Review Article

Atrial Functional Mitral Regurgitation

Alexsander da Silva Pretto[1]
ImagemCor,[1] Tenente Portela, RS – Brazil

Abstract

Secondary mitral insufficiency (MI) in the setting of ventricular disease has always been a topic at conferences and has achieved extensive pathophysiological knowledge over the years. More recently, with the increasing incidence of atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF), a new phenotype that had been little discussed has come to light: atrial functional mitral regurgitation. In this entity, special attention should be addressed to the left atrium and the mitral annulus because, in early stages, they present normal left ventricular dimensions and function.

Introduction

Mitral Insufficiency (MI) is one of the most common valvulopathies in the world[1]. New knowledge about its physiopathology, diagnosis and treatment are arising. In this sense, Atrial Fibrillation (AF) is the disorder of the rhythm more usually observed in the general population[2]**.** The estimation is that the prevalence of MI in the USA in 2030 will be higher than 4 million cases, and FA will reach 12.1 million[3]. Data indicate that, until 2050, the population aged more than 80 years will triple[4]**.**

The "epidemic" growth of the incidence of AF, with approximately 5 million new cases per year around the world[5], and heart failure with preserved ejection fraction (HFpEF), responsible for 37 to 53% of the cases of Congestive Heart Failure (CHF) in the different series make us get to know this subgroup of patients better[6]. Besides, one to two thirds of the patients with HFpEF will experience AF at the time of diagnosis or at some point of the condition[7].

The identification of the MI mechanism is the key for the treatment sequence. The Carpentier classification is the starting point for better understanding, which, in this author's opinion, should be part of all reports of patients with moderate or severe MI (Figure 1). Additionally, MI is classified as primary or organic (PMI) when leaflets and the subvalvular apparatus are normal and it is caused by functional abnormalities in the left heart. It occurs due to the imbalance between the increased tethering forces (resulting exclusively from the global or regional remodeling of the left ventricle (LV), promoting the apical-lateral displacement of papillary muscles (leaflet tethering) and the reduction of closing forces (reduced contractility and dyssynchrony)[8]. This model, which was known until then, began to be called ventricular functional mitral regurgitation (VFMR), and a new concept appeared: atrial functional mitral regurgitation (AFMR).

Historically, AFMR is only owed to mitral annular dilation, but recent evidence showed that this is only one piece of the puzzle, and new mechanisms were added. Its early recognition seems to be extremely important because studies demonstrate that a successful ablation and the maintenance of sinus rhythm reduce its severity[9].

The data about its real incidence and prevalence lack variable diagnostic criteria. Kagiyama et al. revised the prevalence of AFMR in nine studies and identified, initially, very different rates (between 2.8 and 66.7%). After excluding studies that used qualitative methods to classify the MI, and another one that included hospitalized patients, they reached a prevance rate of 3 to 15%[10]**.** Moonen et al. Studied 140,014 adults in 25 centers of Australia, only including patients with severe FMR, and found VFMR in 60% of the cases, and AFMR in 40% of the cases. Patients with AFMR were older (mean of 78 +- 11 years), with higher proportion of women (58%)[11]**.**

Mesi et al., in a study with 283 patients, compared PMI with AFMR and identified that the latter presented more comorbidities, such as systemic arterial hypertension (SAH), Type 2 Diabetes Mellitus, permanent AF, previous non-mitral cardiac surgery and pacemaker insertion[12]**.**

A group from the Mayo Clinic published a study, led by Dziadzko, which analyzed 727 inhabitants of the Olmsted County, in Minnesota, referred to echocardiogram due to a diagnosis of moderate or severe MI, and reported FMI in 65% of the cases; organic, in 32%; and mixed, in 3%. Among the cases of FMI (65%), VFMR was found in 38% of the cases, and AFMR, in 27%.

Physiopathology

The best proposal to understand the genesis of this entity was described by Silbiger[14,21]**.** He described that left atrial dysfunction and the augmented pressure inside it lead this chamber and the mitral annulus to dilate, thus generating the consequent displacement of the posterior mitral annulus to the ridge in the LV input pathway. The progressive growth of the LA in the posterior direction leads to other findings.

At first, we believed this situation happened only and exclusively because of annular dilation; however, other studies added new mechanisms to the process.

Keywords

Atrial Fibrillation; Heart Failure; Echocardiography; Mitral Valve Insufficiency.

Mailing Address: Alexsander da Silva Pretto •
Clínica ImagemCor, Rua Tibiriçá, 155. Postal code: 98500-000. Tenente Portela, RS – Brazil.
E-mail: axspretto@gmail.com
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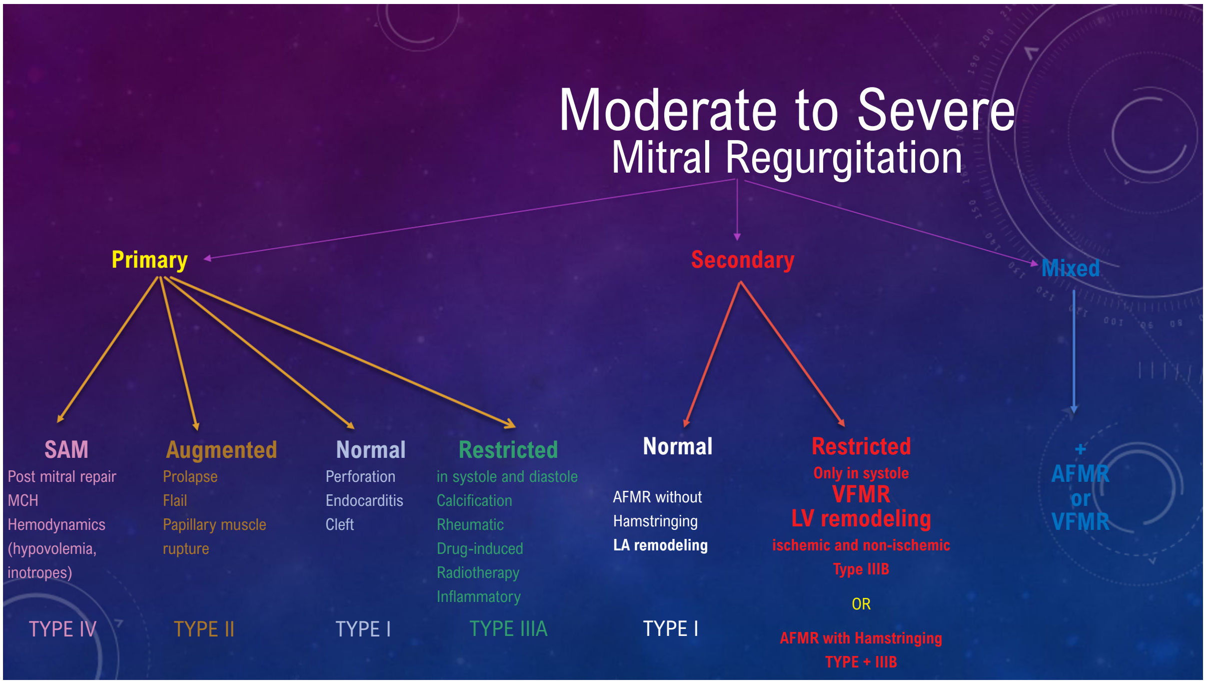

Figure 1 – *Carpentier Classification. AFMR: atrial functional mitral regurgitation; VFMR: ventricular functional mitral regurgitation; MCH: hypertrophic cardiomyopathy; SAM: systolic anterior motion; LV: left ventricle.*

1. ISOLATED MITRAL ANNULAR DILATION: in a retrospective study, Gertz et al.[15], when analyzing 53 patients referred to first AF ablation, who presented with moderate to severe MI, type I, and Ejection Fraction (EF) >50%, demonstrated that the dimension of the mitral annulus was the most important factor for MI in patients with FA (odds ratio 8.39; p= 0.004). Besides, they detected major MI in 82% of the patients with recurrene of FA, and in only 24% of patients with effective ablation. Another study that included 170 patients with AF, structurally normal mitral valve, normal function and dimensions of the LV, who underwent multidetector CT before the ablation, showed that patients with moderate to severe MI presented larger perimeter, annular area and intercommissural and anteroposterior diameters in comparison to patients without MI[16].

2. INSUFFICIENT LEAFLET REMODELING: heart valves are capable of presenting the compensatory growth of leaflets secondary to annular dilation and heart dimensions. This happens thanks to endothelial-mesenchymal cells. Kagiyama et al.[17] found that the leaflet area was significantly larger in all patients with FA. Regarding the total leaflet area (TLA) to mitral annular area (MAA), it was significantly smaller in the MI group when compared to the group without MI and controls. In most patients with significant MI, the TLA/MMA ratio was lower than 1.4. This shows that when the mitral annulus is significantly dilated, leaflet growth does not follow and reaches a plateau, and this insufficient adaptation contributes with the onset of MI.

3. CHANGES IN ANNULAR CONTRACTILITY AND SADDLE SHAPE: the mitral annulus is primarily composed of fibrous and fat tissue. It does not contract actively, but it moves passively with the contraction of the LA and the LV. Annular contraction begins in late diastole and continues through mesosystole, resulting in a reduction of approximately 25% of its area. About 60% of this reduction takes place in late diastole. Anatomic studies by Silbiger and Bazaz[19,20] suggest that, during late diastole, the mitral annulus becomes narrow due to the contraction of circumferential fibers that outlines the base of the LA (atriogenic annular contraction), whereas in systole, annular narrowing is facilitated by the superficial oblique fibers of the LV input pathway = basal twist (ventricular annular contraction). In FA, it is possible to identify the flattening of the mitral annulus and loss of annular movement. The flattening of the mitral annulus increases valvular stress, leading to fibrosis, thickening and calcification;

4. ATRIOGENIC *TETHERING* OF THE LEAFLETS: the anterior portion of the mitral annulus is connected to the aorta, at a more fixed and stable position of the heart. The posterior mitral annulus is anchored between the LA and the ridge in the LV input pathway. With the growth of the LA, it is pushed towards the epicardial surface of the posterior basal wall. The posterior leaflet follows this movement and increases annulo-papillary distance, causing a more abrupt angle and larger curvature towards the LV = atriogenic asymmetric posterior tethering[21].

5. ATRIAL DYSFUNCTION AND CHANGES IN HEART RATE: there is probably a bidirectional relation between AFMR and atrial myopathy. Further studies are required to answer this question.

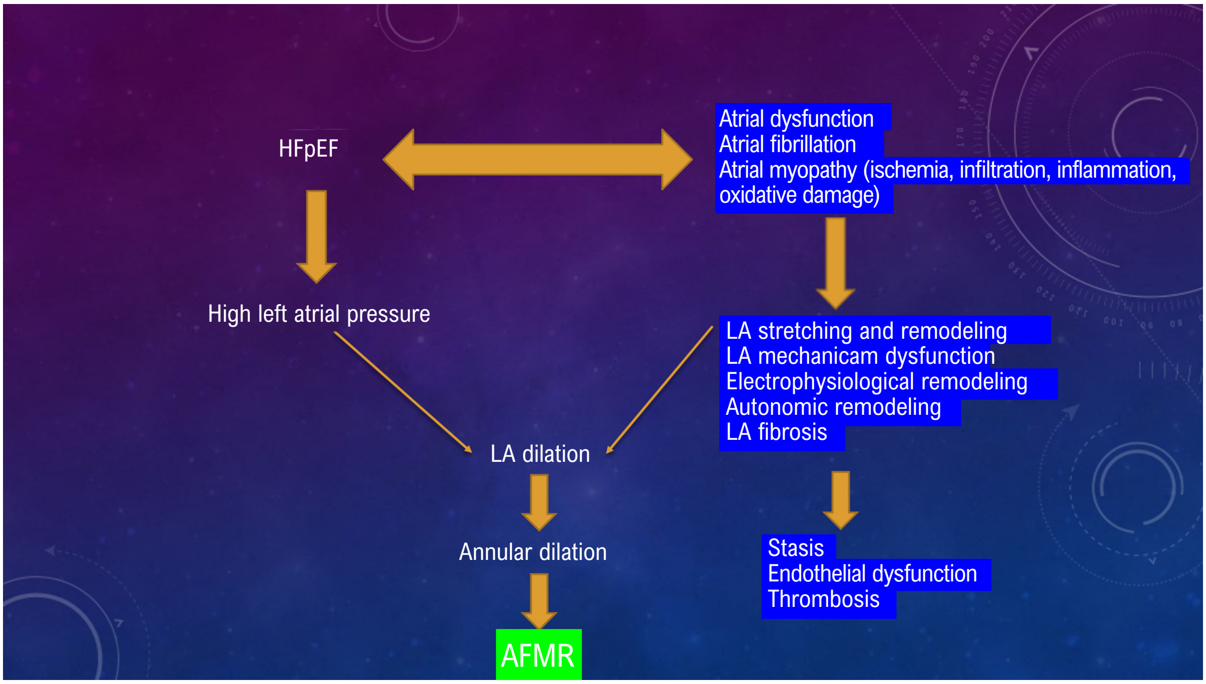

Figure 2 – *Physiopathology of AFMR. AFMR: atrial functional mitral regurgitation; VFMR: ventricular functional mitral regurgitation; LA: left atrium.*

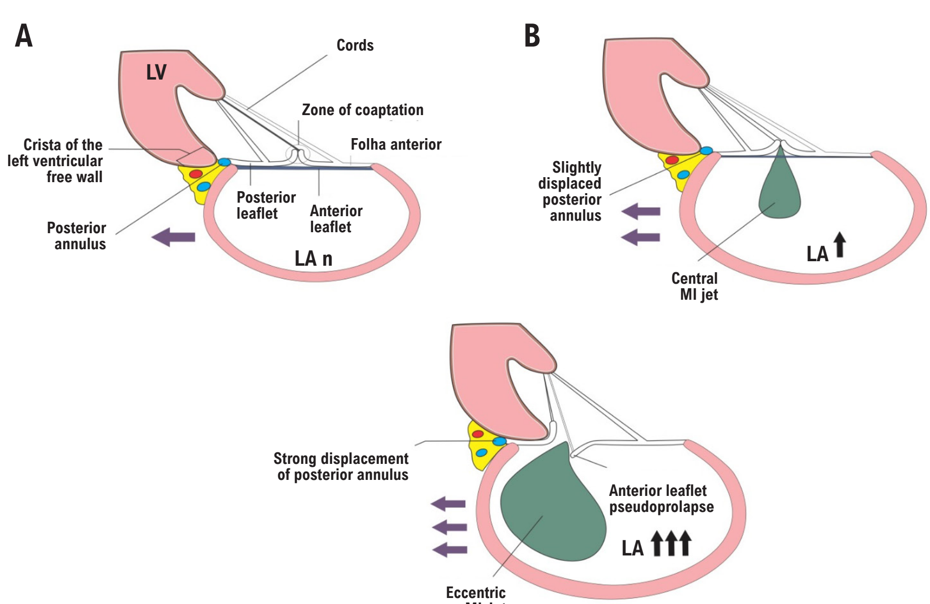

Figure 3 – *Demonstrative model of pathological Evolution. Acknowledge to Kátia Debus for creating this artwork.*

Echocardiographic findings

This item presents findings that are not commonly known, and the approach about the subject is necessary:

Hamstringing: it is identified as a blocked movement of the posterior leaflet, which is practically paralyzed, favoring eccentric jets[12].

1. Bending: it is characterized as a fold or arching of the posterior leaflet, forming an angle between the posterior

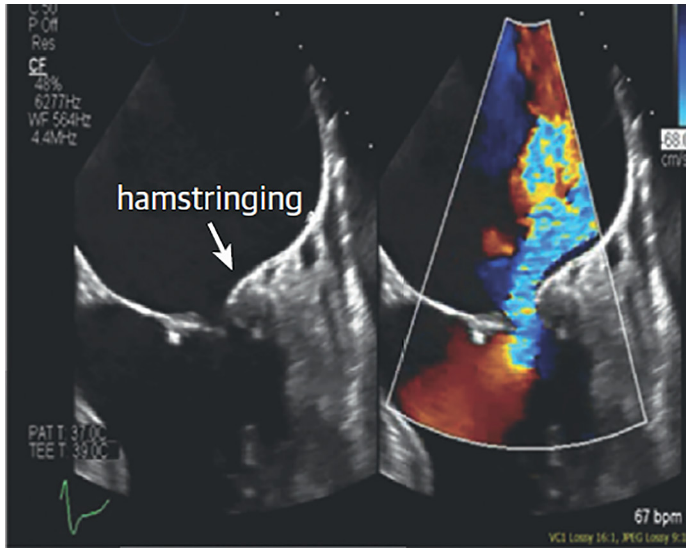

Figure 4 – *Hamstringing. Kindly reproduced with permission from Serge Harb. Image taken from Mesi et al.*[12]

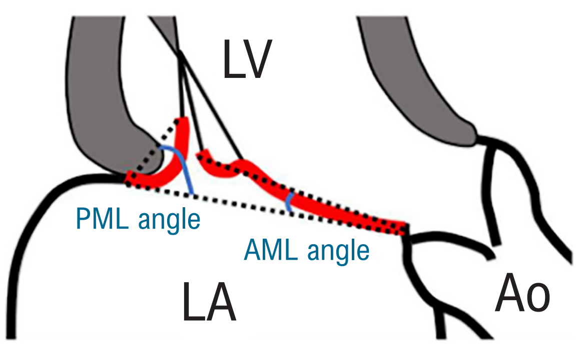

Figure 5 – *Bending. Kindly reproduced with permission from Makoto Miyake. Image taken from Okamoto et al.*[22]

and the anterior leaflet. In a retrospective study, Okamoto et al.[22] examined 118 patients with AFMR and EF > 50%, and compared 24 patients with bending and 94 patients without bending. For that, they defined bending as a relation between the angle of the posterior leaflet and the angle of the anterior leaflet as higher than or equal to 3.1. Survival rate after 36 months of follow-up was significantly lower in the group with bending of the posterior leaflet (63 x 78%, p= 0.047).

2. Anterior leaflet pseudoprolapse: the free border of the anterior leaflet does not meet the border of the posterior leaflet, which is pulled, leading to flawed coaptation and the false impression of a prolapse[21]**.**

The Table 1[1,23] provides data that allow the comparison of aspects for the differential diagnosis between AFMR and VFMR.

Conclusion

This review aimed to approach several current aspects of AFMR. However, new studies are required to bring more information, adjusting the diagnostic criteria of this entity.

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Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, writing of the manuscript, critical revision of the manuscript for intellectual content: Pretto AS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Table 1 - Differential diagnosis between AMIF and CMIF.

PARAMETERS	AFMR	VFMR
LV size and geometry	= Normal by definition (Volume < 78 ml/m2 for women and < 85 ml/m2 for men) with preservation of usual morphology. = Absence of papillary displacement. = Preserved geometry. = In late stages of major AFMR, the LV can dilate and the papillary can be displaced due to volume overload.	= Often dilated (but not necessarily). = Asymmetrical displacement of the papillary muscle (common Acute inferior / dorsal Myocardial Infarction) or symmetrical displacement in Dilated Cardiomyopathy. = Sphericity index (SI) often increased
Wall thickness	= At early stages, usually normal. May present concentric hypertrophy due to associated comorbidities. = Eccentric hypertrophy only at advanced stages.	= Normal thickness, fibrotic of eccentric hypertrophy.
EF	= Preserved regional and global function (EF > 50%) = slightly reduced EF at advanced stages.	= EF usually < 50% with global systolic dysfunction, or up to > 50% with segmental abnormalities = May present intraventricular dyssynchrony
Global Longitudinal Strain	= Usually preserved (> 18%) or borderline (between 16-18%). = Depending on the stage, might be slightly reduced.	= Typically reduced (< 16%).
LA size	= Dilated by definition. Usually, moderated (42-28 ml/m2) or marked (> 48 ml/m2) growth is found in volume	= Often dilated.
Annular size	= Dilated by definition. Systolic Antero-posterior diameter > 35 mm in PLAX or > 36 mm in 4 chambers or indexed annular area > 7 cm2/m2 in 3D in mesosystole; = Relation periphery artery disease /diastolic length of anterior leaflet > 1.3. = Annular flattening.	= Often dilated in response to LA dilatation.
Leaflet morphology	= Normal macroscopic appearance. = Most presents mild thickening.	= Normal macroscopic appearance. = Different levels of thickening.
Leaflet mobility	Usually normal (Carpentier I), but can be classified as III b when Hamstringing is identified.	Restricted (Carpentier III b).
Point of leaflet coaptation	At the annulus level or slightly apically displaced	Apically displaced (subvalvular tethering).
Tenting height	Reduced. Usually between 3.5 +-1.5 mm	Augmented. Usually between 8.1+-2.4 mm.
Jet direction	Usually central, but can be eccentric in case of Hamstringing, or with shorter length of the posterior leaflet .	It is usually central in cases of symmetrical displacement of papillary muscles and eccentric in cases of asymmetrical displacement.
Associated RA dilation	More common	Less common
Moderate / severe RV systolic dysfunction	Less common, but if present, prognosis is worse.	More common
Prognosis	Better prognosis in relation to VFMR[24]. However, its prognosis is worse in comparison to PMI.	It is the worst prognosis. VFMR > AFMR > PMI

EF: ejection fraction; AFMR: atrial functional mitral regurgitation; VFMR: ventricular functional mitral regurgitation; LV: left ventricle.

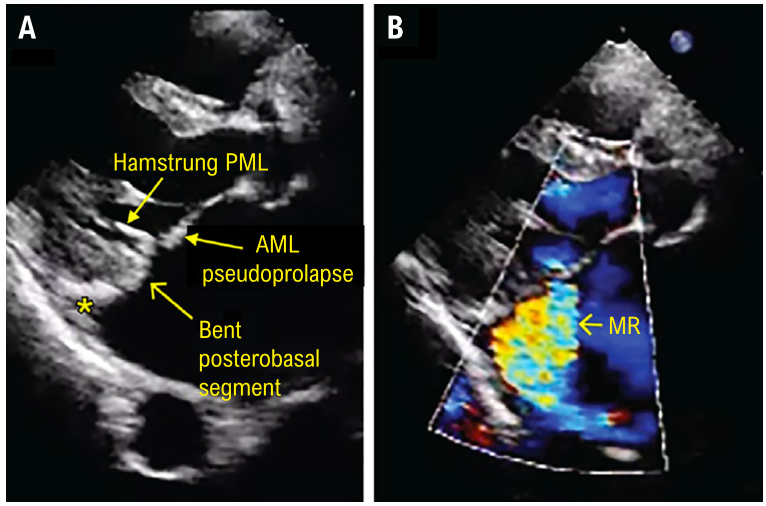

Figura 6 – *Anterior leaflet prolapse and eccentric jet (posteriorly driven). Reproduced with permission from Silbiger.*[19]

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