Markers of increased risk in primary mitral regurgitation

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Myxomatous degeneration is the most common etiology of primary mitral regurgitation (MR) in the developed world (1). Severe MR can impose significant hemodynamic stress on the left ventricle (LV). However, LV can remain in a compensated asymptomatic stage for long time with preserved ejection fraction (EF). After long period of time, EF drops and overt heart failure ensues (2). Mitral surgery is the cornerstone in management of severe MR to halt this process. Nonetheless, LV sustains subclinical structural and microscopic damage early before traditional indications for MV surgery is met (3). Current class I indications for MV surgery are development of symptoms or abnormal ejection fraction (4), and both of these conditions are associated with non-optimal postoperative outcomes. There is a growing concern that EF does not reflect true LV systolic function and it merely reflects ventricular ejection which is a fraction derived from end diastolic volume (EDV) (5). In conditions with supra-physiological EDV and reduced afterload such as severe MR, EF is doomed to be normal even in suboptimal LV performance. LV global longitudinal strain (LV-GLS), which measures myocardial systolic deformation, has been proposed to be more reflective of true LV systolic function (6). As a result to the aforementioned factors, timing of surgery in asymptomatic severe MR patients with preserved EF remains a challenging and a controversial decision (7). With the new advances in cardiac surgery and improvements in perioperative care, postoperative mortality in patients undergoing MV surgery in the last few years is less than 0.1%, with hospital stay as short as 5 days and more than 97% success rate in achieving trivial MR with MV repair (8), which argues for earlier intervention in patients with severe MR before it is too late.

Surrogate tools that can show LV subclinical dysfunction before EF drops and before symptoms develop are profoundly needed. Some markers suggested in the past included development of atrial fibrillation, or moderate to severe pulmonary hypertension with right ventricular systolic pressure (RVSP) >50 mmHg on echocardiogram (4). In a recent study by our group, we showed that the impact of RVSP in this population is progressive and not necessary limited to those with the highest baseline values (9). In our study cohort, every 10 mmHg increase in baseline RVSP above normal cutoff of 30 mmHg was associated with 23% increase in risk of long-term mortality in follow up (9). Pulmonary hypertension in mitral regurgitation usually is a result of high left atrial pressure, which is also associated with high LV end diastolic pressure (LVEDP). Rising LVEDP might suggest that compensatory mechanisms maintained by the LV are failing and overt LV dysfunction is eminent. Brain naturetic peptide (BNP) is a hormone released by the myocardial cells, and its elevation is an indication of elevated left atrial and ventricular pressures and was shown to have an important prognostic value in different cardiac diseases (10). In a study cohort of 548 severe MR asymptomatic patients with preserved EF, higher baseline RVSP and higher baseline BNP levels, both were independently associated with significant mortality over 7 years of follow up (11). Similarly, in a study by Alashi *et al*, higher baseline BNP level, worse LV- GLS and higher RVSP were all significantly associated with worse long-term survival in asymptomatic severe MR patients with preserved EF (12). Important to notice, in this study all patients underwent timely MV surgery according to current guidelines. More importantly, while higher BNP level and

worse LV-GLS independently predicted postoperative LV systolic dysfunction, higher baseline RVSP failed to do so (12). These findings would suggest that subclinical LV dysfunction evident by BNP and impaired GLS occurs even before pulmonary pressure start to rise.

Functional capacity is another important factor to consider in this population. It is important to notice that functional capacity does not necessary correlate with symptomatic status of the patient. In one study, 25% of asymptomatic severe MR patients with preserved EF had severely impaired functional capacity on cardiopulmonary exercise testing (13). In another study, one third of patients with same condition failed to achieve 100% of their age-gender predicted metabolic equivalents (METs) on exercise testing (14). In a recent study by our group, in asymptomatic severe MR patients with non-dilated LV (normal dimensions) and preserved EF, baseline LV-GLS and RVSP were the most important predictors of impaired functional capacity on exercise testing beyond known predictors (15). More importantly, in another study, baseline LV-GLS worse than (–21%) and functional capacity less than 100% of age-gender predicted METs were associated with significantly higher mortality over 8 years of follow up (16).

In conclusion, it seems that the timing of MV surgery recommended by current guidelines might be too late after LV systolic dysfunction already occurred. Potential markers that should be explored are LV-GLS, RVSP, BNP and functional capacity on exercise testing. A prospective study randomizing asymptomatic severe MR patients with normal LV dimensions and EF to either watchful waiting or early surgery based on these potential new markers is profoundly needed to determine the best strategy in managing severe MR.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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