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STATE-OF-THE-ART PAPERS

Significant Mitral Regurgitation Left Untreated at the Time of Aortic Valve Replacement

A Comprehensive Review of a Frequent Entity in the Transcatheter Aortic Valve Replacement Era

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Significant mitral regurgitation (MR) is frequent in patients with severe aortic stenosis (AS). In these cases, concomitant mitral valve repair or replacement is usually performed at the time of surgical aortic valve replacement (SAVR). Transcatheter aortic valve replacement (TAVR) has recently been considered as an alternative for patients at high or prohibitive surgical risk. However, concomitant significant MR in this setting is typically left untreated. Moderate to severe MR after aortic valve replacement is therefore a relevant entity in the TAVR era. The purpose of this review is to present the current knowledge on the clinical impact and post-procedural evolution of concomitant significant MR in patients with severe AS who have undergone aortic valve replacement (SAVR and TAVR). This information could contribute to improving both the clinical decision-making process in and management of this challenging group of patients. (J Am Coll Cardiol 2014;63:2643–58) © 2014 by the American College of Cardiology Foundation

Aortic stenosis (AS) is the most prevalent valvular heart disease referred for treatment, and it is frequently associated with concomitant mitral regurgitation (MR) (1). Surgical aortic valve replacement (SAVR) is the standard treatment for symptomatic severe AS, and there is a general consensus that in the presence of severe MR, a double-valve operation is indicated (2,3). If MR is moderate, the decision of whether to perform a mitral intervention at the time of SAVR has to be carefully evaluated, given that a double-valve operation is associated with increased operative mortality (4,5). Although MR severity may decrease after isolated SAVR, it may not improve or even worsen in a substantial proportion of patients, and a subsequent mitral valve procedure is associated with increased operative risk in such cases (6).

Transcatheter aortic valve replacement (TAVR) has recently emerged as an alternative to SAVR or medical treatment for patients at high or prohibitive surgical risk, respectively (7). Concomitant significant MR in this setting is typically left untreated. The persistence of moderate to severe MR after TAVR is therefore a relatively new and important entity. The objective of this systematic review is to present the current state of knowledge on the prevalence, clinical impact, and evolution of concomitant significant MR in patients with severe AS who have undergone aortic valve replacement (AVR) (SAVR and TAVR). For this purpose, a literature search using PubMed, EMBASE, the Cochrane Library, and Internet-based sources of information on clinical trials (ClinicalTrials, tctmd, and theheart) was performed from November 2002 to September 2013 using "surgical, transcatheter, percutaneous, transfemoral, transapical aortic valve implantation, replacement and/or insertion, and mitral regurgitation and/or insufficiency" as subject headings.

Mitral Regurgitation Etiology, Mechanisms, and Assessment

There are multiple causes of MR, and a specific cause might induce regurgitation by different mechanisms

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Abbreviations and Acronyms

AS = aortic stenosis
AVR = aortic valve replacement
CI = confidence interval
HR = hazard ratio
LV = left ventricle
MR = mitral regurgitation
OR = odds ratio
SAVR = surgical aortic valve replacement
STS = Society of Thoracic Surgeons
TAVR = transcatheter aortic valve replacement

(Online Table 1). The mechanisms of MR are usually classified as organic (valve structurally abnormal) or functional (mitral valve is structurally normal, and the leaflet coaptation deficit is determined by ventricular remodeling) (8). The most common cause of organic MR is degenerative MR from myxomatous processes, or particularly in the elderly, calcification of the mitral apparatus. The most common cause of functional MR is ischemic cardiomyopathy, where the normal leaflets have a restricted motion, driven by tethering because of outward displacement of the left ventricular (LV) walls and papillary muscles. LV wall motion abnormalities may be focal, with a preserved ejection fraction, or global with various degrees of LV systolic dysfunction, geometry changes, and annular dilation. The variable combination of these factors involved in functional MR genesis can explain the heterogeneous response in MR evolution after a given intervention. In addition, a combination of MR etiologies can be seen in many elderly patients with coronary artery disease or cardiomyopathy. Although the concentric LV remodeling seen in isolated compensated AS is not typically associated with functional MR, various factors can influence the presence and severity of functional MR in this population, including the high prevalence of coronary artery disease with subsequent ischemic MR, the LV dilation seen in end-stage AS, and/or with associated aortic regurgitation. The marked increase in the LV-left atrial pressure gradient associated with severe AS can also contribute to increase the driving force through the regurgitant orifice area. Hence, the possibility of mixed etiologies has to be taken into consideration when evaluating MR severity and its potential regression after AVR.

The echocardiographic evaluation of the severity of MR is complex, and the integration of various echocardiographic methods, including quantitative measurements, is recommended in clinical practice (Online Table 2) (2,3,9). An effective regurgitant orifice is less variable compared with regurgitant volume in the presence of increased afterload, and it should therefore be systematically measured in cases of AS with concomitant MR. In addition, the parameters and the prognostic implication of a similar degree of volume overload vary depending on the MR etiology and the underlying LV substrate (Online Table 2) (10,11). In particular, an effective regurgitant orifice area $\geq$0.2 cm^2 and a regurgitant volume $\geq$30 ml/beat have been associated with poorer outcomes in the context of functional ischemic MR (11), but functional MR with a regurgitant orifice area between 0.2 and 0.4 cm^2 can be graded as severe in the presence of other echocardiographic signs of regurgitation severity.

SAVR in the Presence of Significant MR

Most surgical studies to date have focused on single valve disease; data on multivalve disease are scarce (12). The European and American guidelines on the management of valvular heart disease do not provide specific recommendations for the management of multivalvular disease (2,3). There is a general consensus that a double-valve intervention should be performed in the presence of severe MR, especially in cases of organic etiology. However, the surgical management of moderate to severe functional MR in the setting of severe AS remains controversial.

Double mitral and aortic valve surgeries have been associated with a higher mortality rate compared with isolated SAVR (4,5,13–15). In the Euro Heart Survey on Valvular Heart Disease, perioperative mortality in patients with multivalve surgery was 6.5% compared with 2.7% for isolated SAVR and 4.3% for SAVR combined with coronary artery bypass grafting (4). The latest report of the Society of Thoracic Surgeons (STS) showed a rate of 3.5% for double-valve surgery in the past decade (5). Although the ratio of double-valve interventions/SAVR has decreased slightly in the last few years, the total number of double-valve procedures has constantly increased over the last decade (Online Fig. 1). The perioperative mortality after mitral-aortic valve replacement ranged from 8.2% to as much as 11%, whereas the mortality rate after isolated SAVR was between 2.3% and 3.5% (5).

The decision to intervene in MR in the setting of severe AS depends on the severity and the etiology of MR. Although no series of patients with severe MR left untreated at the time of SAVR have been reported, and a higher perioperative mortality has been associated with double-valve interventions, combined aortic and mitral valve surgery seems to be justified in the presence of severe MR (either functional or organic) (12). Although retrospective studies have suggested better outcomes with MR repair versus replacement for ischemic MR (16), this has not been confirmed in a recent randomized trial (17). The use of mitral valve repair techniques is preferred for organic MR, when feasible, due to lower perioperative mortality, improved survival, and better preservation of post-operative LV function (3). However, mitral valve repair options may be very limited in the presence of rheumatic lesions, severe valve prolapse, or extensive leaflet or annulus calcification (18). When repair is not possible, mitral valve replacement with preservation of the subvalvular apparatus is recommended. However, valve replacement can be difficult and of high risk in the presence of severe annular calcification, and this may be a further incentive not to intervene on the mitral valve in such cases.

There is still some controversy regarding the optimal surgical strategy when significant MR is less than severe. Although data about moderate organic MR left untreated at the time of SAVR is very limited (19,20), most investigators support a double-valve operation (21). Barreiro et al. (19)