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Atrial Functional Mitral Regurgitation: Definition, Mechanisms, and Treatment

Perspectives Sebastiaan Dhont [1,2], Sébastien Deferm [1,2], Philippe B. Bertrand [1,2], Pieter M. Vandervoort [1,2]

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Abstract

Purpose of review: This review aims to explore the complex interplay between atrial functional mitral regurgitation (AFMR), atrial fibrillation (AF), and heart failure with preserved ejection fraction (HFpEF). The goal is to define these conditions, examine their underlying mechanisms, and discuss treatment perspectives, particularly addressing diagnostic challenges.

Recent findings: Recent research highlights the rising prevalence of AFMR, now accounting for nearly one-third of significant mitral regurgitation cases. Advances in percutaneous treatment options have improved management for vulnerable HFpEF patients, but long-term outcomes remain unclear, and symptom relief is inconsistent.

Summary: AF and HFpEF share the left atrium as a common pathological substrate, with progressive LA dysfunction contributing to AFMR. Diagnostic limitations hinder effective symptom management with current mitral valve interventions. Future research should focus on better diagnostic tools to determine the contributions of valve disease, arrhythmia, or myocardial dysfunction to clinical outcomes, as we currently lack definitive tests to establish this connection.

Keywords: Atrial functional mitral regurgitation, heart failure with preserved ejection fraction, left atrial myopathy, atrial fibrillation.

Introduction

Nearly 1 in 3 cases of clinically significant mitral regurgitation (MR) between 2000 and 2010 are attributed to atrial functional MR (AFMR).[1] This proportion continues to rise due to the epidemic growth of atrial fibrillation (AF) and heart failure (HF) with preserved EF (HFpEF), the two intertwined primary underlying substrates.[2,3] In fact, HFpEF is frequently underdiagnosed in patients with AF.[3] Notably, AF alone accounts for 3 out of 9 points on the H_2FPEF score, indicating at least an intermediate probability of HFpEF.[4] This association between AF and HFpEF is sometimes described as the atrial-dominant subtype of HFpEF, characterized by left atrial remodeling and dysfunction.[5] The prevalence of AFMR in HFpEF registries varies between 15% and 61%.[6–10]

It is important to note that even mild to moderate AFMR is associated with high all-cause mortality and an increased risk of readmission for HF compared to patients without AFMR.[1,7,11] The increasing attention to this condition in recent years is notable, partly due to the expanding range of percutaneous intervention options available for this vulnerable, older population. Nevertheless, it remains unclear when and how to intervene in the natural progression of AFMR. This review aims to provide an overview of the interplay between AFMR, AF and HFpEF, defining these conditions and discussing their underlying mechanisms and treatment perspectives.

The Left Atrium: The Unifying Substrate

The left atrium (LA) plays a crucial role in regulating left ventricular (LV) filling by functioning as a reservoir that stores venous return during ventricular systole, acting as a passive conduit during early diastolic filling, and serving as a pump to booster LV preload.[12] It

is crucial to recognize that LA function is not solely determined by LA stiffness, relaxation rate, and systolic shortening, but is also significantly influenced by LV function.[13] The piston effect during ventricular contraction pulls the atrioventricular plane downward, playing a key role in the atrial reservoir function.

One of the main reasons why LA function strongly correlates with outcomes in HFpEF (and AF) is its comprehensive nature, as it reflects both diastolic and systolic function of the LA and LV. However, this complexity also makes it challenging to distinguish specific contributing factors. Additionally, triggers for impaired LA function are numerous, including elevated filling pressures, arrythmias (and related ablations), obesity, inflammation, and/or concomitant infiltrative diseases such as amyloidosis. Biopsies, for example, to assess the degree of fibrosis or the composition of the (extra)cellular matrix, could be valuable for further differentiation and investigation.

Thus, although the LA appears to be the common scientific link between HFpEF, AFMR, AF, and related comorbidities, its precise role in daily clinical practice remains unclear. In a cohort study, the prognostic significance of mild to moderate AFMR diminished after adjusting for impaired LA function, which correlates more strongly as an independent predictor.[5] Additionally, both HFpEF and AF frequently result in biatrial enlargement, often accompanied by tricuspid regurgitation, which adds complexity to diagnosis and treatment.

AFMR: Towards a Clearer Definition

There is no widely accepted definition for LA myopathy, and HFpEF also has various definitions, making the diagnosis of this multifaceted condition challenging in certain cases. This lack of clear definitions complicates the identification and classification of AFMR. In

general, definitions are often shaped by the results of positive randomized clinical trials, such as the COAPT criteria for functional MR in HF with reduced ejection fraction (HFrEF). However, similar studies are still lacking in the HFpEF population. Since echocardiography is the first-line assessment tool, a definition based on this modality would likely be widely applicable. A proposed definition of AFMR is illustrated in *Figure 1*, based on three key factors: (1) normal LV cavity size and function, (2) LA enlargement, and (3) mitral annular dilatation with a flattened coaptation line.[14] Furthermore, the absence of primary mitral valve disease is crucial, and note that AF is not a required criterion for the diagnosis of AFMR.

Further assessment of the severity of mitral valve disease relies on a multiparametric approach, as detailed extensively elsewhere.[15,16] Specifically, for AFMR, the proximal isovelocity surface area (PISA) method appears feasible due to the central jet, but it is complicated by the typically biphasic occurrence (predominant in early and late systole), variations due to AF and the elliptical orifice (rather than circular, as assumed in the PISA formula). Moreover, the MR severity can be highly dynamic: moderate or severe AFMR can improve significantly after rhythm control for AF or effective decongestion in decompensated HFpEF. Moreover, approximately one-third of AFMR cases intensify during handgrip exercise testing, yet the prognostic and therapeutic implications of this phenomenon are unclear and warrant further investigation.[22] Of note, the current assessment of MR severity mainly focuses on the amount of regurgitant volume, but incorporating patient impact could enhance the severity assessment.[17] A relatively small regurgitant volume can cause significant pressure swings in a stiff LA. Lastly, the role of stress testing, advanced cardiac imaging, and invasive diagnostics is important, but these

methods are not widely available. Their exact place and added value in the diagnostic process have yet to be determined.

Decoding the Mechanism

Functional MR is caused by an imbalance between leaflet tethering and closure forces, resulting in inadequate coaptation, despite the mitral valve itself being structurally normal.[2,14] AFMR occurs almost exclusively in the setting of AF and/or HFpEF, and most often as a combination of both. The central pathophysiological mechanism involves annular dilatation, despite relatively normal LV geometry and function. Of note, evolution towards severe LV dysfunction is rare in AFMR.[18] Due to annular dilatation, the mitral leaflets lose their concavity towards the LV, becoming stretched so that the coaptation plane shifts more towards the LA (annular plane). This typically occurs symmetrically, resulting in a central jet across the entire coaptation line. Not everyone with the same degree of annular dilatation develops the same severity of MR. It is important to note that the leaflets can adaptively grow. Therefore, more critical than the annular dilatation itself is the leaflet-to-annular ratio.[19] As part of this adaptive growth, the leaflets are often slightly thicker due to valve fibrosis and (extra)cellular transformation.[19]

In addition to annular dilation, there is also impaired annular function. This is especially evident in patients with AF, where blunted presystolic narrowing contributes to AFMR.[20] Additionally, elevated LA pressures and microvascular dysfunction may play a role by reducing closure forces, though this requires further investigation. Over time, all these factors can synergize, making AFMR a progressive condition *(Figure 2)*.

In extreme cases of atrial dilation, the posterior leaflet can be pulled towards the posterobasal LV, resulting in asymmetric coaptation. This mechanism differs from that seen in HFrEF. In AFMR, the LA can become so dilated that the posterior leaflet is drawn over the posterior mitral annulus, increasing the annulo-papillary distance and leading to tethering – a phenomenon referred to as 'atriogenic leaflet tethering'.[21] This is a rare occurrence.

Evolving Treatment Perspectives

Current valvular and HF guidelines do not provide specific guidance on the management of AFMR. Specific studies focused on AFMR are still lacking, but there are increasing signals from sub-analyses of both pharmacological and interventional studies that suggest the management approach may not need to differ significantly from that used for HFpEF in general. All the hypotheses mentioned below have yet to be formally tested.

Pharmacological treatment

Recently, SGLT2 inhibitors have emerged as a cornerstone in the treatment of HFpEF. The DAPA-MODA trial demonstrated a significant reduction in LA volume, independent of LV function. It can be hypothesized that this reduction in LA volume may have a beneficial impact on AFMR, both directly and indirectly, by decreasing the recurrence rate of AF. In contrast, the TOPCAT echocardiography substudy found that spironolactone was not associated with significant changes in LA structure over time. Evidence suggests that in hypertensive patients, blood pressure control with angiotensin II receptor blockers (ARBs) can reduce LA volume and improve LA function.[23] In animal models, ARBs have also been shown to modulate profibrotic changes during mitral valve leaflet remodeling. Sacubitril/valsartan appears to be even more effective than valsartan in promoting atrial

remodeling, as it has demonstrated a reduction in LA diameter and LA volume index over a 24-week period.[24,25] The ongoing PRAISE-MR trial (NCT05991284) is currently recruiting and may provide further insights.

Rhythm vs rate control

Rhythm control has been proposed as a strategy to reduce AFMR by promoting atrial and annular reverse remodeling, thereby restoring both atrial and ventricular contributions to atrial contractions. Several studies, often retrospective, have reported improvements in LA volume and function, along with a consequent decrease in AFMR, following cardioversion or catheter ablation.[26] Moreover, sinus rhythm restoration allows gradual recovery of presystolic annular dynamics improving leaflet coaptation.[20] Early rhythm control is also an increasingly favored approach in the general patients with AF and in HFpEF, although the results of the AMPERE trial (Ablation Versus Medical Management of Atrial Fibrillation in HFpEF**,** NCT04282850) are still awaited.

Mitral Valve Intervention

Surgical mitral annuloplasty may be the most reliable and durable interventional treatment for AFMR, as reported in small studies.[27,28] However, the increasingly vulnerable HFpEF patient is not always a suitable candidate for surgical procedures, despite the advancements in less invasive techniques. With the emergence of percutaneous interventions, additional treatment options are now available.

After percutaneous edge-to-edge mitral valve repair, procedural success, defined as MR reduction to ≤ 2+, was achieved in a very high percentage of patients, ranging from 87% to 99.5%.[29–33] Nonetheless, our inability to consistently address symptoms highlights a

limitation not in therapeutic options, but in our diagnostic accuracy. One could hypothesize that even less severe MR might be significant in a stiff LA and addressing it could potentially benefit long-term remodeling. On the other hand, in cases of severe MR associated with an underlying restrictive cardiomyopathy, an intervention may have little impact on filling pressures.[34] The "sweet spot" in managing this pathology has yet to be identified, and only randomized interventional studies, similar to those conducted for functional (ventricular) MR in HFrEF, can provide clear answers. Regardless, it is essential to first maximize non-pharmacological approaches, especially given the dynamic nature of the condition over time, as illustrated in *Figure 3.*

Conclusion

The prevalence of AFMR is rapidly increasing, driven by heightened awareness and the epidemic growth of both HFpEF and AF. The LA serves as the common link, with annular dilatation being the central mechanism for AFMR. Treatment strategies to address AFMR, including sinus rhythm restoration, percutaneous interventions, and pharmacological approaches, are still awaiting prospective outcome studies.

KEY REFERENCES

Tamargo M, Obokata M, Reddy YNV, et al. Functional mitral regurgitation and left atrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020; 22: 489–498.

Key finding: Functional MR in patients with HFpEF reflects LA myopathy, even in the absence of AF, and is associated with worse outcome parameters.

Dhont S, van den Acker G, van Loon T, et al. Mitral regurgitation in heart failure with preserved ejection fraction: The interplay of valve, ventricle, and atrium. *Eur J Heart Fail*. Epub ahead of print 17 April 2024. DOI: 10.1002/ejhf.3231.

As a call to action: There is a compelling need for a more integrated diagnostic approach that considers the functional status of the ventricle, atrium, and valve.

Deferm S, Bertrand PB, Verbrugge FH, et al. Atrial Functional Mitral Regurgitation: JACC Review Topic of the Week. *J Am Coll Cardiol* 2019; 73: 2465–2476.

This review summarizes the prevalence and prognostic importance of AFMR, providing mechanistic insights compared with those of secondary MR and suggesting potential therapeutic targets.

Figures

Figure 1: Proposed Definition of AFMR

AFMR—atrial functional mitral regurgitation; GLS—global longitudinal strain; LA—left atrium; LV—Left Ventricle; LV-EF—left ventricular ejection fraction; PLAX—parasternal long-axis.

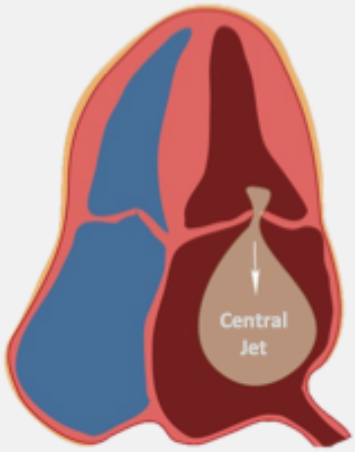
ATRIAL FUNCTIONAL MR	Left Ventricle
	LV volume ≤ 85 mL/m² male; ≤ 78 mL/m² female LV-EF ≥ 50% GLS may be impaired
	Left Atrium and Mitral Annulus
	LA ≥ 34 mL/m² Annulus > 35 mm (systole in PLAX) Annular flattening Systolic annular diameter to diastolic anterior leaflet > 1.3
	Mitral Leaflets
	Loss of systolic leaflet concavity towards the LV Leaflet coaptation at annular lever Leaflet thickening

Figure 2: Determinants of AFMR: HFpEF and AF with LA as Common Substrate

AF—atrial fibrillation; AFMR— atrial functional mitral regurgitation; HFpEF—heart failure with preserved ejection fraction; LA—left atrium; LV—left ventricle; MR—mitral regurgitation; RV—right ventricle.

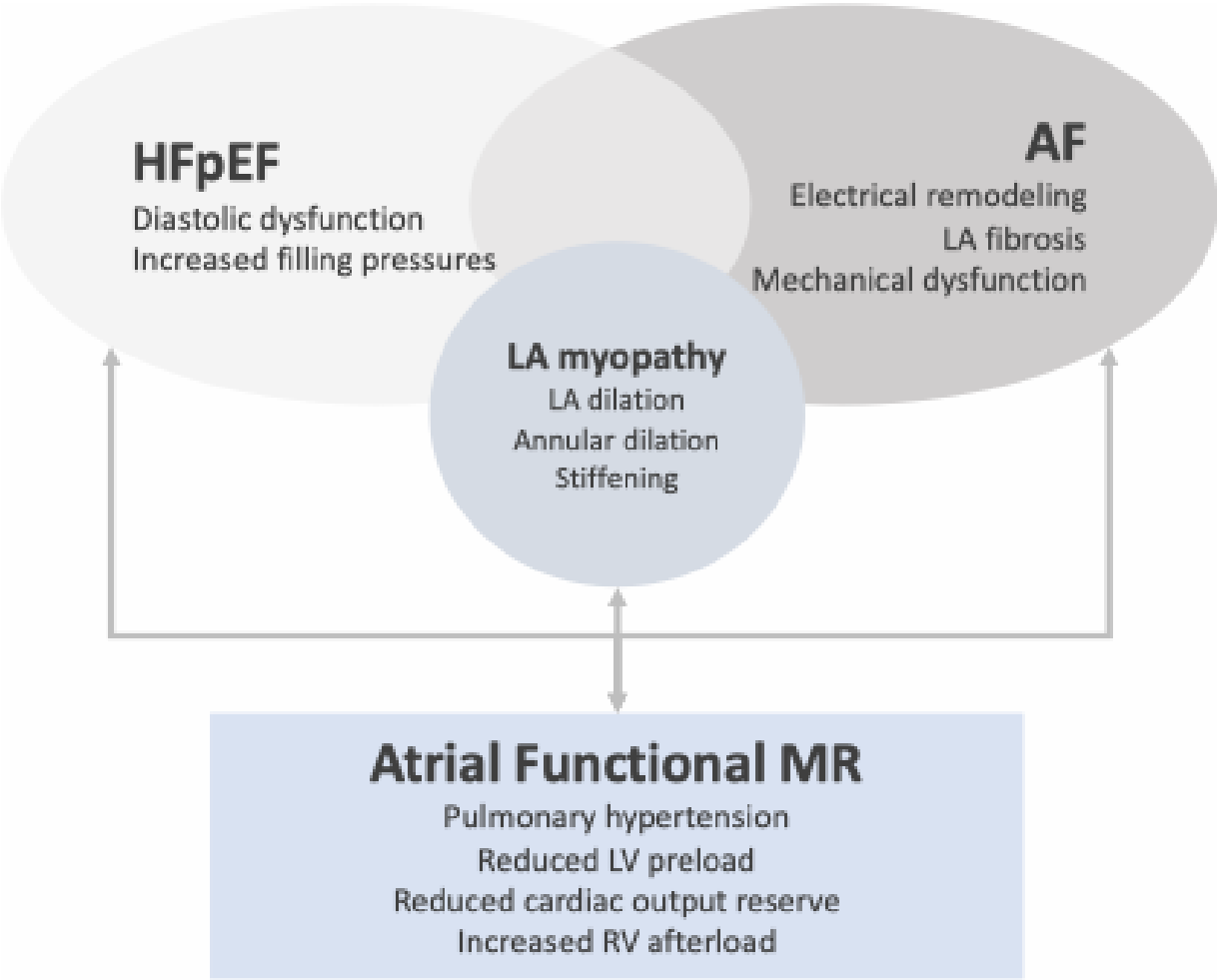
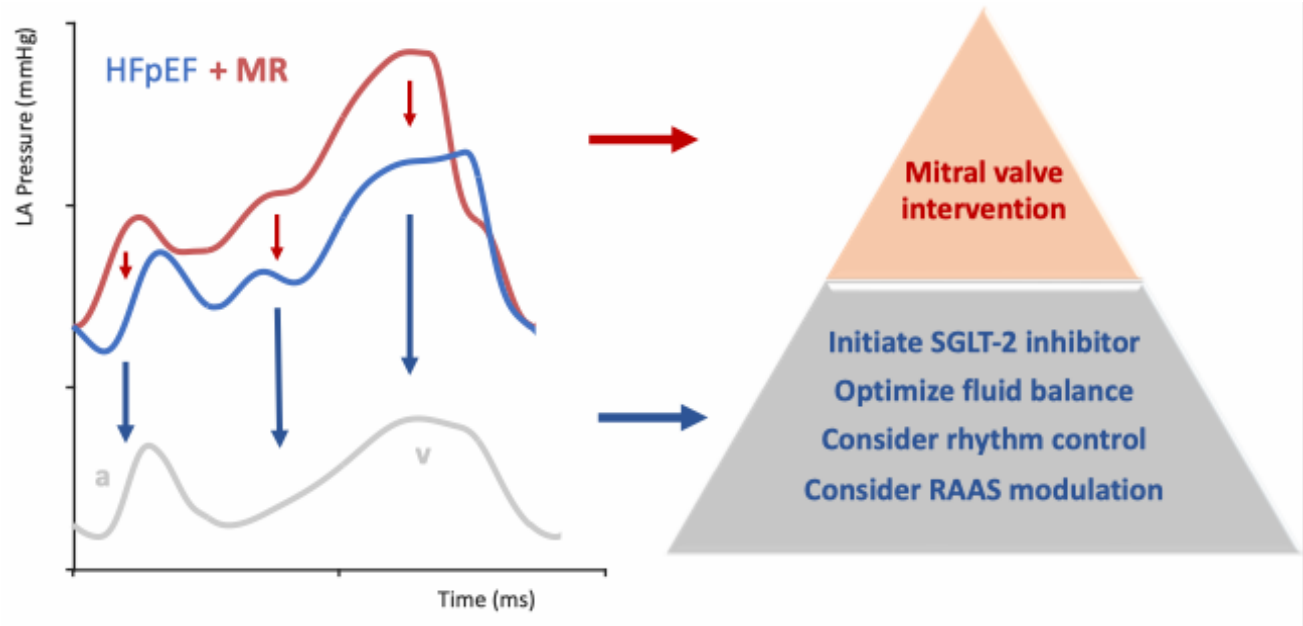


Figure 3: Proposed Treatment Strategy for AFMR with Emphasis on Initial Non-Invasive Optimization. (Adapted from: Dhont S, et al. Eur J Heart Fail. 2024 Apr;26(4):974-983; with permission from John Wiley and Sons) [34].

AFMR— atrial functional mitral regurgitation; HFpEF—heart failure with preserved ejection fraction; LA—left atrium; MR—mitral regurgitation; RAAS—renin-angiotensin-aldosterone system; SGLT-2—sodium-glucose cotransporter-2.



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