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Surgical Therapy for Mitral Regurgitation: The Key to Preventing Heart Failure?

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Abstract

Five million Americans suffer from heart failure (HF). Despite innovative new pharmacologic and device therapies, the 5-year mortality rate for patients remains near 50%. Conservatively, 300,000 patients with HF also have severe functional mitral regurgitation. Over the past decade, the surgical approach to these patients has become more aggressive because the extent of the problem has become widely recognized, and surgeon familiarity with annuloplasty techniques has increased. Although clinical experience and enthusiasm have resulted in an expansion of literature, the role that mitral valve repair surgery plays in the treatment of HF is not fully established. In this article, we review the existing data on the efficacy of mitral valve surgery in HF patients. Specifically, we will review the available data regarding the effect of mitral valve surgery on longevity, ventricular remodeling, and symptoms. No randomized prospective data are available, but careful analysis of existing retrospective studies allows important conclusions to be made.

Introduction

Functional mitral regurgitation (FMR) is defined as valvular insufficiency that occurs when the leaflets and chordal structures are normal, but the valve is rendered incompetent due to distortion of the subvalvular apparatus associated with ventricular remodeling. Remodeling may be caused by a myocardial infarction (ie, ischemic mitral regurgitation [IMR]) or a generalized nonischemic myocardial injury. In this review, we will use FMR as a general term to indicate mitral regurgitation (MR) of ischemic and nonischemic etiology and make the distinction of IMR when the data under consideration resulted from a study of only ischemic patients.

Over the past decade, as the awareness of the high incidence of MR in patients with heart failure (HF) has rapidly grown, there has been increasing interest in FMR as a potential surgical target in patients with end-stage HF. Increased application of mitral valve repair (MVR) surgery has been stimulated by growing surgeon familiarity with basic valvuloplasty techniques (ie, ring annuloplasty placement) and improved surgical outcomes in patients with severely depressed left ventricular (LV) function.

Approximately 5 million Americans suffer from HF [1], and it has been estimated that 40% to 50% of these patients have some degree of MR. In 15% to 30% of cases, the MR is

graded as moderate to severe (approximately 300,000 HF patients with severe MR) [2]. In patients with impaired LV function, even a mild degree of MR is associated with decreased longevity, and increasing severity of MR progressively worsens 5-year survival statistics [2]. These sobering data and the established efficacy of mitral valve surgery in altering the natural history of structural mitral valve disease led Bolling et al. [3-8,9•] at the University of Michigan to first propose and then consistently apply mitral valvuloplasty as a treatment for end-stage HF patients with significant FMR. Clinical data specifically focused on the large IMR subpopulation of FMR that has also begun to emerge.

There are no significant, prospective, randomized trials evaluating the efficacy of MVR over medical management or revascularization alone. Such trials are currently being developed as part of the recently funded United States National Institutes of Health Networks for both HF and cardiac surgery. Until these trials are completed, definitive conclusions regarding the place of mitral valve surgery in the treatment of HF will not be possible. However, there are a number of large and reasonably well-done retrospective studies that foreshadow what may be expected from the planned definitive clinical studies.

We will review the existing data on the efficacy of MVR for treating HF patients with significant FMR. Specifically, the data will be assessed regarding the effect of MVR on longevity, ventricular remodeling, and symptoms.

Results of MVR for FMR: Longevity

MVR or replacement in HF currently requires open heart surgery and is associated with a perioperative mortality rate of 1.6% to 8% at centers with expertise in treating both mitral valve disease and HF [9•,10••,11•]. This wide range in operative mortality likely reflects recent improvements in perioperative management of patients with severe LV dysfunction, as reflected by the 1.6% operative mortality reported in the “MVR stratum” of the Acorn clinical trial [11•]. This was a multicenter trial, which was recently completed over a relatively short time period and primarily involved patients with nonischemic HF. Single-center series reporting on IMR patients typically document higher mortality rates (5%–10%), suggesting that such patients may be at higher risk, especially when concomitant myocardial revascularization is required [10••].

There are no randomized and controlled data to assess the efficacy of mitral valve surgery in improving longevity in HF patients; however, during the past 7 years, five studies have been published that are of sufficient quality to allow some reasonably certain conclusions to be drawn. In 2001, Gillinov et al. [12] reported the Cleveland Clinic’s experience with MVR and replacement for IMR. The study was well done in that it involved a large number of patients, rigidly defined IMR, and had excellent patient follow-up. The authors’ primary goal was to determine whether valve repair is preferable to replacement in patients with IMR; although it was not explicitly stated, their obvious bias was that some type of valvular intervention was generally indicated. No attempt was made to compare valve intervention with patients treated medically who had IMR of similar severity. The 5-year survival for all patients in this study was near 50%, which is consistent with what would be expected with medical management [13].

Most patients who undergo MVR for IMR have concomitant myocardial revascularization [10•,14-16, 17•]. This is a powerful confounding covariate because revascularization of hibernating myocardium has been demonstrated to have a pronounced salutary effect on LV size, LV function, and long-term outcomes [18]. Therefore, it is essential to control this parameter in retrospective analyses.

Three recent studies have used rigorous retrospective propensity analysis to develop acceptable control groups to compare patients with moderate to severe IMR having surgical revascularization and concomitant MVR with those having revascularization alone. All three studies were large and utilized a meticulous definition of IMR. In all reports, no survival benefit could be attributed to the valve intervention beyond what was obtained with revascularization alone [14,15,17•].

The largest and most recent of these studies was from the Cleveland Clinic Foundation by Mihaljevic et al. [17•], which reported on 390 patients who came to surgery for myocardial revascularization with at least 3+ MR. Two-hundred and ninety had revascularization and undersized mitral annuloplasty; 100 had revascularization alone. Groups were propensity-matched using demographics, extent of coronary disease, regional wall motion, and quantitative echocardiography.

Survival, echocardiographic severity of MR, and New York Heart Association (NYHA) functional class were compared. One-, 5-, and 10-year survival were 88%, 75%, and 47% after revascularization alone and 92%, 74%, and 39% after revascularization and MVR ($P = 0.6$). Patients undergoing revascularization alone were more likely to have more than 3+ postoperative MR than those undergoing revascularization and MVR (48% vs 12% at 1 year; $P = 0.0001$). The NYHA functional class substantially improved in both groups, and remained so over time. After 5 years, 25% of both groups were in NYHA functional class III/IV.

The University of Michigan group has championed the use of MVR in patients with end-stage HF and FMR. Early reports from this group demonstrated a low perioperative mortality rate, but conclusions regarding efficacy were difficult to make because of a lack of a control group [3,6]. Recently, Wu et al. [9•] updated the University of Michigan experience. These authors retrospectively analyzed consecutive patients with significant MR and LV systolic dysfunction on echocardiography between 1995 and 2002. Cox regression analysis, including MVR as a time-dependent covariate, and propensity scoring to adjust for differing probabilities of undergoing MVR were used to identify predictors of death, LV assist device implantation, and heart transplantation. Of 682 patients identified, 419 were deemed surgical candidates; 126 underwent MVR. In this analysis, there was no clearly demonstrable mortality benefit conferred by MVR for significant MR with severe LV dysfunction. This conclusion persisted even after the removal of patients with ischemic HF.

Results of MVR for FMR: LV Remodeling

Data on how the relief of FMR reverses or limits the progression of ventricular remodeling in HF patients are limited. This is due to a general failure to systematically collect quantitative echocardiographic data in both the preoperative and postoperative time periods.

Braun et al. [10••,19,20] from the University of Leiden are a notable exception; these authors followed a cohort of IMR patients who were treated with a standardized surgical approach that used revascularization and undersized annuloplasty. This work is notable for its meticulous quantitative follow-up assessment of ventricular size and MR. In the most recent report [10••] on this cohort, 100 consecutive IMR patients underwent restrictive mitral annuloplasty (stringent downsizing by two ring sizes; median size, 26 mm) and coronary revascularization. Survivors were clinically and echocardiographically assessed at intermediate (18 months) and late (mean, 46 months) follow-up. Early mortality was 8%, and late mortality was 18%. Actuarial 1-, 3-, and 5-year survival rates were 87%, 80%, and 71%. Preoperative LV end-diastolic diameter (LVEDD) greater than 65 mm correlated with increased early and late mortality. Five-year survival rate for patients with LVEDD of 65 mm or less was 80% versus 49% for LVEDD greater than 65 mm ($P = 0.002$). MR was more than 2+ in 15% of patients at late follow-up. LV reverse remodeling was sustained with time for the group with LVEDD of 65 mm or less. Late deaths did not show intermediate term systolic LV reverse remodeling, indicating a more extensive intrinsic LV abnormality. The survival rates reported in this study are very similar to those reported by Mihaljevic et al. [17••] from the Cleveland Clinic and suggest that survival in this group would have been similar with revascularization alone. Unique to this study is the stratification of responders and nonresponders by preoperative LV size. These types of data will be helpful in selecting patients with FMR who are most likely to respond to MVR; however, it would suggest that MVR is not efficacious for the large fraction of HF with MR and ventricles greater than 65 mm.

Acker et al. [11•] recently presented the results of a prospective, randomized, multicenter trial to assess the efficacy of mitral valve surgery (MVR or replacement) with and without the CorCap cardiac support device (Acorn Cardiovascular, St. Paul, MN) in patients with NYHA class II to IV HF. The report focused primarily on the 102 patients who had isolated MVR or replacement (no cardiac support device). The patients enrolled in this study had large hearts with an average LV end-diastolic volume (LVEDV) of 270 cm³ and an average LVEDD of 70 mm. At 18 months, follow-up LVEDV decreased 40 cm³ on average in the MVR only group. Survival in this group was 85% at 24 months. Recurrence of 2+ MR was 15% at 12 months. This study is important because it represents a first attempt to study MVR in HF patients in a prospective and randomized fashion. The data also suggest that modest LV remodeling can be affected by MVR in dilated hearts. This trial was different from other studies of FMR because the majority of the patients were female (54.4%) with a large percentage of nonwhite minorities (39.9%). Most patients were in NYHA class III (71.5%), with 23.3% in class II and 5.2% in class IV. The cause of HF was idiopathic in most patients; only 12 patients (6.2%) had ischemic heart disease.

Results of MVR for FMR: Symptoms

There is widespread belief, based on extensive empiric clinical experience, that MVR has a beneficial effect on symptomatic HF; however, quantitative data supporting this conclusion are limited. Most of the studies already report improvement in functional class with MVR and concomitant revascularization, but, as already indicated, the relative contribution of revascularization to this salutary effect is likely quite high.

The mitral valve stratum from the Acorn trial is unique among FMR studies in that it reports semiquantitative data regarding functional status [11•]. These data are supportive of the efficacy of MVR in HF patients. Overall scores in the Minnesota Living with HF questionnaire decreased significantly at 3, 6, 12, 18, and 24 months, consistent with an improvement in quality of life. Improvements were similarly observed with the Short Form 36, a general quality-of-life instrument, with significant improvements in the general health domain at 3, 6, and 12 months. NYHA functional class also improved. The baseline NYHA class of 2.82 was reduced to 2.25 at 24 months ($P = 0.0001$). Exercise performance, as measured by the 6-minute walk test, also increased significantly in the MVR group. There were no significant changes in peak oxygen consumption related to MVR.

How Can These Findings Be Explained?

Although the most recently available data suggest that there may be a potential benefit of MVR in properly selected HF patients with regard to functional status and reverse remodeling, there are little data to support that the procedure improves longevity for most patients with HF. Given the success of mitral valve surgery for degenerative, rheumatic, and congenital disease, how can we explain the seemingly paradoxical results of mitral valve surgery for FMR?

One possibility is that current repair techniques are not durable, and recurrent MR limits efficacy of the procedure. This hypothesis has been difficult to assess because even short-term echocardiographic follow-up has not been routinely reported. Three studies were recently published suggesting there is a high rate of early recurrent MR after ring annuloplasty for IMR. Tahta et al. [21] reported on 100 patients who had repair with a complete flexible annuloplasty ring. The mean followup period was 36 months. Follow-up transesophageal echocardiography on 82% of patients showed 0 to trace MR in 42% of patients, grade 1+ MR in 29%, 2+ MR in 24%, and 3+ to 4+ MR in 5%. McGee et al. [22] from the Cleveland Clinic reported on 585 patients who had repair for IMR with three different annuloplasty devices over a 17-year period. During the first 6 months after repair, the proportion of patients with 0 or 1+ MR decreased from 71% to 41%, whereas the proportion with 3+ or 4+ MR increased from 13% to 28%; the regurgitation grade was stable thereafter. More recently, Serri et al. [23] reported their experience in 78 IMR patients treated for MVR. This study is significant for its relatively long follow-up and the 94% success rate in obtaining long-term echocardiographic data. These authors demonstrated that recurrent moderate MR (2+) was present in 37% of patients, and severe MR (3+ to 4+) was present in 20% of patients at mean follow-up of 28 months. Even the most recent studies reported by Braun et al. [10••] and Acker et al. [11•], in which meticulous attention was paid to appropriately undersizing the annuloplasty device recurrence of significant MR, still occurred in 15% of the patients.

Another more problematic hypothesis may help to explain the difficulty in demonstrating survival or remodeling benefit for MVR in HF patients. It is possible that slowly progressive MR represents a relatively mild stimulus for remodeling that takes years to impact the ventricle, whereas a moderately sized myocardial infarction is an intense and immediate stimulus for remodeling, in which the order of magnitudes are more severe. Additionally,

unlike structural mitral valve disease, FMR is notoriously dependent on loading conditions and activity levels [24,25]. It is possible that this waxing and waning characteristic further decreases the impetus for remodeling that is imposed on the ventricle by FMR.

Conclusions

There is no doubt that the presence of almost any degree of FMR in HF patients is a poor prognostic sign, and increasing degrees of MR are associated with progressively worse survival statistics. However, as we have demonstrated, there are little data suggesting that MVR increases longevity in these patients. The data regarding MVR effects on remodeling and symptoms are limited, but the most recent data suggest small but significant changes, which can be achieved in selected (LVEDD < 65 mm) IMR patients and in patients with nonischemic HF.

These conclusions are somewhat sobering for surgeons and cardiologists alike, but it must be remembered that they are primarily the result of retrospective and uncontrolled data that are generally very incomplete. It seems likely that a properly designed prospective study will identify patient groups that derive significant survival and/or symptomatic benefit from mitral intervention for FMR. Given the vast and rapidly growing number of HF patients with FMR, such a randomized study needs to be designed and implemented as soon as possible. There are few issues in the care of HF patients, at least from a surgical perspective, that are more pressing.

Acknowledgments

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