Atrial functional mitral regurgitation: Insufficiently understood and recognized

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Abstract

Atrial functional mitral regurgitation (AFMR) is a form of functional mitral regurgitation that is still insufficiently recognized and characterized. The driving cause of AFMR is atrial, not ventricular dilatation, usually due to long-standing atrial fibrillation, and often in association with left ventricular diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF). An increase in mitral annular area leads to a loss of central coaptation of the leaflets, often resulting in an "override" configuration and flattening of the annulus, as well as a loss of annular contraction. The left ventricle (LV) has a normal size; thus, there is usually only minor tenting of the leaflets. The regurgitant jet is mostly central, although posterior jet direction also occurs, frequently in a subform with posterior leaflet tethering and a marked localized dilatation of the posterior annulus. Because of the normal-sized and normally or nearly normally contracting LV, the amount of regurgitation is typically not more than moderate (or moderate-to-severe). Over time, functional mitral regurgitation may become mixed atrial and ventricular, with remodeling of the LV. However, the time course and the relation to symptoms have yet to be elucidated. This review presents current concepts and published insights into this form of mitral regurgitation.

Key words: mitral valve regurgitation, heart failure, valvular heart disease

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Background

Mitral regurgitation (MR) is traditionally classified as:

(1) primary (acute or chronic), typically due to mitral valve prolapse, flail, endocarditis, papillary muscle rupture, cleft, or other diseases causing a structural abnormality of the leaflets or subvalvular apparatus; or

(2) secondary, due to chronic pathologic changes originating in non-valvular structures, most often eccentric remodeling of the left ventricle (LV) leading to changed mechanics of the subvalvular apparatus with an eccentric pull of the papillary muscles on the mitral leaflets, a constellation of the closed leaflets described as tenting, and the dilatation of the mitral annulus.

Another form of secondary or functional MR is atrial functional mitral regurgitation (AFMR), where the causative mechanism is atrial dilatation, typically due to atrial fibrillation. This form of MR is less common than ventricular secondary or functional MR (VFMR). Certainly, there are overlaps between atrial and ventricular forms of functional MR, and probably both can initiate vicious circles leading to mixed forms of functional MR. However, AFMR occurs without VFMR, and has received less attention and has been less clearly characterized than VFMR. In the following paper, we will briefly review the existing concepts and published data on AFMR.

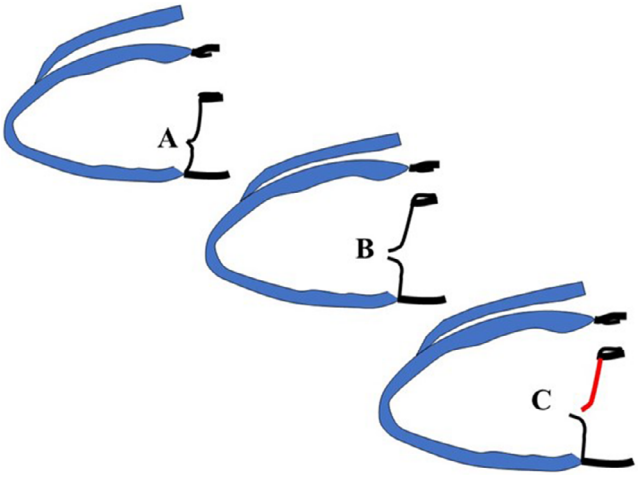

Fig. 1. Schematic drawing of hypothetic evolution of atrial functional mitral regurgitation (AFMR) with progressive dilatation of the left atrium (LA). Left (A) – normal anatomy in systole, no mitral regurgitation. Note slight concavity of mitral leaflet bodies towards left ventricle (LV), but no prolapse. Center (B) – dilated LA with central gap between the leaflets; loss of concavity of leaflets towards LV. There is functional atrial mitral regurgitation through the central gap due to disparity between leaflet size and annular orifice size. Right (C) – further enlargement of LA. There is an "anterior leaflet override" configuration of the mitral valve with tethering of the posterior leaflet and a systolic anterior leaflet (in red) tip position on the atrial side of the posterior leaflet, with further increase in mitral regurgitation

Definition and mechanism

Atrial functional mitral regurgitation occurs due to atrial dilatation, and in the majority of cases due to long-standing atrial fibrillation, flutter or tachycardia. Atrial dilatation leads to mitral annular dilatation and flattening, pulling the mitral leaflets apart and causing central malcoaptation of the leaflet tips, often in the form of an "override" constellation, or a frank gap between the tips of the leaflets (Fig. 1). Decreased annular contraction during the cardiac cycle contributes to the leakage. Pronounced tenting is not typical for isolated AFMR, since there is no eccentric pull of the papillary muscles. The regurgitant jet is usually central, although posteriorly directed jets may also occur (see the last paragraph of this section). The LV by definition is not dilated in pure AFMR and shows normal or near-normal ejection fraction.[1–5] Since AFMR leads to a volume load of the left atrium (LA), it reinforces atrial dilatation in a vicious circle. Therefore, in its strict sense, AFMR requires a substantially dilated LA, mostly, but not always associated with atrial fibrillation or flutter, a normal sized LV with normal or slightly reduced ejection fraction, and a mitral valve without major structural abnormalities such as major tenting, prolapse or leaflet restriction; however, a small amount of tenting may be present (Table 1). The mechanism of regurgitation is a central leakage, often caused by an "override" configuration of the leaflets where the tip of one leaflet, mostly the posterior, is positioned on the atrial side of the other (mostly anterior), hence "overriding" the anterior leaflet without prolapsing beyond

Table 1. Defining features of isolated atrial functional mitral regurgitation (AFMR) compared to ventricular functional mitral regurgitation (VFMR) (adapted from Zoghbi et al.[5])

Features and parameters	AFMR	VFMR
Left atrial size	very dilated	dilated
LV size	normal	dilated
LV function	normal or mildly reduced (EF $\geq$ 40%)	mostly reduced
Mitral leaflet configuration	no or minor tenting, with a loss of concavity towards the LV; possible anterior leaflet override and posterior leaflet tethering	progressive tenting of both leaflets
Mitral annulus diameter/area	very dilated	dilated
Prevalence of atrial fibrillation	very high (>50%)	approx. 30%
Mitral regurgitant jet direction	central, sometimes posterior	central, sometimes posterior

LV – left ventricle; EF – ejection fraction. Note that the presence of mixed AFMR and VFMR is probably clinically not rare.

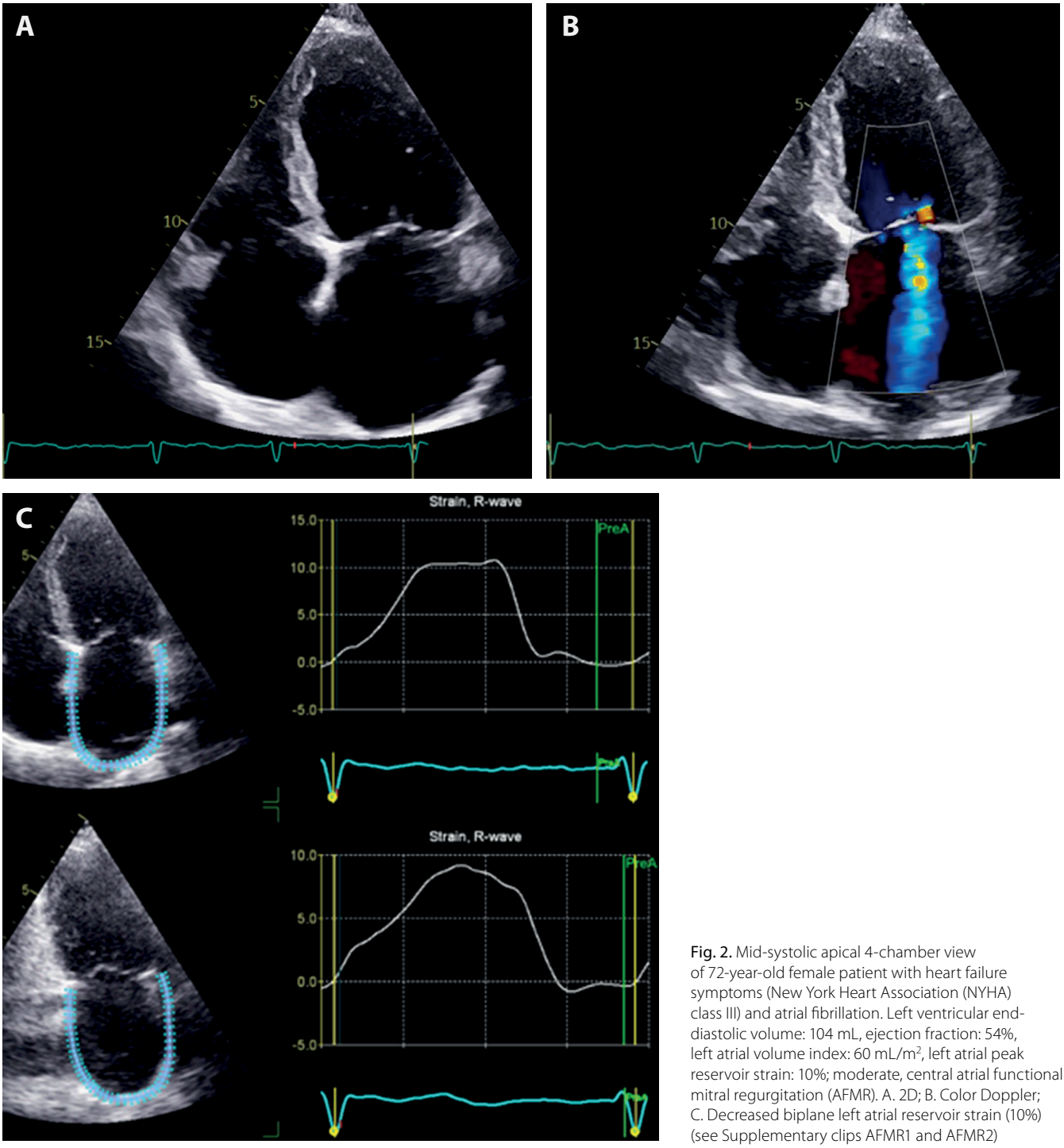

Fig. 2. Mid-systolic apical 4-chamber view of 72-year-old female patient with heart failure symptoms (New York Heart Association (NYHA) class III) and atrial fibrillation. Left ventricular end-diastolic volume: 104 mL, ejection fraction: 54%, left atrial volume index: 60 mL/m^2, left atrial peak reservoir strain: 10%; moderate, central atrial functional mitral regurgitation (AFMR). A. 2D; B. Color Doppler; C. Decreased biplane left atrial reservoir strain (10%) (see Supplementary clips AFMR1 and AFMR2)

the annular level. The resulting jet is mostly central, but can be posteriorly directed (see Fig. 2).

The initial causative mechanism of AFMR can be understood as a disparity between the enlarged and flattened mitral annulus and the disposable leaflet area to seal it during systole. The 3D echocardiography has shown that the amount of AFMR relates to the magnitude of this disparity.[2] The mitral apparatus is able to at least partially compensate for annular enlargement by initiating leaflet growth, and this compensatory growth can be inhibited in animal models of VFMR by cyproheptadine.[6] Hence, it is possible that the described vicious circle of AFMR is amenable to beneficial modulation by drugs.

In the further course of the disease, the volume load of the regurgitant mitral volume likely affects the – initially normal – LV, leading to left ventricular dilatation and mixed atrial and ventricular FMR, with typical tenting configuration of the mitral valve. However, the time course of AFMR, and whether it inexorably leads to VFMR, has not been systematically studied.

The association of AFMR with atrial fibrillation, which analogously can lead on the right side of the heart

to functional tricuspid regurgitation, implies that AFMR is a relatively frequent finding in patients with risk factors for atrial fibrillation, or with heart failure with preserved – or mildly reduced – left ventricular ejection fraction (HFpEF). These patients have a high incidence of atrial tachyarrhythmias and elevated left ventricular diastolic pressures due to LV diastolic dysfunction. Both diastolic dysfunction and AFMR increase left atrial pressure, which in turn impairs atrial mechanical function, as evidenced by impaired left atrial strain. It is very difficult, if not impossible, in this scenario to tease out the relative contributions of diastolic dysfunction and of MR to symptoms, natriuretic peptide elevation, pulmonary congestion, and right-sided pressure increase, which are all affected by both pathophysiological mechanisms. Hence, AFMR and HFpEF often coexist and are difficult to separate clinically. A recent study showed that patients with HFpEF and AFMR display greater hemodynamic severity of disease and poorer functional capacity than in HFpEF without AFMR.[7]

Some authors have described a subform of AFMR that occurs as the result of a posteriorly located dilatation of the mitral annulus leading to a herniation of the annulus beyond the circumference of the ventricular myocardium, and a particularly strong tethering of the posterior leaflet, with the consequence of a posteriorly directed regurgitant jet.[4,8–10] Several terms, such as "hamstringing" or "atriogenic MR", have been used to describe this configuration.

Hemodynamic features of AFMR

By definition, the regurgitant volume of AFMR cannot be very large, because chronic occurrence of a large mitral regurgitant volume would lead to critical impairment of systemic stroke volume in the absence of left ventricular dilatation. Hence, as long as the LV is not dilated, AFMR is typically rather moderate than severe. However, this may change once the LV starts to dilate and produce a larger total stroke volume. It is also currently unclear whether the quantitative cutoffs of severe regurgitation used for primary and ventricular FMR (effective regurgitant orifice area (ERO) $\geq$0.4 cm^2, regurgitant volume > 50 mL, regurgitant fraction > 50–60 mL)[11] are adequate for AFMR.

Epidemiology

In a recent report on the etiology of all cases of moderate and severe MR seen at the Mayo Clinic over 10 years, functional MR made up 65% of a total of 727 MR cases, and about 40% of functional MR cases were diagnosed to be of atrial origin.[12] Survival curves in AFMR cases were similar to those in primary MR, with considerable excess mortality compared to expected survival of age- and sex-matched general population cohort. Given that atrial fibrillation is a chief driver of AFMR, the data provided by Abe et al. are of a great importance.[1] They show that in atrial fibrillation patients without other apparent heart disease and a LVEF $\geq$ 50%, the incidence of at least moderate AFMR increased from 3% (in patients with duration of atrial fibrillation <1 year) to 28% (in those with duration of atrial fibrillation >10 years).

Treatment and outcomes

Atrial functional mitral regurgitation is amenable to current surgical and interventional mitral repair techniques, apart from valve replacement. In the so far largest published cohort study of severe AFMR patients with follow-up, it has been shown that these patients had worse overall survival, more heart failure hospitalizations (and more diastolic dysfunction), and underwent valve surgery less often than similarly aged patients with severe primary MR and normal LV function.[10] Recently, the results of percutaneous edge-to-edge repair in 126 patients with AFMR were published, with good procedural success and symptomatic improvement[13]; however, whether this translates into improved prognosis cannot be currently determined.

Since atrial tachyarrhythmias are a key factor in the development of AFMR, the ablation of atrial arrhythmias is an appealing treatment option.[14] In a cohort of 136 AFMR individuals who underwent atrial fibrillation ablation, MR decreased in 64%, and only in those patients the LA volume also decreased.[15] Patients who had sinus rhythm restored had less MR and more reduction in LA volume than those who did not. The extent of low-voltage areas in the LA thought to reflect left atrial fibrosis and correlated with less reduction in MR and LA volume, suggesting that in the presence of extensive low-voltage areas AFMR may not be improved by ablation even if sinus rhythm is restored.

Areas of uncertainty in need for further research

Although the association of left atrial enlargement, atrial fibrillation and MR with a mitral leaflet without major visible abnormalities has been known for a long time, a more precise definition was lacking. Very recently, an expert panel viewpoint document has suggested a detailed framework for the definition of AFMR.[5] The most important open question related to AFMR is the time course of the disease and LA remodeling. Does AFMR develop to become mixed ventricular and atrial FMR over time, as we know it from functional tricuspid regurgitation? How to define severe AFMR when a normal-sized LV precludes large regurgitant volumes given that enough forward stroke volume must be preserved? Is a substantial proportion of what we call HFpEF in fact the consequence of AFMR? These questions await further research.

Conclusions

Atrial functional mitral regurgitation needs to be recognized as an important type of functional MR with morphological and pathophysiological characteristics that set it apart from other types of MR. Similar to functional atrial tricuspid regurgitation, the driver of this disease is neither a diseased valve nor the ventricle, but the remodeled atrium, in particular the dilated mitral annular area, with close association with the burden of atrial fibrillation over time. This is important not only for diagnosis, but also for the choice of therapy. The avoidance of major left atrial remodeling is crucial for the prevention of AFMR, and the induction of reverse remodeling is the ideal therapeutic principle. The time course of AFMR, its impact on the LV, the potential of reverse remodeling of the LA if sinus rhythm can be restored, and a bespoke therapeutic approach remain to be determined.

Supplementary material

The supplementary clips (AFMR1 and AFMR2) are available at https://doi.org/10.5281/zenodo.7273770.

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