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REVIEW ARTICLE

# Functional mitral regurgitation, updated: ventricular or atrial?

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**Abstract**
Lone atrial fibrillation (AF) can cause functional mitral regurgitation (MR), commonly referred to as "atrial functional MR (AFMR)." This type of MR has recently received much attention as an important cause of heart failure, and it represents a considerable therapeutic target in heart failure patients with AF. Mitral annular dilatation due to left atrial (LA) dilatation can be recognized as an original cause of AFMR, whereas the exact cascade of AFMR etiologies has not been established. AFMR is typically classified as Carpentier type I, and is likely to have a central jet. In contrast, a proportion of AFMR is classified as a combination of Carpentier type I for a flattened anterior mitral leaflet and Carpentier type IIIb for a tethered posterior mitral leaflet and is likely to have an eccentric jet directed toward the LA posterior wall. The traditional functional MR occurring in patients with left ventricular (LV) dilatation and/or systolic dysfunction, which is classified as Carpentier type IIIb, has since been designated "ventricular functional MR (VFMR)" to distinguish it from AFMR. Traditional VFMR, newly recognized AFMR, and their etiologic relations to LV/LA size and function are discussed in this review article.

**Keywords** Atrial fibrillation · Atrial functional mitral regurgitation · Echocardiography · Valvular heart disease · Ventricular functional mitral regurgitation

## Introduction

The incidence of atrial fibrillation (AF) increases with age [1–3], and heart failure is the most important cause of mortality in elderly patients with AF. In fact, cardiac death is more frequent than stroke-related death in patients with AF, and a substantial proportion of the cardiac death results from heart failure, especially in the present era of well-developed anticoagulation therapies [4–6]. Consequently, interventions beyond anticoagulation are needed for further reductions in mortality in patients with AF.

AF and heart failure are part of a vicious cycle. AF can develop after heart failure, but it can also predate heart failure with a reduced left ventricular ejection fraction (LVEF) or heart failure with a preserved LVEF [7–9]. Functional mitral regurgitation (MR) has recently been recognized to occur as a result of left atrial (LA) dilatation secondary to AF, despite preservation of LVEF [10–17]. This can be termed "atrial functional MR (AFMR)" as "another functional MR," a condition that has recently received much attention as an important cause of heart failure and that represents a considerable therapeutic target in heart failure patients with persistent AF and preserved LVEF [11, 12, 14, 16, 17]. The traditional functional MR occurring in patients with LV dilatation and/or systolic dysfunction has since been designated "ventricular functional MR (VFMR)" to distinguish it from AFMR [17].

## VFMR

Secondary MR (i.e., functional MR) generally results from papillary muscle displacement and the accompanying mitral leaflet tethering–tenting due to LV systolic dysfunction and remodeling in patients with ischemic heart disease or dilated cardiomyopathy [18–20]. Otsuji et al. [21] demonstrated that isolated mitral annular (MA) dilatation due to LA dilatation does not often cause significant functional MR in patients with lone AF. They analyzed their entire population, including both patients with ischemic cardiomyopathy and those

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with lone AF and preserved LV systolic function, and they concluded that the mitral leaflet tethering and tenting occurring due to LV dilatation and systolic dysfunction are the main determinant of functional MR (Fig. 1). VFMR with mitral leaflet tethering–tenting has since been considered equivalent to functional MR and is classified as Carpentier type IIIb. However, these earlier results did not refute the association between MA dilatation and functional MR. Instead, the findings suggested that the association between MA dilatation and functional MR severity was similar to the association between mitral leaflet tethering and functional MR severity when the analysis was restricted only to patients with ischemic cardiomyopathy.

Park et al. [22] reported the ironic finding that VFMR severity is not determined by the LV size but by the LA, which is closely related to the end-systolic MA area. They studied only patients with advanced heart failure with LV dilatation and LV systolic dysfunction, and they demonstrated that both mitral tethering and tenting and MA dilatation are strongly associated with the degree of VFMR. The results of these previous studies [21, 22] support the hypothesis that mitral tethering and tenting due to LV dysfunction (i.e., longitudinal deformation of mitral valve structure) are primarily necessary for functional MR generation but are not sufficient for it. The addition of MA dilatation due to LA dilatation (i.e., transverse deformation of the mitral valve structure) may be secondarily required for the generation and worsening of functional MR. Our results from a previous examination of the changes in functional MR and mitral morphology by preload alterations are consistent with these hypotheses [23]. Our findings showed that mitral tenting was the strongest determinant of resting VFMR, whereas the changes in VFMR by preload alterations were affected more by changes in the systolic MA area than by changes in mitral tenting. We also found that the increase in preload induced MA dilatation, which was determined more strongly by LA dilatation than by LV dilatation. These results suggest that the grading of resting VFMR is determined by the longitudinal deformation of the mitral geometry, whereas the changes in FMR by preload alterations depend on the transverse deformation of the mitral geometry. The addition of LA and MA dilatation to prerequisite tethering–tenting due to LV dilatation and systolic dysfunction is a more comprehensive etiologic explanation for traditional VFMR.

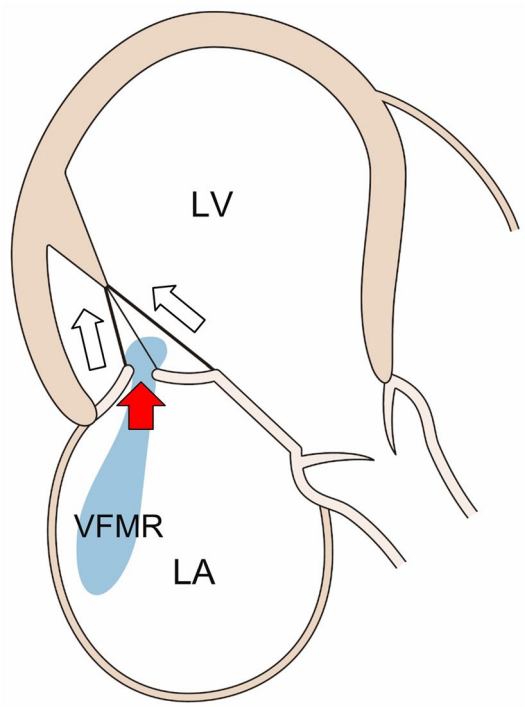


**Fig. 1** Mechanism of ventricular functional mitral regurgitation (VFMR). Mitral leaflet tethering (white arrow) and tenting (red arrow) due to left ventricular (LV) dilatation and systolic dysfunction causes VFMR. *LA* left atrium

Another of our previous studies showed that the changes in ischemic VFMR induced by intravenous administration of dobutamine were determined by the changes in mitral tethering and tenting [24]. Changes in VFMR with preload alterations are due to transverse MA area changes resulting from changes in the LA volume, whereas changes in VFMR with inotropic effects are due to the longitudinal changes of the mitral apparatus (i.e., the improvement in mitral leaflet tethering–tenting) resulting from enhanced LV contractility. These insights could help to clarify the mechanisms underlying the bidirectional changes in VFMR with the worsening or improvement of heart failure.

## AFMR: definition

One long-held belief is that lone AF sometimes causes significant functional tricuspid regurgitation (TR) but does not usually cause significant functional MR [21, 25]. In contrast, a number of studies have shown that functional MR occasionally occurs in patients with AF and an enlarged LA, despite having a preserved LV systolic function [10–17]. This MR has recently been designated as AFMR. In general, AFMR can be defined as MR with: (1) LA dilatation mainly seen in patients with AF; (2) no significant degenerative change in mitral valve complex; and (3) no significant LV systolic dysfunction or dilatation. However, no cut-off values for LVEF and LV size have yet been determined to define AFMR. Most previous studies that have examined AFMR have expediently used 50% as the cut-off value for LVEF, and some of them have also used the cut-off value of the LV diastolic diameter or volume using some references that established the normal values [12, 26, 27]. In the real-world clinical settings, however, patients with AFMR can also have mildly dilated LV or mildly

reduced LVEF due to volume overload resulting from chronic MR, especially in the advanced stage. Therefore, patients with mild LV dilatation or 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 [28]. Patients with sinus rhythm can also have AFMR due to LA dilatation resulting from LV diastolic dysfunction rather than from AF, whereas the prevalence of significant AFMR in patients with sinus rhythm may be rare.

## AFMR: prevalence and prognosis

Some recent studies have begun to provide missing details on the prevalence and prognosis of patients with both AF and significant AFMR [14, 16, 17, 28]. We recently found that the prevalence of significant AFMR was 8.1% in patients with lone AF who underwent transthoracic echocardiography and 28% in patients with longstanding, persistent AF (duration > 10 years) [14]. The patients with AFMR had a significantly higher prevalence of adverse events. The event-free rate for cardiac death or hospitalization for worsening heart failure was not high (53%) even at a mean follow-up of only 24 months in patients with significant AFMR. Patients with significant AFMR in conjunction with secondary TR had the poorest prognosis, with an event-free rate of 27% at 24 months. This combination of TR due to right atrial dilatation and tricuspid annular dilatation is also referred to as atrial functional TR (AFTR). The combination of AFMR and AFTR should receive more therapeutic attention as a "dual valve disease." Some other articles have reported that patients with AF who were hospitalized due to heart failure experienced significant AFMR more frequently (37–44%), even at discharge after medical therapies, and their AFMR was associated with readmission due to heart failure during the post-discharge follow-up [16, 17].

The Mayo Clinic group has recently reported that 32%, 38%, and 27% of the 727 Olmsted County residents with a first diagnosis of isolated moderate or severe MR (determined by clinically indicated echocardiography) had organic MR, VFMR, and AFMR, respectively [28]. 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. The appropriate treatment of AFMR will, therefore, become more important to prevent cardiac death and heart failure in patients with AF in our aging societies.

## AFMR: etiology

Gertz et al. [11] reported that functional MR could occur as a result of LA and MA dilatation in patients with AF, and they initially referred to this as AFMR. Another early study using 3DTEE also reported that LA dilation led to MA enlargement and reduced leaflet coaptation, thereby resulting in MR even without LV systolic dysfunction [29]. At present, LA dilatation and MA dilatation are both recognized as common etiologies of AFMR.

Other factors have also been reported as the etiologies of AFMR [10, 11, 13, 26, 27, 30–34] (Table 1). These include disruption of the MA saddle shape [26, 32–34], reduction in MA contractility [26, 31, 34], inadequate compensation for the MA dilatation resulting from the lack of leaflet remodeling [27, 32, 33], and tethering of the atriogenic posterior mitral leaflet (PML) [13, 26]. However, the main determinant and the relationship among the various etiologies still need to be established.

An experimental histopathological study and a clinical study have both confirmed that mitral leaflets expand to fully occlude systolic MA in patients with VFMR [35, 36]. This phenomenon represents "leaflet remodeling," and patients with significant VFMR have a smaller mitral leaflet–closure leaflet area ratio that represents "insufficient leaflet remodeling." The same findings have also been reported in 3DTEE studies as an important etiology of AFMR without LV dysfunction [27, 33].

Our previous study, which also used 3DTEE, showed that the anterior mitral leaflet (AML) was flattened along the MA plane and that the PML was bent toward the LV cavity at mid-systole in patients with significant AFMR [13]. In fact, the PML bending seen in our patients with AFMR is consistent with a traditional concept that used to be observed in patients with giant LA caused by advanced rheumatic mitral valve disease. In those patients, the posterior wall of the LA extends behind the basal posterior wall of the LV, while the posterior MA is displaced backward to the LA side from the crest of the posterior LV. This backward LA enlargement causes an inward bending of the basal posterior LV, and the tip of the PML becomes tethered to the posterior LV by the papillary muscles and the chordae tendineae. The PML, therefore, curves and overlies the muscle layer of the basal posterior LV edge, thus restricting its movement. This functional restriction of the PML has traditionally been referred to as the "hamstringing of the posterior cusp" [37]. The PML hamstringing seen in current patients with AFMR can be recognized as being more purely functional [13] (Fig. 2) and is thought to be controlled by the same mechanism as the atriogenic PML tethering described in a recent study [26] and review [38]. Atriogenic tethering of the PML, in conjunction with annular dilatation, can result in a further reduction of leaflet coaptation and thereby worsen MR. Consequently, AFMR with the PML hamstring is classified as a combination of Carpentier type I for AML and type IIIb for PML. This concept should be one of the important or typical etiologies of AFMR. However, the prevalence of atriogenic tethering or the hamstring phenomenon of the PML in

**Table 1** Determinants of AFMR in patients with AF

| First author | Publication year | Objective variable | LV dilatation | LA dilatation | MA dilatation | Flattened MA saddle shape | Reduced MA contractility | Lack of leaflet remodeling | PML tethering or hamstringing | Other factors with I |
|---|---|---|---|---|---|---|---|---|---|---|
| Kihara et al. [10] | 2009 | MR ≥ moderate | III | II | II | NA | NA | NA | NA | NA |
| Gertz et al. [11] | 2011 | MR ≥ moderate | III | II | I | NA | NA | NA | NA | Age, persistent AF |
| van Rosendael et al. [30] | 2014 | MR ≥ mild | II (LVESVI) | I | I | NA | NA | NA | NA | Age |
| Itabashi et al. [31] | 2016 | MR ≥ moderate | III | NA | II | III | I | NA | NA | Bending ratio (non-coapted rough zone length/non-coapted AML length) |
| Machino-Ohtsuka et al. [26] | 2016 | EROA of MR | III | I | I | I | I | NA | I | NA |
| Kagiyama et al. [27] | 2017 | MR ≥ moderate | III | II | II | NA | NA | I | NA | NA |
| Ito et al. [13] | 2017 | MR ≥ moderate | II (LVDd, LVDs) | II | II | III | NA | NA | II | NA |
| Cong et al. [32] | 2018 | MR ≥ moderate | III | II | I | I | NA | II | NA | NA |
| Kim et al. [33] | 2019 | MR ≥ moderate | III | II | I | II | NA | II | NA | NA |
| Tang et al. [34] | 2019 | MR ≥ moderate | III | III | II | I | I | NA | NA | Not LA strain (II) but LVGLS (I) when MA parameters were excluded |

I—confirmed by a multivariate analysis, II—confirmed only by a univariate analysis or a simple comparison, III—confirmed as not significant

*AF* atrial fibrillation, *AFMR* atrial functional mitral regurgitation, *AML* anterior mitral leaflet, *EROA* effective regurgitant orifice area, *LA* left atrial, *LV* left ventricular, *LVDd* left ventricular diastolic dimension, *LVDs* left ventricular systolic dimension, *LVESVI* left ventricular end-systolic volume index, *MA* mitral annular, *MR* mitral regurgitation, *PML* posterior mitral leaflet, *NA* not applicable

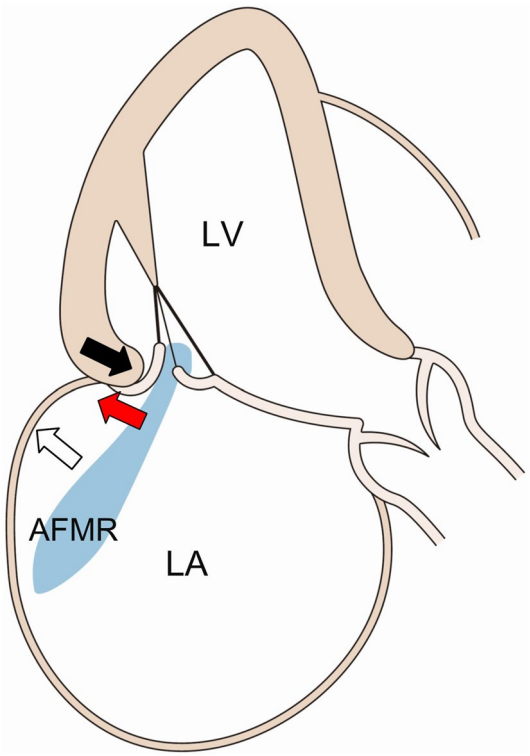


**Fig. 2** Mechanism of a proportion of atrial functional mitral regurgitation (AFMR). The left atrial (LA) posterior wall extends behind the posterior mitral annulus when LA dilatation (white arrow) due to atrial fibrillation exceeds mitral annular dilatation (red arrow). The backward LA enlargement leads to the inward bending of the basal posterior left ventricle (LV) (black arrow). The posterior mitral annulus is displaced backward to the LA side from the crest of the posterior LV. In contrast, the tip of the posterior mitral leaflet (PML) is tethered toward the posterior LV by the papillary muscles and the chordae tendineae. As a result, the PML curves and functionally loses its mobility and coaptation with the anterior mitral leaflet (hamstringing of the PML). This PML tethering is observed in a proportion of, but not all, the patients with AFMR, and is likely to cause an eccentric jet directed toward the posterior LA wall

patients with AFMR is unknown. The determinant factors of this phenomenon are also not fully elucidated. Future studies will need to clarify these issues.

A recent review article suggested that PML tethering may be a relatively rare subtype of the AFMR etiologies and may be more frequently observed in patients with extremely advanced LA remodeling [39]. In fact, the studies that reported atriogenic tethering or hamstringing of the PML as the main mechanism of AFMR also noted that the LA volume index was notably larger than reported in other studies (the mean values of 95–128 ml/m$^2$) [13, 26]. AFMR without the hamstringing phenomenon, which is classified as pure Carpentier type I, is likely to have a central jet (Fig. 3) [40]. In contrast, AFMR with the hamstringing phenomenon of PML, which is classified as a combination of Carpentier type I for AML and type IIIb for PML, is likely to have an eccentric jet directed toward the posterior LA wall (Fig. 4) [40]. 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 an override.

## AFMR: treatment

Current guidelines do not address the treatment of AFMR [41, 42]. In general, medical therapies for heart failure should be mandatory before considering an intervention for AFMR. Maintaining sinus rhythm with catheter ablation of pulmonary veins can decrease the MR burden and reduce the LA volume and annular size in patients with both AF and AFMR [11]. Surgical experience with mitral ring annuloplasty in patients with severe AFMR is still limited at this time [10, 12, 43–45]. However, several small series have shown a reduction in MR grade and a decreased LA size at mid-term follow-up [43, 45]. In patients with marked atriogenic leaflet tethering and a small PML, leaflet augmentation can serve as a useful adjunct to ring annuloplasty [46].

AFMR is likely to accompany secondary AFTR due to right atrial dilatation. Patients with both AFMR and AFTR, therefore, require concomitant tricuspid annuloplasty when they undergo mitral annuloplasty. However, excessive atrial remodeling may defeat the beneficial effects of mitral valve and tricuspid valve repair in patients with AFMR and AFTR. Takahashi et al. [45] performed mitral valve and tricuspid valve repair in 45 patients with AFMR, AFTR, and a large LA with the mean LA volume index of 108 ml/m$^2$. In their series, both the preoperative LA volume index $\geq$ 142 ml/m$^2$ and the preoperative TR grading were associated with postoperative cardiovascular events. Appropriate interventions for AFMR and AFTR may differ by the degree of atrial remodeling. A Maze procedure or LA plication should be considered as concomitant procedures in a patient-by-patient evaluation. In contrast, surgery in elderly patients with AFMR and a high surgical risk is challenging. Various less-invasive catheter-device therapies may be good options for the treatment of elderly high-risk patients with AFMR in the near future [47].

## Conclusions

The concept of AFMR substantially differs from that of traditional VFMR. The original cause of atrial functional MR should be clearly distinguished from that of VFMR. These causes would be atrial dilatation in patients with AF for "atrial" functional MR and LV dysfunction and/or dilatation in ischemic heart disease or dilated cardiomyopathy

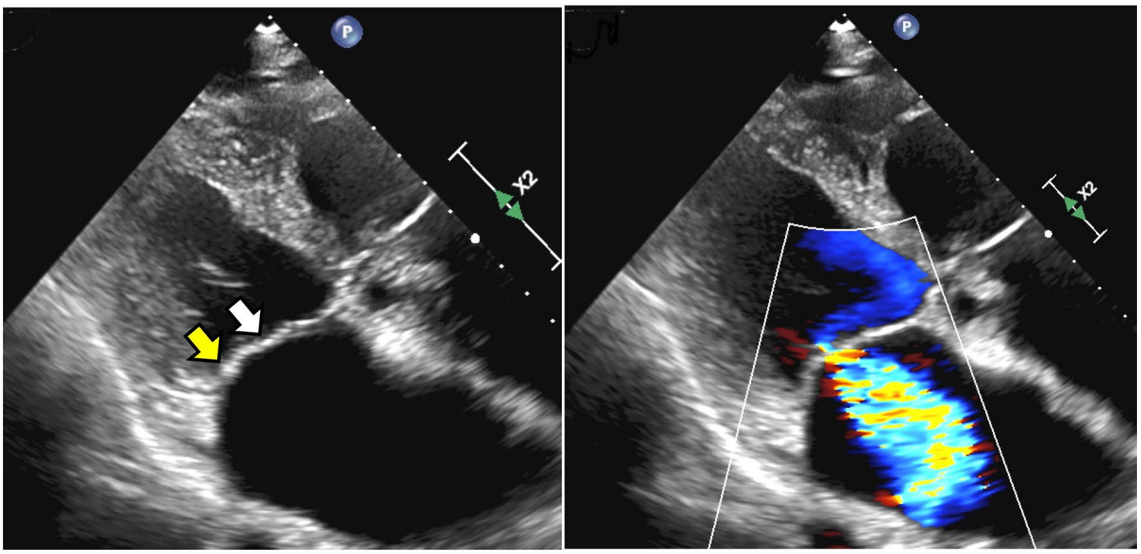

**Fig. 3** Atrial functional mitral regurgitation with a central jet classified as Carpentier type I. Both an anterior mitral leaflet (white arrow) and a posterior mitral leaflet (yellow arrow) are flattened along the mitral annular plane

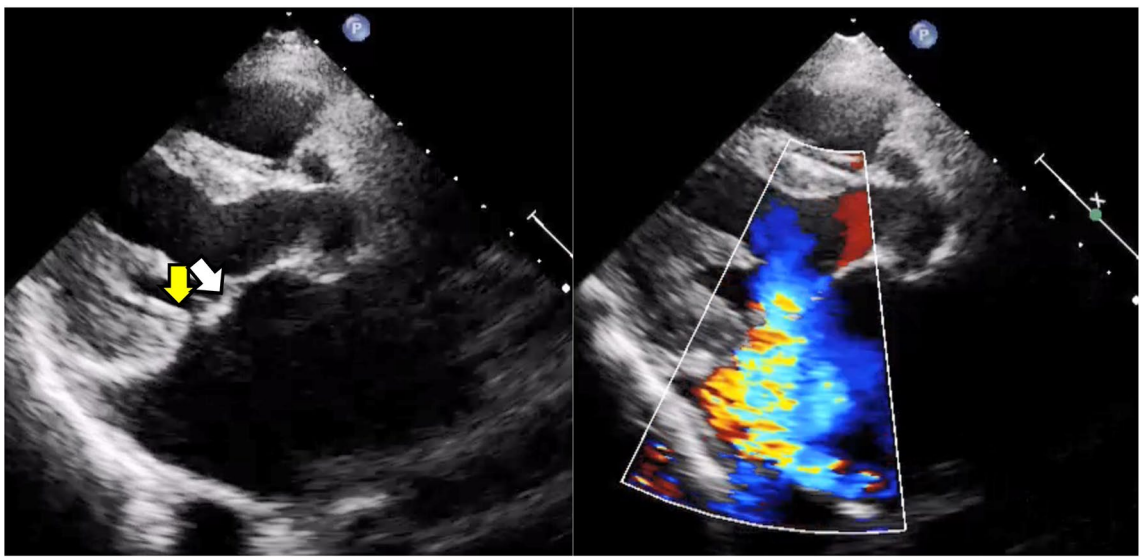

**Fig. 4** Atrial functional mitral regurgitation with an eccentric jet classified as Carpentier type I for a flattened anterior mitral leaflet (white arrow) and type IIIb for hamstringing of a tethered posterior mitral leaflet (yellow arrow)

for traditional "ventricular" functional MR. However, a relationship also exists between LV dilatation and the worsening of AFMR [13, 30], as well as between LA dilatation and the worsening of VFMR [22, 23]. Both LV dilatation and LA dilatation ultimately are related to worsening in both types of functional MR, despite their different original causes (Fig. 5). Our belief is that the MA dilatation due to AF-induced LA dilatation is primarily necessary for the generation of AFMR and that further MA dilatation and the PML hamstringing, due to progressive dilatations of both LA and LV with MR-induced volume overload, deteriorate AFMR.

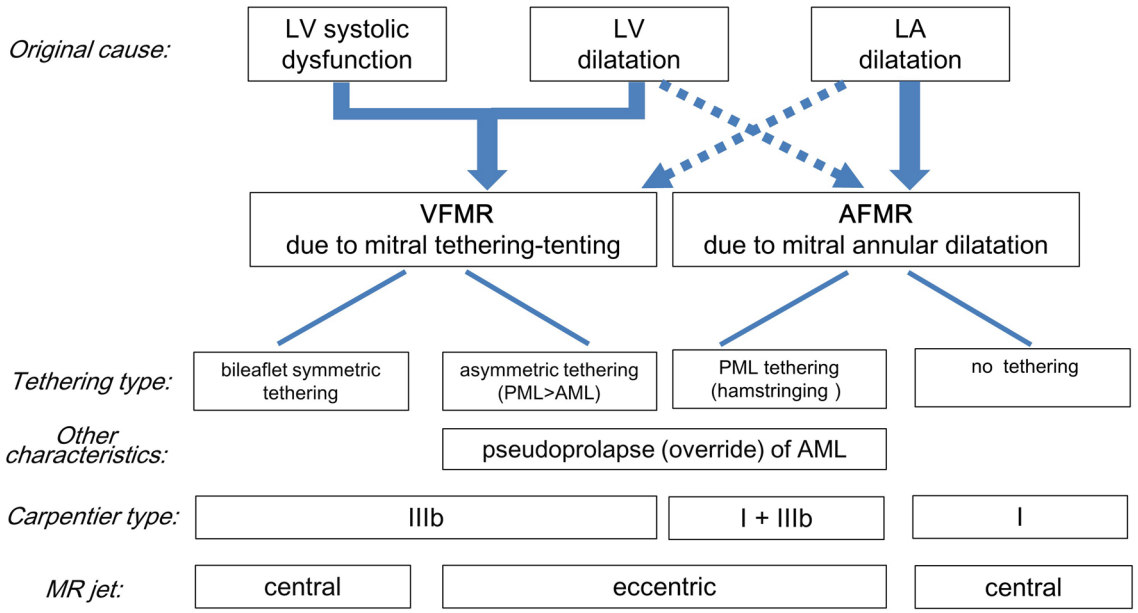


**Fig. 5** Relationships among ventricular functional mitral regurgitation (VFMR), atrial functional mitral regurgitation (AFMR), and left ventricular (LV) or left atrial (LA) dilatation. Both LV dilatation and LA dilatation are also related to both VFMR and AFMR with different original causes. *AML* anterior mitral leaflet, *PML* posterior mitral leaflet

## Compliance with ethical standards

**Conflict of interest** Yukio Abe, Yosuke Takahashi, and Toshihiko Shibata declare that they have no conflicts of interest.

**Ethical approval** All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions.

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