Concomitant significant mitral regurgitation in patients with aortic valve stenosis undergoing valve replacement: Practical indications

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Abstract

Significant mitral regurgitation (MR) - either of structural or functional origin - is a frequent condition in patients with severe aortic stenosis (AS), candidate to aortic valve replacement (AVR), and raises the problem whether or not to intervene on mitral valve at the same time. Surgical risk related to the double valve intervention is still significantly higher compared to isolated AVR and international guidelines do not always give definite indications in the presence of multiple valve disease. Furthermore, the increasing diffusion of transcatheter aortic valve replacement for patients at high surgical risk has risen the problem of leaving the concomitant MR untreated. This review is an attempt to give a practical guide for the decision-making process about the treatment strategy of patients with concomitant severe AS and significant MR, analyzing the impact of a persistent MR on prognosis after surgical or transcatheter AVR, the main predictors of MR improvement after isolated AVR - according to the current literature – and displaying the emerging approach involving transcatheter treatment of both AS and MR.

Key words: aortic stenosis, mitral regurgitation, prognosis, TAVR, MitraClip

1. Introduction

Significant mitral regurgitation (MR) is a frequent condition in patients with severe aortic stenosis (AS) (Figure 1), candidate to aortic valve replacement (AVR), and raises the problem whether or not to intervene on mitral valve at the same time. ACC/AHA Guidelines give a clear indication to mitral valve repair/ replacement in patients undergoing cardiac surgery for other indications when MR is severe, while the indication is not as strong when MR is moderate1. Conversely, guidelines of the European Society of Cardiology (ESC) do not give a specific indication on multiple valve disease, but underscore how the decision should be based on a global assessment of the

Figure 1: In the upper panels, color-Doppler imaging of concomitant mitral regurgitation in a patient with severe aortic stenosis. In the left lower panel, the parasternal short axis view shows the severe sclerosis-calcification of the aortic cusps. In the right lower panel, continuous-wave Doppler shows a mean gradient across the stenotic aortic valve of 53.21 mmHg.
consequences of the different valve lesions and on the extra surgical risk rising from a combined valve intervention. Surgical risk itself is still a problem in combined aortic and mitral valve replacement since, despite its progressive reduction during the last decade, it still carries a conspicuously higher mortality compared to AVR alone. Moreover, the increasing diffusion of transcatheter aortic valve replacement (TAVR) for patients with high surgical risk has risen the problem of leaving the concomitant MR untreated, although new approaches involving transcatheter treatment of both AS and MR are now emerging.

The aim of this review is to analyze the main critical points to take into account during the decision-making process about the treatment strategy of patients with concomitant severe AS and significant MR.

2. Impact of significant MR on mortality in patients undergoing AVR

Seen the excess of surgical risk carried by a double valve surgery compared to isolated AVR, it is crucial to establish whether the impact of MR on mortality in patients undergoing isolated AVR is significant.

Several studies compared mortality in patients undergoing surgical AVR with and without significant MR (considered at least moderate or ++/++++): most of them showed an excess in mortality in patients with significant MR compared to those with no/trivial/mild MR (4-7), but some failed to demonstrate this association. A 2011 meta-analysis performed on 17 studies concluded that patients with moderate/severe MR had higher mortality compared to mild or no MR at 30 days (OR 0.41; CI at 95%: 0.24-0.72), and worse survival at 3 years (HR 0.49; CI at 95%: 0.35-0.69), 5 years (HR 0.46; CI at 95%: 0.34-0.61) and 10 years (HR 0.61; CI at 95%: 0.40-0.92) after AVR. More recently, the PARTNER study showed an increased mortality during a 24 months follow-up in patients with significant MR among 299 patients undergoing surgical AVR (HR 1.96; CI at 95%: 1.26-3.06).

In 2013 Coutinho et al. compared mortality in two groups of patients with severe AS and associated hemodynamically significant MR: one underwent AVR alone, the other underwent combined mitral and aortic valve surgery. This study failed to demonstrate a significant better survival in patients undergoing combined surgery; however, patients with persistent MR at discharge had significantly higher mortality compared to patients without persistent MR, underscoring the role of persistent MR on mortality after AVR. Lack of difference in survival between patients with isolated and combined valve surgery can be explained with the high rate of MR improvement in patients undergoing AVR alone (67.4%). However, absence of mitral surgery remained an independent predictor of MR persistence in this cohort of patients.

3. Significant MR and functional status in patients undergoing AVR

The impact of concomitant MR on the improvement of symptoms and quality of life after AVR is also of great interest. A 2011 study showed that severe MR was an independent predictor of poor treatment response to TAVR, with treatment response defined as improvement of at least one NYHA class 6 months after TAVR. In a study by Ruel et al., significant MR was associated with a higher incidence of heart failure symptoms in patients which had undergone AVR for AS, but only when it was associated with at least one risk factor (left atrial diameter >5 cm, peak aortic gradient >60 mm Hg, mean aortic gradient >40 mm Hg and atrial fibrillation). Takeda et al. showed a significantly higher rate of re-hospitalization for heart failure in patients with concomitant significant MR compared with non/trivial and, among patients with significant MR, a trend for a higher readmission rate for patients without any improvement in MR after AVR. On the other hand, the PARTNER study showed an improvement in NYHA functional class after both surgical AVR and TAVR which was independent of the concomitant MR.

Figure 2: Modified from Barbanti et al. (32). Fluoroscopic view of the CoreValve aortic prosthesis and the MitraClip correctly implanted after the double transcatheter approach.

Figure 3: Algorithm for the treatment of severe aortic stenosis with concomitant significant mitral regurgitation. AS: aortic stenosis; MR: mitral regurgitation; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement.
on the presence and severity of concomitant MR. A similar result emerged from a study by Toggweiler et al.\textsuperscript{12} on patients undergoing TAVR, with a general improvement in NYHA class regardless of MR grade.

4. Impact of AVR on concomitant MR: is there an improvement?

The question whether AVR itself is able to significantly improve the grade of MR is a point of paramount importance, since the decisions about the management of concomitant MR cannot prescind from the consideration that AVR itself could have a positive effect on it. In a meta-analysis by Harling et al.\textsuperscript{10} on patients undergoing surgical AVR, it seems to be a globally positive effect of AVR on MR grade, with an improvement in 55.5% of patients versus 37.7% in which MR remained unchanged and 6.8% worsened. The effect appeared to be even greater when only functional MR was taken into account (improvement in 60.8%), when only moderate MR was taken into account (improvement in 62.8%), with the highest rate of improvement in patients with functional moderate MR (83.1%).

The effect of TAVR on MR evolution was evaluated in the meta-analysis by Sannino et al.\textsuperscript{22}; a significant improvement was evident only at 3–6 months follow-up, but a non-significant trend toward MR grade reduction was present at 30-days and 1-year follow-up. The role of functional etiology as a predictor of MR improvement after TAVR is highlighted by Toggweiler et al.\textsuperscript{12} in a study on 478 patients. Depressed LV ejection fraction and larger LV diameters have also been associated with better improvement of MR\textsuperscript{7, 25, 26, 27}, while calcific degeneration of mitral valve\textsuperscript{25}, atrial fibrillation, large left atrial size and pulmonary arterial hypertension have been found to be associated with lack of improvement in MR after AVR\textsuperscript{28, 29, 30}. Furthermore, a 2010 study by Matsumura et al.\textsuperscript{31} identified preoperative tenting area, tenting height and mitral annulus area – measured by standard echocardiography - as independent predictors of persistent MR after AVR.

5. Percutaneous treatment of both aortic stenosis and mitral regurgitation: a new frontier for invasive cardiology.

The first case of transcatheter treatment of both AS and MR in the same patients was described by Barbanti et al. in 2011\textsuperscript{32} (Figure 2): the authors experienced a successful staged approach of TAVR and subsequent percutaneous mitral valve repair by MitraClip in two severely symptomatic patients with severe AS and MR at high risk for surgical treatment. Other authors have reported cases of successful combined percutaneous aortic and mitral intervention\textsuperscript{33–37}, but only 2 studies dealing with this issue are available at the moment\textsuperscript{28, 38}. Both of them confirmed the feasibility of the combined procedure and the ability to improve both the aortic valve area and MR severity, but the results of the follow-up were different between the two studied. Kische et al.\textsuperscript{38}, in fact, reported an improvement in NYHA class in all of the 12 patients who underwent the combined procedure at 6 months follow up, as well as an increased average walking distance at 6 minutes walking test. Conversely, in the study by Rudolph et al.\textsuperscript{39}, only 2 of the 8 patients clinically followed (median 208 days) had improved NYHA class, with 6 patients still in NYHA class III and only 2 in NYHA class II; 4 patients had also re-hospitalization during follow-up. More studies with a wider number of patients and longer follow-up are needed to establish whether there is a real benefit from the combined transcatheter approach of AS and MR.

6. Conclusion

Concomitant MR in patients undergoing AVR for severe AS represents an intriguing issue, which present practical implications. The management of these patients is not always supported by a precise indication in guidelines, and the gap in surgical risk between single and double valve operation is still important. In literature, significant MR is associated with higher mortality in patients undergoing AVR and, despite with a lower level of agreement between studies, also with a worse functional status. However, it has been shown that MR can significantly improve after isolated AVR or TAVR in a considerable portion of patients. Furthermore, it is noteworthy that when patients undergoing double valve intervention were compared with patients undergoing isolated AVR, the prognosis appeared to be linked to the improvement or persistence of MR rather than to the combined or isolated intervention. In the light of these data, the decision on whether to perform double mitral/aortic valve intervention, isolated surgical AVR or TAVR should be also based, in addition to the evaluation of the individual surgical risk of the patients and the severity of MR, on the identification of the predictors of MR improvement after isolated AVR/TAVR (Table 1). Thus, a patient with functional MR associated with depressed LV ejection fraction and enlarged LV diameters will most likely benefit of an improvement in MR after an isolated AVR or TAVI, especially in absence of concomitant atrial fibrillation and pulmonary arterial hypertension, whereas a patient with preserved LV ejection fraction and organic MR, mainly due to structural alteration of mitral leaflets like fibro-calcifications, will have a lower probability to improve MR grade after isolated AVR, and could be addressed to a double valve surgery, after an accurate evaluation of surgical risk. For patients at high surgical risk, addressed to TAVR, the recent experiences of contemporary or subsequent transcatheter treatment of MR using MitraClip represent an intriguing perspective; yet, prognostic data available at the moment on this emerging combined approach are insufficient and conflicting, and larger trials are needed before it can be taken into account for a large-scale application. Based on the above mentioned assumptions we propose an algorithm (Figure 3) which is planned taking into account the nature of MR (organic or functional) and the surgical risk grade.

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