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EDITORIAL

Mitral regurgitation, the left atrium and atrial fibrillation: *unlikely bedfellows or natural kindreds?*

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This editorial refers to 'Even mild mitral regurgitation is associated with incident atrial fibrillation in the general population', by M. Yafasov *et al.*, https://doi.org/10.1093/ehjci/jead337.

There is a close association between mitral regurgitation (MR), left atrial (LA) size and function, and atrial fibrillation (AF). This association is highlighted in the ESC/EACTS and the ACC/AHA guidelines for the management of valvular heart disease. Indeed, in asymptomatic patients with chronic primary MR, surgical mitral valve repair should be considered in case of LA dilation [defined as an LA volume index ≥ 60 mL/m^2] or the onset of new AF (both IIa, level of evidence B).[1]

In this issue of this issue of the journal, Yafasov *et al.* reported data from a prospective population-based fifth Copenhagen City Study. Of the nearly 4500 participants who had transthoracic echocardiograms, MR was quantifiable using the colour flow Doppler MR jet area indexed to LA area (MR/LA ratio) in about 90% of the participants.[2] Some degree of MR was found in about 48%, and of those ones 39% had trace/mild MR. During a median follow-up duration of 5.3 years, slightly less than 5% of the participants in the study were found to have developed AF. The MR/LA ratio was independently associated with incident AF but only in participants ≤ 73 years. Additionally, this relationship persisted even in patients with mild MR. Our existing knowledge regarding the association between MR and AF and the current guideline recommendations to intervene predominantly relies on data from individuals who sought medical attention at hospital echocardiography centres or laboratories or from specifically selected communities. To that extent, the data from the Copenhagen City Study offer some additional insights. The data from the study by Yafasov *et al.* study emphasize the interplay between MR, LA, and AF. This intimate connection also raises the question of which came first, akin to the chicken and egg dilemma. If the cause–effect relationship between FA and MR is more plausible in primary MR, it is less so in secondary MR (SMR). This is supported by the fact that in the Copenhagen City Study, only 5% of the enrolees had SMR. It is interesting that while 43% had primary MR by predefined criteria, the rest were not categorized as primary or secondary MR. It is likely that the definitions used by the authors (SMR was defined as MR with ischaemic heart disease, heart failure, or left ventricle dilation at baseline, while primary MR was defined as any MR not fulfilling the criteria for SMR) underestimated the number of SMR, particularly atrial SMR (ASMR). Although the original definition of ASMR was that MR improved significantly if sinus rhythm was restored, there is evidence that up to 40% of individuals with heart failure with preserved ejection fraction (HFpEF) may have ASMR with or without a history of AF. There is also evidence that the size of the LA may be less dilated in individuals with ASMR plus HFpEF but without AF than in those with HFpEF plus AF. Those with AF only and no HFpEF have been reported to have the largest LA size. Yet the survival was lowest in the two HFpEF groups with relatively smaller LA size and ASMR. LA function measured as LA work and strain was lowest in the two HFpEF groups with ASMR, especially in the HFpEF with ASMR plus AF. This perhaps highlights LA as an important mediator of the risk of AF and may be even reduced survival.[3]

In the study by Yafasov *et al.*, LA size was normal in people who developed AF, and this was even the case in those with moderate-to-severe and severe MR. While the latter is difficult to understand, it emphasizes the fact that LA size may not be as sensitive as LA function to predict the occurrence of AF.[4] LA function is of paramount importance in stratifying the risk of patients with MR. The main role of the LA is to prevent pulmonary congestion by damping pressure swings between the LV and the pulmonary vasculature, and this regulation of LA pressure is influenced not only by its size but also by its contractility and its compliance. Recently, the analysis of LA myocardial deformation parameters has been proposed as a surrogate for LA fibrosis and therefore a 'stiff' LA. Indeed, it has been shown that LA strain but no LA size was predictive of adverse clinical outcomes in patients with ASMR and ventricular SMR.[3,5] Noteworthy, Yafasov *et al.* demonstrated that MR/LA ratio remains significantly associated with AF after adjustment for CHARGE-AF risk score in a sensitivity analysis restricted to patients with moderate or severe MR and normal LAVi. Furthermore, reduced LA reservoir strain has been shown to predict new-onset AF in adults regardless of LA size[6] or to predict stroke recurrence and death in patients with cryptogenic stroke.[7] Thus, LA strain is an important factor in AF risk stratification. The interaction between MR, LA, and AF is less relevant in elderly people (over 73 years old). Indeed, AF in the elderly occurs as a consequence of cardiovascular aging and an age-related increase of co-morbidity. Thus, it is not surprising that the data from the Copenhagen City Study did not show MR as a predictor of AF in elderly patients.

Finally, to assess MR severity, the authors chose to index the MR jet area to the LA area. The concept of indexing the MR colour Doppler area to LA area is clearly fraught with limitations but relating the size of the cardiac chamber that first receives the volume overload may be relevant. This was recently explored in patients included in the COAPT trial. Interestingly, low regurgitant volume to LA volume ratio

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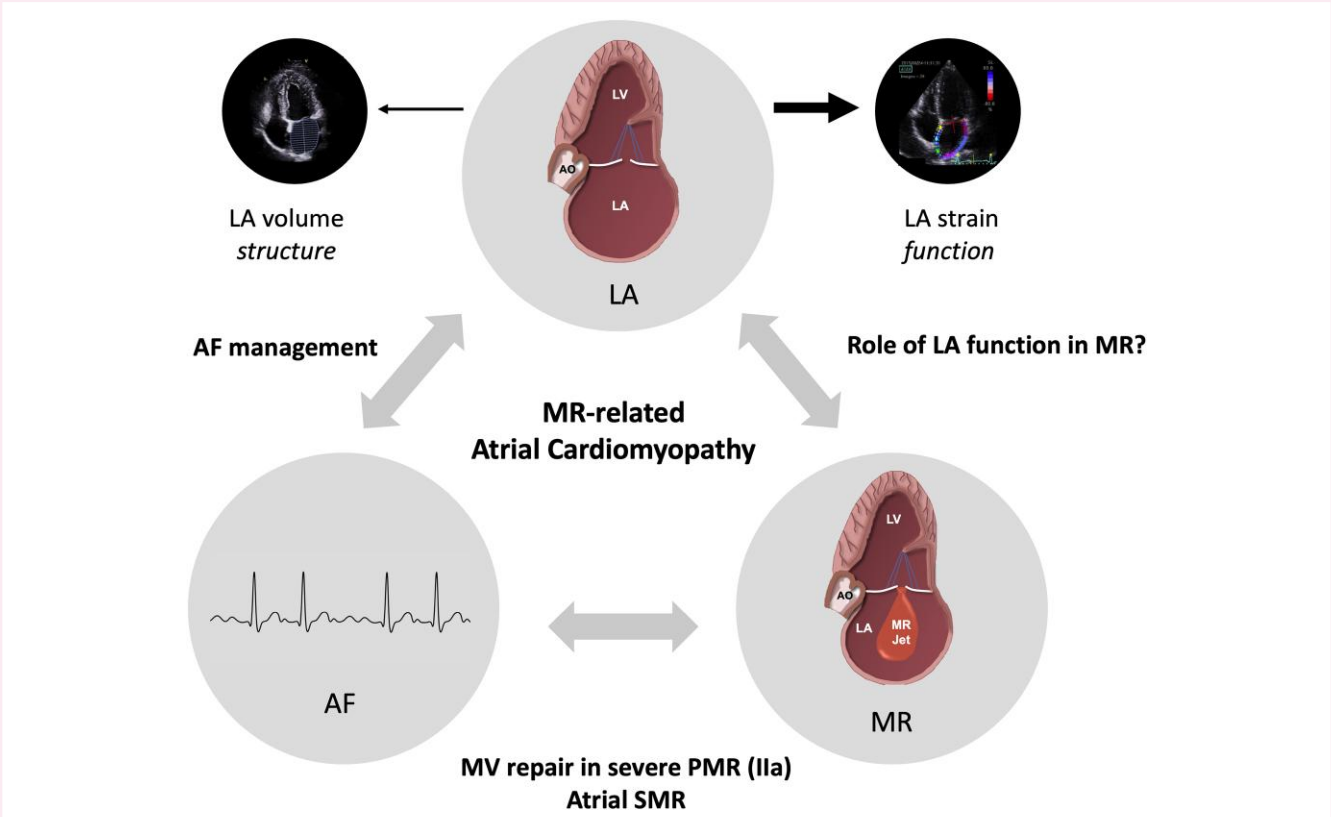

Figure 1 Interaction between mitral regurgitation, the left atrium and atrial fibrillation.

was an independent predictor of 2-year heart failure hospitalizations in HF patients with severe MR treated with guideline-directed medical therapy alone.[8] Future studies are needed to validate the utility of the indexing MR severity to LAV, to define its optimal cut-off to predict events, and to explore whether it has a role in patients with primary MR.

Although the study of Yafasov *et al*. has notable shortcomings, it does highlight the interaction between MR, LA, and AF or the concept of atrial cardiomyopathy (*Figure 1*). The role of LA function, not just the size, in the risk stratification of patients with valvular heart disease is missing in the guidelines for intervention particularly in patients with MR. Further studies on the role of the LA in valvular heart disease are needed. 'Realize that everything connects to everything else' (Leonardo DaVinci).

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Data availability

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