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EDITORIAL COMMENT

The Challenge of Timing Surgery in Degenerative Mitral Regurgitation

Is B-Type Natriuretic Peptide the Solution?*

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Degenerative mitral regurgitation (MR) with prolapse or flail of mitral leaflets has become the most frequent cause of severe primary MR in Europe and North America (1,2). In its chronic stage, even severe MR is tolerated very well for a surprisingly long time, and patients may remain asymptomatic for years. During this compensated stage of disease, pre-load, afterload, and both contractility and ejection fraction of the left ventricle (LV) remain normal, and the total stroke volume is increased as a result of the compensatory enlargement of the end-diastolic LV volume, which is enabled by an adaptive process of the LV myocardium (3). However, these compensatory adaptions of the LV eventually fail, and patients enter via a still-reversible transition phase into a decompensated stage where myocardial damage becomes irreversible (3). Without timely relief of the burden of volume overload to the LV and left atrium by surgical correction of MR, patients develop left heart failure, atrial fibrillation, and secondary pulmonary hypertension with eventually right heart failure (1,2). Considering the high long-term morbidity and mortality of degenerative MR on the one hand and the increasingly good results of surgical valve repair on the other, intervention has become recommended earlier and earlier over the years. Two critical questions remain, however: what is early enough, and what may possibly be too early? Observational studies have demonstrated that patients who already have severe symptoms, reduced LV function, markedly enlarged LVs or left atria, severe pulmonary hypertension, or persistent atrial fibrillation have a worse outcome after surgery compared with those treated before this stage (1,2). Many of these data were collected at times when surgical techniques were different, and the results were worse than what can be achieved today. Despite this fact and although prospective studies that compare treatment strategies are lacking, on the basis of these observational data, current guidelines recommend surgery when mild symptoms occur, and in absence of any symptoms, when LV ejection fraction declines below 60% or LV end-systolic diameter exceeds 45 mm. In asymptomatic patients with low surgical risk and high likelihood of successful valve repair it is recommended that surgery should be considered when LV end-systolic diameter exceeds 40 mm in the presence of flail leaflet, when atrial fibrillation occurs, or when systolic pulmonary artery pressure exceeds 50 mm Hg. In patients without these criteria, surgery may be considered when left atrial enlargement is severe despite sinus rhythm or when exercise echocardiography reveals pulmonary hypertension (1,2). Although these recommendations in fact indicate surgery early, they have been questioned, and surgical intervention has been suggested in asymptomatic patients with low surgical risk and high likelihood of reparability even in the absence of such triggers (4,5). The benefit of surgery in these patients remains, questionable, however. Studies suggesting such a strategy were retrospective analyses of observational data. Adjustment for differences in patient characteristics was attempted when comparing surgical and conservative strategies in these retrospective analyses, but this remains limited. The fact that

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patients who have been operated on without any symptoms have been reported to have a better survival than the general population (6) indicates selection bias. The decision to operate in studies favoring early surgery in the absence of guideline-defined triggers was left to the discretion of the attending physicians, and the actual reasons remain unclear. It is therefore almost impossible to provide comparable patient cohorts in such studies. In addition, the "conservatively treated group" included patients who were not closely followed and were not operated on as soon as recommended triggers occurred. The most recent paper (5) that sought to compare immediate surgery and watchful waiting could, indeed, not find a difference in overall mortality. Notably, there was a markedly higher rate of atrial fibrillation and more fatal strokes in the "early surgery" group. Even in highly experienced centers, the risk of surgery is not zero. There also remains the risk of unsuccessful repair and the necessity of valve replacement with all of its long-term risks. Endocarditis and reoperations must be considered, too. Thus, there is no question that surgery can indeed also be too early and, in some patients, not only of no benefit, but actually harmful. Surgery in asymptomatic patients without clear signs of volume overload becomes even more worrisome when considering recent studies that reported frequent overestimation of MR severity by echocardiography when comparing it with cardiac magnetic resonance (7).

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Better tools to define the optimal time for surgery in degenerative MR are therefore indeed highly desirable. In this regard, the study by Clavel et al. (8) in this issue of the *Journal* deserves particular interest. Several previous studies have already demonstrated that plasma levels of B-type natriuretic peptide (BNP) increase with severity of MR, LV remodeling, and symptoms, and may predict outcome (9–11). Therefore, there is great hope that BNP can improve the timing of surgery. However, the currently available data were considered insufficient by guideline task forces to justify a recommendation for decision making in primary MR (1,2). Clavel et al. (8) now present data from a very large, multicenter registry including 1,331 consecutive patients with degenerative MR in whom BNP values were available. To account for the effects of age, sex, and assay on measurements, they calculated BNPratios, the ratio of actual measurements to upper limits of normal for age, sex, and assay. Although BNPratio was a powerful independent predictor of overall mortality, absolute BNP was not. Higher BNP activation was associated with higher mortality. Excess mortality with BNP activation was particularly, but not only found in severe MR. Finally, BNP activation did not predict a higher long-term mortality in those patients who underwent initial surgery (i.e., within 3 months of BNP measurement).

How can this study help us to optimize timing of surgery in primary MR? The strongest finding is certainly that patients without BNP activation have excellent outcomes. Thus, in asymptomatic patients who have not reached currently recommended cut-offs for LVEF and LV dimensions or developed atrial fibrillation or pulmonary hypertension, a normal BNP is reassuring that further conservative follow-up is safe and surgery is not indicated. The second important finding may be that it is not too late to achieve a good long-term outcome with surgery when patients present already with BNP activation. What remains more difficult to answer from the results of this study is whether BNP activation in general or a certain degree of activation is an indication for surgery by itself even if the other currently accepted triggers for intervention are not present. The strength of the study is the large patient cohort. However, the multicenter, registry-like design of this observational study brings the drawback of limited details in data and lack of control for the actual patient management, which was left to the discretion of the treating physicians. The adherence to the guidelines during follow-up remains uncertain. In addition, the study population is heterogeneous. The majority of patients who underwent immediate surgery were symptomatic. Surprisingly, 51% of those managed conservatively also had dyspnea, 45% were on diuretic agents, and 19% had atrial fibrillation. Although the authors state that dyspnea and atrial fibrillation may have been judged by the treating physician to have other reasons than MR, such a high percentage of symptomatic patients is disturbing and is problematic for solid data interpretation. The fact that 58% of patients had hypertension may provide an explanation for symptoms besides MR, but may also be a reason for BNP activation. In a subgroup analysis, the authors selected 287 asymptomatic patients without guideline recommended class I or IIa triggers for surgery who were followed conservatively. Even in this group, BNP activation remained independently associated with mortality, and even with this information, the data interpretation with regard to conclusions on BNP's effect on patient management remains difficult. Because patients who underwent surgery after 3 months of medical follow-up ("initial medical treatment group") were censored at the time of surgery and only follow-up under