22,25] Some may wonder why the LV connected with MA has less impact on MA than is observed with the LA. In fact, however, the MA that is defined as the edge at the root of the mitral leaflet is usually positioned at the junction of the LV and LA or at the LA wall, out of touch with the LV. By contrast, no MA is positioned at the LV wall out of touch with the LA. The phenomenon whereby the MA is positioned away from the LV edge is referred to as MA disjunction.[26–28] MA disjunction is not seen in all patients and is not homogenous, even in the same patient. The MA dilatation owing to the LA dilation reduces the coaptation of the leaflets and is likely to generate MR with a central jet, corresponding to Carpentier type I MR (**Fig. 3**). The cut-off value for the MA dimension index for generating significant AFMR (moderate or more degrees) is 21 to 22 cm^2/m^2, as measured in the long axis view with transthoracic echocardiography.[22]

Other factors have also been suggested as etiologies of AFMR.[11–13,17,18,22] These factors include the disruption of the MA saddle shape,[11,17,18] a decrease in MA contractility,[11,18] inadequate compensation for the MA dilatation resulting from the lack of leaflet remodeling,[13,17] and tethering of the posterior mitral leaflet (PML).[11,12,22] However, the main determinants and the relationships among the various etiologies have not been fully elucidated.

Insufficient leaflet remodeling cannot compensate for the MA dilatation and can cause the generation and worsening of MR. An experimental histopathologic study and a clinical study have both confirmed that mitral leaflets expand to occlude systolic MA in patients with VFMR.[29,30] This phenomenon represents leaflet remodeling, and patients with significant VFMR have a smaller mitral leaflet closure to leaflet area ratio, which represents insufficient leaflet remodeling. The same findings have also been reported in 3-dimensional transesophageal echocardiography studies as an important etiology of AFMR without LV dysfunction.[13,17]

Our previous study using 3-dimensional transesophageal echocardiography showed that the anterior mitral leaflet (AML) was flattened along the MA plane and that the PML was bent toward the LV cavity at midsystole in patients with significant AFMR.[16] The LA dilates posteriorly, and the posterior MA is displaced backward to the LA

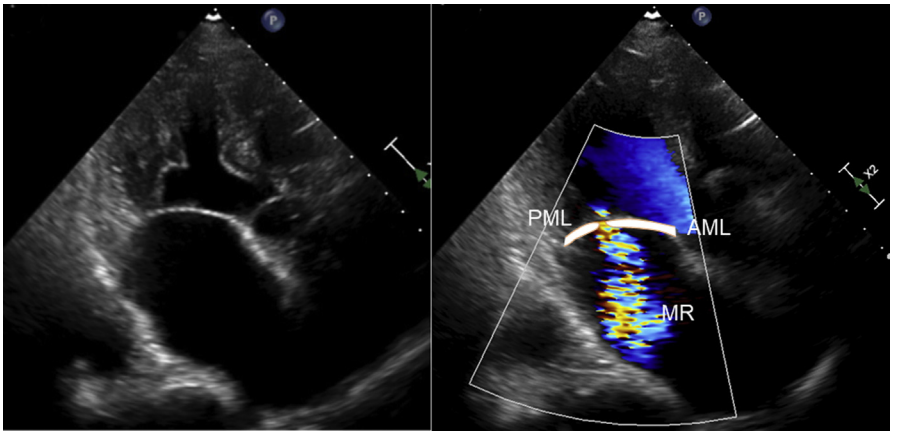

Fig. 3. Atrial functional mitral regurgitation with a flattened anterior mitral leaflet, flattened PML, and central mitral regurgitant (MR) jet (Carpentier I). AML, anterior mitral leaflet.

side from the crest of the posterior LV. This backward LA enlargement causes an inner bending of the basal posterior LV. The posterior displacement of the MA is emphasized at systole by the paradoxic posterior movement of the basal LV.[19] The tip of the PML then becomes tethered to the posterior LV by the papillary muscles and the chordae tendineae. This PML tethering that originates from LA dilatation is referred to as atriogenic leaflet tethering.[19] The result of this atriogenic leaflet tethering is a curving of the PML, which restricts its movement. This functional restriction of the PML was originally seen in patients with giant LA owing to rheumatic mitral valve disease and has traditionally been referred to as the hamstringing of the posterior cusp.[31] The PML hamstringing seen in the current patients with AFMR can be recognized as being more purely functional than that seen in patients with rheumatic mitral valve disease (**Fig. 4**).[12,21] Atriogenic leaflet tethering of the PML, complicated with MA dilatation, further decreases the leaflet coaptation, thereby deteriorating the MR. AFMR with PML hamstringing is classified as a combination of Carpentier type I for AML and type IIIb for PML and is likely to have an eccentric jet directed toward the posterior LA wall (see **Fig. 4**). The AML with a coaptation gap from the tethered PML in patients with AFMR with an eccentric jet can be considered to have a pseudoprolapse or override.

AFMR is defined as secondary MR with LA and MA dilatation and can be classified into 2 types: one has the flattened AML, a flattened PML, and a central jet, and the other has the flattened AML with pseudoprolapse, a tethered PML with the hamstringing phenomenon, and an eccentric jet (**Fig. 5**). The factors that divide these 2 types of AFMR remain unknown. Another recent article of ours that included 159 consecutive patients with atrial fibrillation and preserved LVEF demonstrated that a total of 7 of 13 patients (54%) with significant AFMR had PML hamstringing, and 4 of the 7 patients with both significant MR and PML hamstringing had eccentric MR jets.[22] The findings in this article also suggested the following important information: (1) the systolic LV size, as well as the LA size, were the independent determinants of MR grading; (2) the MA size and the presence of the PML hamstringing were both the independent determinants of MR grading among the parameters of systolic mitral morphology; (3) the LA size was the strongest determinant of the MA size, but the LV size was also an independent determinant of the MA size; and (4) the LA size was associated with the hamstringing phenomenon of PML, whereas the LV systolic dimension index was not. These results have led us to now believe that both the MA dilatation and the PML hamstringing can occur owing to atrial fibrillation-induced LA dilatation and generate MR. Subsequently, additional LA and LV dilatations, which may be induced by volume overload owing to the MR, can lead to further dilatation of the MA and worsening of the MR (**Fig. 6**).[22]

TREATMENTS FOR PATIENTS WITH ATRIAL FUNCTIONAL MITRAL REGURGITATION

Recently published guidelines have not addressed the treatment of AFMR.[1,2] However, the Japanese guidelines for the treatments for valvular heart disease have been the first to address AFMR.[32] The new Japanese guidelines indicate that:

- Symptomatic patients with AFMR should first receive standard medical therapy for heart

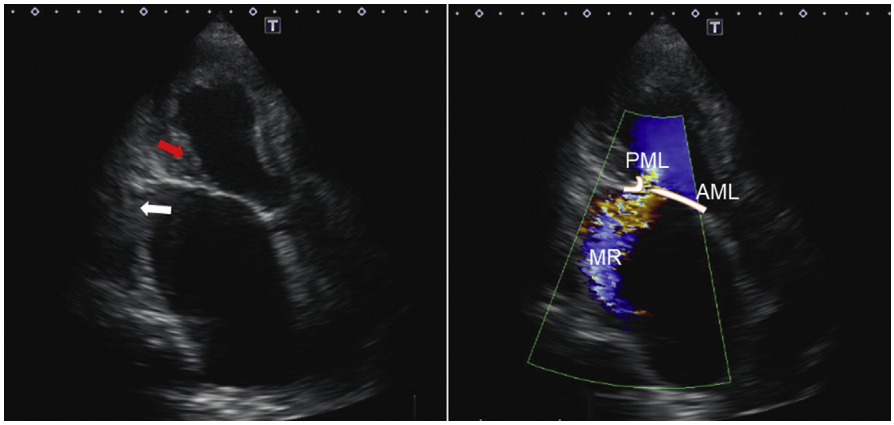

Fig. 4. Atrial functional mitral regurgitation (MR) with a flattened AML with pseudoprolapse, a tethered PML with the hamstringing phenomenon, and an eccentric MR jet (Carpentier I for AML and IIIb for PML). The left atrium (LA) dilates posteriorly (*white arrow*), and the posterior mitral annulus is displaced backward to the LA side from the crest of the posterior LV. This backward LA enlargement causes inner bending of the basal posterior left ventricle (*red arrow*).

failure, including diuretics (Class I but evidence level C);

- Atrial fibrillation catheter ablation is reasonable for symptomatic patients with persistent atrial fibrillation and severe AFMR, if successful ablation and maintenance of sinus rhythm can be expected from the duration of atrial fibrillation and the LA size (class IIa but evidence level C); and
- Mitral valve surgery is reasonable for patients with severe AFMR who are consistently symptomatic, despite standard medical therapy for heart failure (class IIa but evidence level C), and can also be applied to patients with chronic moderate AFMR if the MR is severe upon worsening of the heart failure or during exercise stress tests.

Appropriate interventions for AFMR and AFTR may differ depending on the degree of atrial remodeling. However, an appropriate cut-off value for atrial size or some other parameter for selecting catheter ablation or surgery remains undetermined. The recommendation regarding atrial fibrillation catheter ablation is based on an article showing that maintaining a sinus rhythm with catheter ablation of the pulmonary veins can decrease the MR burden and decrease the LA volume and MA size in patients with both atrial fibrillation and AFMR.[9] The recommendation regarding mitral

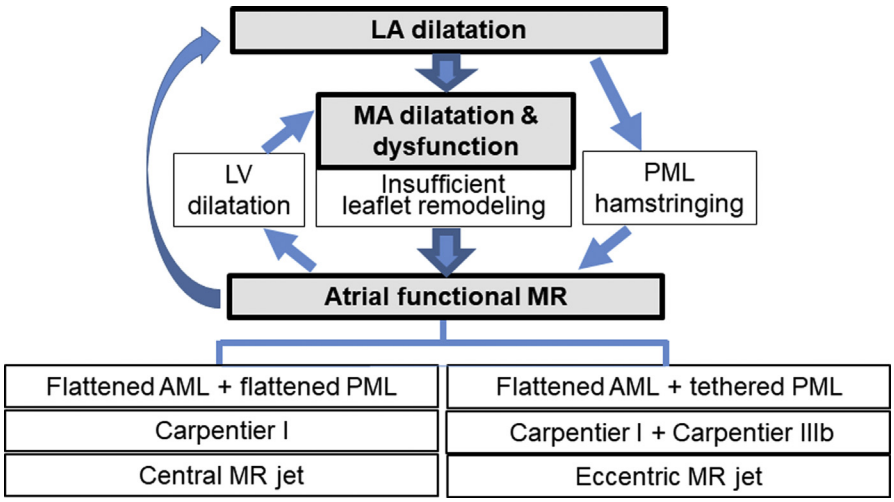

Fig. 5. Mechanisms and 2 types of atrial functional mitral regurgitation (MR).

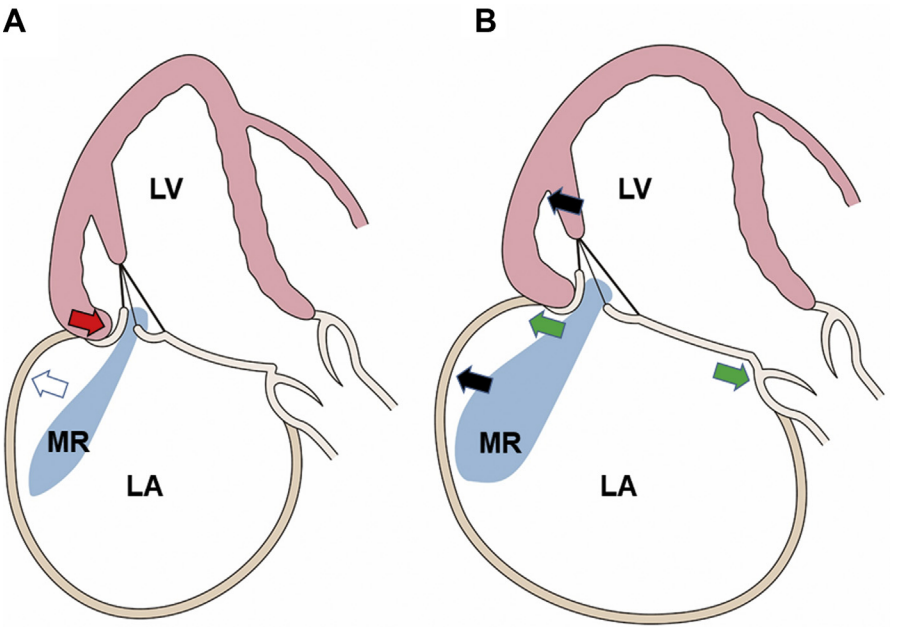

Fig. 6. Genesis and worsening of atrial functional mitral regurgitation (AFMR). (*A*) The left atrial (LA) posterior wall extends behind the posterior mitral annulus (MA) with LA dilatation (*white arrow*). The backward LA enlargement leads to an inward bending of the basal posterior left ventricle (LV) (*red arrow*). The posterior mitral annulus is displaced backward, whereas the tip of the PML is tethered toward the posterior LV. As a result, the PML curves and loses its functional mobility and coaptation with the AML (hamstringing). The result is generation of MR. This PML tethering is observed in a proportion, but not all, of the patients with AFMR and is likely to cause an eccentric jet directed toward the posterior LA wall. (*B*) Secondary LA and LV dilatations (*black arrows*), which may be induced by the MR, lead to further MA dilatation (*green arrows*) and worsening of the MR. (*From* Akamatsu K, Abe Y, Matsumura Y, et al. Etiology of atrial functional mitral regurgitation: insights from transthoracic echocardiography in 159 consecutive patients with atrial fibrillation and preserved left ventricular ejection fraction. Cardiology 2020;145:511–21; with permission.)

valve surgery is based on articles suggesting that surgical mitral valve repair may be useful in addressing AFMR and the coexisting heart failure.[10,33,34]

AFMR is likely to accompany secondary AFTR owing to right atrial dilatation. Consequently, patients with both AFMR and AFTR will require concomitant tricuspid valve repair when they undergo mitral valve repair. A valve replacement may also be a better option for the treatment of AFMR and AFTR in patients with excessive atrial dilatations. Bilateral atrioventricular valve annuloplasty alone may not be beneficial in patients who have AFMR and AFTR with apparent giant LA and RA. Atrial plication should be considered as a concomitant procedure on a patient-by-patient basis. A need for a Maze procedure should also be considered on a patient-by-patient basis. By contrast, surgery in elderly patients with AFMR and a high surgical risk is challenging. Various semi-invasive catheter device therapies may be good options for the treatment of elderly high-risk patients with AFMR.[35]

SUMMARY

AFMR can occur in atrial fibrillation patients despite a preserved LV systolic function. Our belief is that the MA dilatation owing to atrial fibrillation-induced LA dilatation is necessary for the generation of AFMR. Insufficient leaflet remodeling leads to the development of AFMR. Hamstringing of the PML also relates to the occurrence of AFMR. Further MA dilatation owing to progressive dilatations of both LA and LV with MR-induced volume overload worsens the AFMR. However, AFMR is not a homogenous disease; it can be classified into 2 types: one has the flattened AML, a flattened PML, and a central jet (Carpentier I), and the other has the flattened AML with a pseudoprolapse, a tethered PML with the hamstringing phenomenon, and an eccentric jet (Carpentier I for AML and IIIb for PML). AFMR seems to have been present in the past, but is a new disease entity that has recently become highlighted. Appropriate diagnosis and treatments need to be established.

CLINICS CARE POINTS

- Atrial functional mitral regurgitation (AFMR) can occur as a consequence of left atrial dilation in patients with atrial fibrillation.
- AFMR can be a cause of heart failure.
- AFMR can be a target of invasive therapies.

DISCLOSURE

Y. Abe, Y. Takahashi, and T. Shibata declare that they have no conflicts of interest.

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