Revista Portuguesa de Cardiologia 41 (2022) 1033–1035

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

EDITORIAL COMMENT

And the quest continues...

E a busca continua...

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Available online 30 August 2022

Mitral regurgitation (MR) is one of the most common valve diseases in western countries. Its frequency and severity increase with age, and its presence is associated with worse prognosis.[1] The largest European echocardiography-based study reported MR in 15 501 patients (24%) of a total of 63 463 consecutive echocardiographic studies performed in 19 centers. The incidence of MR was higher than previously described, and significant MR representing 30% of the patients.[2]

Mitral regurgitation is not only a problem because of its prevalence but also because it is subject to medical inertia. In a recent nationwide study, 107 412 patients with MR that were admitted to French hospitals between 2014 and 2015, only 8% underwent surgery, the remaining 92% were treated under a conservative strategy. Hard endpoints as in-hospital mortality and one-year mortality were determined in the conservative arm. In this population, one-year mortality was 14%, and readmission rates (all-cause or heart failure) were high, but secondary MR (SMR) performed worse than primary MR (PMR) for one-year mortality 18% vs. 13% ($p<0.0001$) and one-year heart failure hospitalization 21% vs. 36% ($p<0.0001$). The mean cumulative cost of all readmissions following the index admission was 10 080±10 847 euros for the first hospital stay and readmissions were higher for SMR than for PMR (both $p<0.0001$). In this study, the annual cost was extrapolated to a value between 350 and 550 million euros (390-615 million US dollars), revealing a high health cost burden to society.[3] Strategies to improve overall MR management and outcomes are urgently needed.

First, we should clarify where is the inertia. In the diagnosis? In patient stratification? In the treatment approach/options?

In fact, diagnosis and quantification of MR is very demanding and most of the time it is not a case of inertia, but of lack of high-level imaging skills. Mitral valve anatomy is very complex with a variable three-dimensional (3D) saddle annular morphology with different dimensions according to different intravascular volume and hemodynamic status, in addition to the leaflets, the multiple tendinous chords and two papillary muscles, together posing significant challenges for the imager.[4] As treatment decisions are completely dependent on accurate diagnosis of both mechanism and severity of MR, the aim is to do it correctly.

Transthoracic echocardiography is the most used imaging test for MR and transesophageal echocardiography is often needed to define morphology and MR severity better. Ideally, MR would be measured by quantitative parameters along a continuous scale. Such parameters would include effective regurgitant orifice area (EROA), regurgitant volume (RVol), and regurgitant fraction (RF), which is the percentage of

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https://doi.org/10.1016/j.repc.2022.08.001

MR volume relative to total LV stroke volume. These values interact with each other in a complex way. For example, a given value of EROA could have a larger or smaller RVol depending on the driving velocity of flow across the valve and the duration of MR, which is often not holosystolic. A given RVol could have a different RF depending on the size and systolic function of the LV. Another pitfall we should beware of is that non-holosystolic MR is frequently overestimated when only single-frame measurements are used, such as EROA by proximal isovelocity surface area (PISA), vena contracta width, or vena contracta area (3D) and finally noncircular orifices and multiple orifices are challenging for quantification.[5] Therefore, there are often inconsistences between clinical and imaging findings, so patients should be immediately referred to a valve center where the experience and the high volume precludes misdiagnosis of severity.

Another hallmark of inertia, as previous mentioned, is the undertreatment, not only because in severe SMR an expressive number of patients had comorbidities and advanced age that prohibits surgical intervention, but also because it is not clear that the addition of mitral valve repair to surgical coronary artery bypass grafting has survival improvement.[6] Meanwhile, based on the results of the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial,[7] current European Society of Cardiology/European Association for Cardio-Thoracic Surgery practice guidelines recommend that when revascularization is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary mitral regurgitation and left ventricle ejection fraction (LVEF) >30% who remain symptomatic despite optimal medical management (including cardiac resynchronization therapy, if indicated) and who have a suitable valve morphology based on echocardiography, always avoiding futility.[8] The word futility is the cornerstone of this quest, as not all the transcatheter edge-to-edge repair (TEER) trials were shown to be beneficial. One example is the MITRA-FR (Multicentre Randomized Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) trial,[9] in which the transcatheter mitral valve repair and guideline-directed medical therapy did not lead to superior outcomes compared with medical therapy alone. The diametrically opposed results of the previous two landmark trials were the trigger for an exceptional discussion exposing the main differences and weakness of the two populations included. Two main differences between the trials were exposed: EROA was lower in MITRA-FR compared with COAPT (31 vs. 41 mm^2), and mean left ventricular end-diastolic diameter at baseline in MITRA-FR was 6.9 cm, while it was 6.2 cm in COAPT. They were the main drivers behind a change in paradigm and emergence of a new concept: proportionate and disproportionate MR.[10] This means that not all SMR is the same, and ultimately the degree of dilatation of the left ventricle and its proportionality to EROA probably dictate whether mitral valve intervention is likely to be beneficial or not.

Regarding this change of paradigm, the correct selection of patients who will benefit from TEER has become paramount, in other to avoid not only futile expenses but also frivolous patient procedures.

Presume et al., in the present study,[11] assessed the prognostic value of two different concepts of proportionality and their ability to improve MR stratification on top of the ASE guidelines. Two formulas were used: one proposed by Grayburn, et al.,[12] disproportionate SMR defined as $\frac{EROA}{LVEDV} > 0.14$ and other by Lopes, et al.,[13] disproportionate SMR whenever measured EROA > theoretical EROA (determined as $\frac{50\% \times LVEF \times LVEDV}{MitralVIT}$). The agreement between the formulas in the study was different as expected. The Presume et al. cohort included patients with LVEF < 50% (mean 33±9%) and the Grayburn formula was built only for patients with an LVEF around 30%, in contrast to the Lopes formula which is more versatile and covers all ranges of LVEF.

The disproportionality definition proposed by Lopes et al. seems to be more robust in the different spectrum of stratification as it was the only one that was able to predict all-cause mortality in the multivariate analysis (hazard ratio 1.5; 95% confidence interval 1.07-2.1, p=0.018) and improved the risk stratification of American Society of Echocardiography (ASE) SMR classification. A conservative approach and critical appraisal should always guide our practice, so validation studies to confirm this data are required.

At the end of the day, we should probably be discussing the validity of searching for EROA and RVol in SMR, which includes itself a high range of LVEDV and LVEF. The definition for severe mitral regurgitation endorsed by the American Heart Association/American College of Cardiology and ESC is defined as a RVol that exceeds half of the total stroke volume in both primary and secondary MR. Although derived from a volumetric measurement (50% of stroke volume), it is a dimensionless index that does not require allometric adjustments, unlike EROA or RVol. As previous mentioned, a value of 30 ml of RVol can be severe if the stroke volume is 60 ml or not if the stroke volume is 70 ml; it is only a number, which if taken out of context is of low value. We should note that not only EROA has important caveats but also stroke volume measured by echocardiography is not error-proof. Our question is: should we not use cardiac magnetic resonance more often as it is accurate, reproducible, and estimates volume data more reliably?[14]

Despite the promising new data, the quest for TEER patient selection continues...

Conflicts of interest

The author has no conflicts of interest to declare.

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