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EDITORIAL COMMENT

The Left Atrium

Passive Receptacle or Active Contributor to Mitral Regurgitation Severity and Outcome*

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The left atrium is the reservoir for the blood flowing out of pulmonary veins during ventricular systole and the receptacle for the regurgitant blood volume when there is mitral regurgitation (MR). The simplistic view of a mostly passive and limited pathophysiological left atrial (LA) function has evolved with new data and understanding. First, in patients with overt MR, the left atrium plays a considerable regulatory role. Indeed, with MR, the excess regurgitant volume entering the left atrium in systole yields LA v-wave and mean pressure increase, with reduced compliance and secondary elevation of pulmonary capillary pressure associated with the risk of pulmonary edema.[1] The magnitude of the LA pressure increase depends on MR acuity and severity. However, LA dilatation that follows MR occurrence directly increases LA compliance,[1] secondarily yielding normalization of LA pressure, even in patients with severe MR,[2] explaining a frequent long phase of asymptomatic status among those patients.[3]

Second, data have further emphasized the importance of the left atrium in patients with MR. Although MR severity is the major determinant of LA enlargement, the latter shows prominent variability between individual patients with similar MR severity.[4] Such individual variability in LA response to MR remains poorly defined in term of genetic mechanisms[5] but is remarkable in that LA dilatation severity is highly predictive of long-term outcome,[6] independently of all the baseline characteristics, particularly of those linked to LA enlargement.[7] Furthermore, the intrinsic LA function is now measurable and is even more strongly associated with long-term outcome than LA enlargement, in all types and degrees of MR.[8,9] Thus, LA characteristics are truly crucial to consider, particularly in patients with MR.

However, there is a third aspect of the left atrium that has recently been conceptualized. The left atrium is attached to the mitral annulus, which anchors it to the left ventricle. The mitral annulus is a dynamic structure preventing early systolic MR and is affected by myxomatous degeneration.[10] In turn, LA dilation affects the mitral annulus, pulling it eccentrically and resulting in annular dilatation that may yield MR progression in patients with myxomatous degeneration[11] but also resulting in a specific type of functional MR, called atrial-functional MR (A-FMR).[12] A-FMR, despite the normal mitral leaflets, is due to insufficient valvular coverage of the enlarged mitral annulus secondary due atrial enlargement. Although this form of FMR is common in patients with atrial arrhythmias,[13] it also occurs in sinus rhythm and may be an aggravating factor of the FMR occurring in patients with predominant ventricular remodeling caused initially by mitral leaflets' tethering due to excess tension on the chordae and the leaflets they support (**Figure 1**). Thus, mixed A-FMR and ventricular FMR, with LA enlargement causing pronounced annular enlargement and contributing to tethering of leaflets, is increasingly recognized, as shown in the case presented by Donia et al[14] in this issue of *JACC: Case Reports*.

In this case, the authors report on an 81-year-old woman presenting with severe MR, symptomatic for

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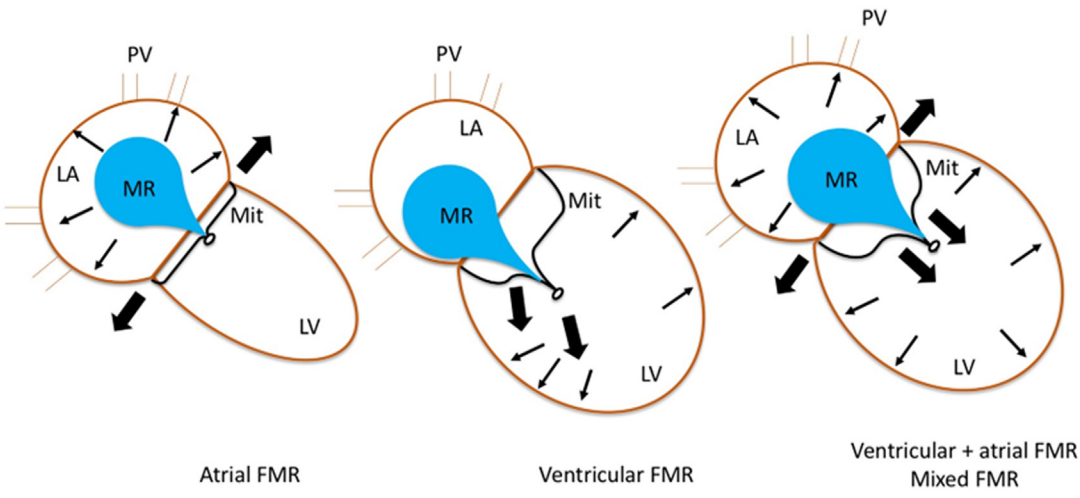
FIGURE 1 Functional Mitral Regurgitation Types



Functional mitral regurgitation (FMR) types: atrial FMR (left), ventricular FMR (middle), and mixed ventricular + atrial FMR (right). Schematic representation of the mitral valve, left atrium, and left ventricle. The small arrows indicate the effect of pressure on left atrial and left ventricular walls. The thick black arrows indicate the tethering forces on the annulus and on the leaflets. The blue shape depicts FMR. LA = left atrium; LV = left ventricle; Mit = mitral valve; MR = mitral regurgitation; PV = pulmonary veins.

acute pulmonary edema.[14] Although the left ventricular size and ejection fraction were preserved, the normal leaflets attested to FMR, but the mechanisms leading to leaflet malcoaptation were a combination of local left ventricular remodeling due to inferolateral hypokinesia associated with disproportionate LA enlargement and deformation of the mitral annulus. A first therapeutic attempt was made with only medical treatment; because of persistent symptoms, the patient underwent successful transcatheter edge-to-edge repair (TEER).

The merit of the case reported by Donia et al[14] is to reappraise the dual classification of atrial vs ventricular FMR that may not fully depict complex and combined FMR mechanisms. The many potential mechanistic components of the FMR hypothesized in this case remain interesting hypotheses. Indeed, the authors suggest that aortic root dilatation increases the antero-posterior dimension and contributes to anterior leaflet tethering. Whether, as the authors assert, bileaflet ventricular tethering, usually a hallmark of ventricular FMR,[15] can be accentuated by LA enlargement and atrial FMR remains insufficiently evaluated.[16,17] However, the case is important because of the complex nature of the FMR, with both leaflet restriction and outsized LA enlargement causing marked annular enlargement (ie, a mixed FMR).

The limit of such hypotheses is that we do not have information on LA enlargement and mitral deformation/tethering before the MR occurrence. The history of atrial fibrillation, previous pulmonary vein isolation, and brady-tachy syndrome indeed suggest an atrial myopathy.[18] However, without imaging data preceding the MR, it is difficult to be fully conclusive regarding the various contributors to FMR. Nevertheless, the modest valvular tenting combined with marked annular enlargement resulting in severe functional MR suggest the combination of type IIIb (restrictive systolic leaflet movement) with type I (normal leaflet movement with annular enlargement) mechanisms suggest that the outsized LA enlargement may have greatly amplified the MR due to the restriction of leaflet movement due to the regional wall motion abnormality.[14]

In line with this mixed mechanistic nature, the question arises as to whether TEER may be a valid treatment. In the present case, TEER provided a beneficial effect by reducing MR degree and preventing its clinical heart failure consequences. It is

interesting to note that TEER reduced the antero-posterior annular diameter, restoring partly mitral annular dimensions and facilitating improved coaptation. Current guidelines do not specifically address the criteria to indicate intervention, including TEER in patients with a full or partial A-FMR,[19] but clinical cohorts suggest that TEER is effective in A-FMR.[20] Although randomized clinical trials are desirable to evaluate the benefit of TEER in A-FMR, such trials may not be ethical in the context of the existence of an approved treatment for MR, particularly in patients at high risk for surgery.

What is the way forward with LA enlargement/function and its consequences in term of MR and outcome? The link of LA characteristics to the development of atrial arrhythmias or of A-FRM and the occurrence of excess mortality[13] have been insufficiently studied. The documentation of specific atrial myopathy has been scarce, and it is essential to develop programs combining detailed multi-modality imaging with genomics and proteomics to address the profound gaps in knowledge surrounding the function of the atrial myocardium.[21] Although LA volume measurements are now widely accepted, LA functional assessment and the degree of fibrosis affecting the atrial wall warrant consistent evaluation.[8,9,22] A-FMR represents a sizable proportion of MR,[13] the most frequent valve disease affecting the population,[23] and the transition from LA enlargement to FMR warrants analysis in large cohorts. A-FMR is a troubling entity with modest regurgitant volume and a small left ventricle of generally normal function but nevertheless is associated with excess mortality and high incidence of heart failure. The contribution of A-FMR to the clinical complications warrants in-depth analysis with long-term cohorts so that the specific indications for surgical/interventional therapies in these elderly patients can be fully defined.

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