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EDITORIAL COMMENT

Atrial Functional Mitral Regurgitation

Many Questions, Few Answers*

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Mitral regurgitation (MR) is the most common valvular disease in the population and the community[1] and is a frequent reason for referral to valve centers for treatment.[2] MR has always been known to be heterogeneous, but even recent authoritative reviews did not mention the existence of atrial functional mitral regurgitation (aFMR).[3] Isolated reports mentioned aFMR, but the concept was not fully adopted.[4] More recently, a detailed analysis of all consecutive cases in an entire community revealed the considerable importance of aFMR.[5] Indeed, while organic MR affects approximately one-third of patients and is dominated by degenerative MR, functional MR (FMR) is the leading cause in the population (65% of cases) and is most frequently associated with left ventricular (LV) remodeling (ventricular FMR [vFMR]), but a substantial proportion (28% of all cases of MR) is linked to predominant atrial remodeling, usually with a type I mechanism of predominant annular enlargement (**Figure 1**).[5] However, despite recognition of the existence of aFMR and of its magnitude, considerable questions remain unresolved.

First, from a mechanistic point of view, it is surprising that patients with aFMR present with similar left atrial dilatation as patients with vFMR, in whom MR is attributed mostly to leaflet tenting (type IIIb). How is it possible that vFMR with similar atria and annulus but with additional tenting incurs the same regurgitant volume as aFMR? Does the very high prevalence of atrial fibrillation (AF) in aFMR explain this discordance, or is the annular deformation by calcification the culprit?[5] From a pathophysiologic standpoint, the association of aFMR with heart failure is difficult to reconcile. With a similar ejection fraction (EF) as organic MR, aFMR, despite a smaller left ventricle and smaller regurgitant volume, incurs much higher heart failure incidence than organic MR.[5] Is the discordance related to a component of heart failure with preserved EF rather than the MR itself? What is not in doubt is that aFMR is associated with a very high incidence of heart failure and excess mortality,[5] in the context of profound undertreatment by surgery, similar to vFMR.[6]

These gaps of knowledge probably explain the lack of consideration of aFMR in clinical guidelines[7,8] but raise crucial questions about therapy. Because these patients are quite advanced in age, transcatheter treatment is the preferred option, and whether the effectiveness of transcatheter edge-to-edge repair (TEER) observed in organic MR[9] and in vFMR[10] in controlling MR applies to aFMR remains undefined. Similarly, the possibility that control of MR by TEER may not bring a similar clinical benefit in aFMR as in organic MR[9] or vFMR[10] remains untested. In this context, analysis of the impact of TEER on patients with aFMR in a large European registry is of importance.

THE PRESENT STUDY

Doldi et al[11] bring the first and an interesting contribution in reporting clinical characteristics and outcomes of the largest cohort of 126 patients with symptomatic aFMR undergoing TEER, compared with 133 patients without aFMR and 1,349 patients with vFMR, derived from the international multicenter EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation) registry. They define aFMR as the combination of a dilated left

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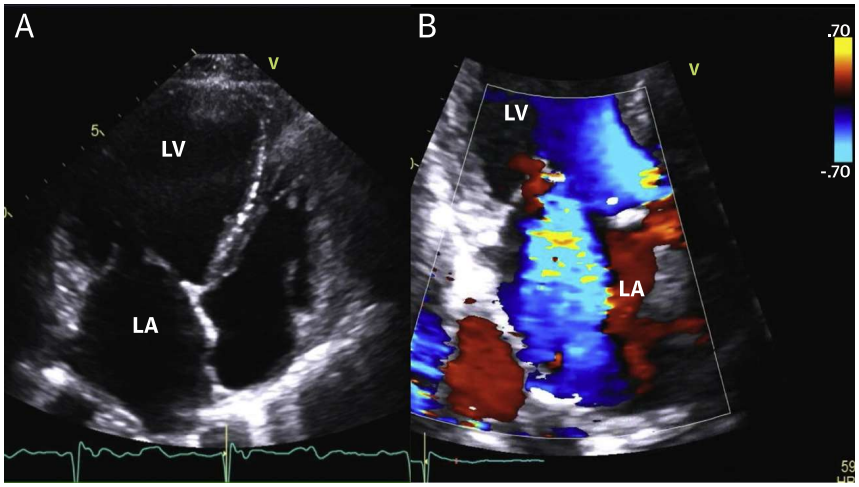
FIGURE 1 Example of An Echocardiographic Diagnosis of Atrial-FMR



Transthoracic echocardiographic apical 4-chamber view displaying **(A)** normal and thin mitral leaflets with marked left atrial enlargement, responsible for **(B)** significant atrial functional mitral regurgitation. LA = left atrium; LV = left ventricle.

atrium, type I MR, and EF ≥ 50% by retrospective review. aFMR represented 8% of all cases of FMR in this European registry of TEER, with confirmation of the high prevalence of AF, of the advanced age of patients affected (mean age 80 years), of the large left atrium (but similar to the other FMR subsets), of impaired clinical status (shortest 6-minute walk distance), of the high surgical risk (European System for Cardiac Operative Risk Evaluation [EuroSCORE] II 5%), and of the relatively modest MR severity (effective regurgitant orifice area 0.27 ± 0.14 cm^2). In the context of the coherent findings with previous studies of aFMR[5] with the expected preserved LVEF (57% ± 6%) and small left ventricle (mean LV end-diastolic volume 53 mL/m^2, mean LV end-systolic volume 23 mL/m^2), TEER success is an important observation. Indeed, procedural TEER success was achieved in most patients, with MR ≤2+ in 87% and ≤1+ in 62%, along with significant symptomatic alleviation in New York Heart Association (NYHA) functional class (from 86% to 37% in NYHA functional class ≥III), all similar to results obtained for other forms of FMR. Furthermore, post-TEER survival of 70% at 2 years in aFMR is not different from the other FMR types.

Additionally, the investigators focus on right ventricular function and NYHA functional class at baseline as determinants of post-TEER outcome. They assess right ventricular dysfunction (RVD) as the ratio of tricuspid annular plane systolic excursion to systolic pulmonary pressure and apply a previously defined threshold for this variable. RVD by this definition was observed in 35% of patients with aFMR and was an independent predictor of worse outcomes (2 years), along with NYHA functional class IV.

The study has some evident limitations. Mechanistically, we presume that the patients without aFMR have a component of class IIIb, which would be compatible with larger effective regurgitant orifice area and left ventricle, but this combination is compatible with aFMR of more severe degree that may have evolved. Detailed measurements of tenting and annular size and shape would have been desirable, including assessment of the impact of TEER on annular remodeling, not mentioned in the report. In terms of outcome, comparing survival in populations of patients with FMR of different ages makes the affirmation of similarity tenuous. It would have been useful to compare survival with that expected in the general population. The presence of RVD was associated with higher EuroSCORE II, leaving doubt regarding the model used and the true independence of RVD. Even if the role of RVD were confirmed adjusting for age and EuroSCORE II, it is not very novel to observe, as in any disease, that RVD adds to the severity of the condition, and conversely the crucial information is the gain in survival achieved with TEER vs no treatment in patients with or without RVD. It may be that patients with RVD are those who benefit the most, but we cannot verify this

hypothesis, because the registry includes only treated patients. Whether RVD is linked to the more frequent tricuspid regurgitation in aFMR is unclear.

However, although the present study cannot resolve differences among randomized trials of TEER,[10,12] as those regard vFMR and not aFMR, the limitations of the study should not distract from the important information it provides. The crucial issue provided by the present study is that in a restricted population of patients with aFMR, notable success in controlling MR is achieved post-TEER, a result that may not have been easily predictable. Although the absolute benefit cannot be defined for TEER, the marked symptomatic reduction following TEER is a harbinger of better control of heart failure and possibly of improved survival. Thus, in this elderly population at high surgical risk, markedly symptomatic, and severely undertreated by surgery, TEER success is truly welcome and an important information provided by the registry.

MOVING FORWARD WITH aFMR

The high prevalence of aFMR in the population and its mediocre outcomes emphasize the considerable gaps in knowledge and unmet needs for treatment. Treating patients involves a necessary understanding of the mechanisms and pathophysiology of MR. From a mechanistic point of view, aFMR involves predominant atrial remodeling, but surprisingly the left atrial volume is not larger than in vFMR. Thus, one unresolved question is whether type I FMR is due to insufficient annular coverage because of tissue paucity. We do not observe tissue retraction as in rheumatic disease, but more data collection using 3-dimensional and 4-dimensional methods is necessary to understand the complete mechanism of aFMR. Also, is non-aFMR in fact an aFMR complicated by papillary muscle displacement and tenting, and should these patients be grouped with aFMR? Pathophysiology is also mysterious, with MR of low volume similarly to vFMR but with a normal EF; Furthermore, the link between aFMR and outcome is not obvious and requires large, well-quantified cohort studies. In the same vein, is there associated diastolic dysfunction or restriction that contributes to (or causes) the left atrial pressure elevation? Is the poor prognosis dependent on the frequently associated tricuspid regurgitation[13] rather than on the aFMR itself? From a therapeutic point of view, the type I mechanism of aFMR, whereby the coaptation gap is considered as caused by annular enlargement or deformation, suggests that simple annuloplasty may be sufficient.[14,15] However, annuloplasty is rarely performed, given the old age, high surgical risk, and frailty of this population. Thus, percutaneous annuloplasty might be a valuable alternative, more effective than in vFMR.[16] Whether the effectiveness of TEER depends on leaflet traction and annular size reduction remains uncertain. Although a combination of both TEER and percutaneous annuloplasty may become feasible,[17] percutaneous valve replacement is a concern for aFMR with small LV size and possible LV outflow obstruction.[18] Restoration of sinus rhythm in patients with aFMR with persistent AF may reduce annular size and reduce the severity of aFMR[19] but may be difficult to sustain with marked left atrial enlargement. Thus, future well-designed clinical trials should evaluate the benefits of transcatheter mitral therapies vs medical management alone to eventually improve the therapeutic armamentarium for this disease and reduce its profound undertreatment.

Much remains to be understood and evaluated in aFMR, and we invite wide-ranging collaborations to provide the science that will make it possible to improve the outcomes of patients with aFMR.

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