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Secondary mitral regurgitation (part 2): deliberations on mitral surgery and transcatheter repair

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ABSTRACT

Secondary mitral regurgitation (MR) develops as a consequence of postinfarction remodelling of the ventricle or other causes of left ventricular (LV) dilatation and dysfunction. The presence of MR amplifies the poor prognosis of the failing ventricle, but it has not been established whether the adverse outcomes stem from the MR or whether the MR is simply a marker of progressive LV dysfunction. In this article, an attempt will be made to clarify the clinical impact of mitral surgery and transcatheter repair in patients with secondary MR. Observational studies indicate symptomatic improvement, but the results of randomised trials are mixed. Furthermore, neither mitral surgery nor transcatheter repair consistently leads to reversal of the adverse LV remodelling. There is, however, general agreement that these procedures do not have a salutary effect on survival. Certainly mitral surgery and transcatheter repair can substantially reduce the mitral regurgitant flow, but inconsistencies and uncertainties regarding clinical outcomes persist in the published literature. Some such problems could be resolved by utilisation of more accurate and reproducible imaging modalities in randomised studies of patients who are most likely to benefit from a reduction in the regurgitant volume—namely those with the most severe MR.

INTRODUCTION

Secondary mitral regurgitation (MR) is associated with a heightened morbidity and mortality in patients with ischaemic and non-ischaemic cardiomyopathies.[1–5] In such patients with left ventricular (LV) dysfunction and dilatation, MR is an independent predictor of adverse outcomes. Moreover, adverse outcomes tend to increase in concert with the severity of MR. Therefore, it seems reasonable to assume that successful correction of the MR should reduce the untoward effects of the regurgitant lesion. Indeed, the rationale for surgical or transcatheter correction of the MR is based largely on the notion that the regurgitant volume (RegV) contributes significantly to the functional impairment and poor prognosis of secondary MR, and that correction of the MR promotes a reversal of adverse LV remodelling, a reduction in symptoms and potentially a survival benefit. Such salutary results might very well be possible, but only if the haemodynamic burden imposed by the MR causes or contributes to the LV dysfunction and the congestive low-output state that is typically seen in patients with severe secondary MR. Unfortunately, it has not been established whether the worse outcomes stem from the MR per se or whether the MR is simply a marker for adverse LV remodelling. For these and other reasons, if mitral surgery or transcatheter repair is considered, it is important to make reliable assessments of the severity of the MR and to dissect out the contributions of the RegV from those of the LV dysfunction.[6]

In this article, emphasising secondary MR, results of mitral surgery and transcatheter repair will be summarised and scrutinised, and an attempt will be made to clarify the clinical impact of these surgical and transcatheter procedures.

Guidelines

The American Heart Association /American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC) guidelines for the management of valvular heart disease acknowledge a limited potential for a survival benefit of mitral surgery in secondary MR, but they recognise a tendency for symptomatic improvement in many patients.[7 8] Accordingly, mitral surgery is not 'recommended' in secondary MR. However, the AHA/ACC indicates that mitral surgery may be 'reasonable' in patients with severe chronic MR who are undergoing coronary artery bypass grafting (CABG) or aortic valve replacement (class IIa indication)[7]; the ESC provides a class I or IIa indication depending on whether the ejection fraction (EF) is above or below 30%.[8] In the absence of CABG, mitral surgery may be 'considered' in patients with severe chronic MR if they remain severely symptomatic despite optimal medical treatment (class IIb indication).[7 8] Surgery for moderate MR may be 'considered' only in patients undergoing other cardiac surgery (class IIb indication). The ESC guidelines indicate that a transcatheter mitral clip repair may be 'considered' in patients with severe secondary MR (class IIb indication).[8] The AHA/ACC valve guidelines do not comment on this procedure (pending randomised clinical trials). The ACC/AHA heart failure guidelines indicate that transcatheter mitral valve repair or mitral valve surgery for functional MR is of uncertain benefit, and should only be 'considered' in carefully selected patients with a background of optimal medical treatment (class IIb indication).[9]

MANAGEMENT

Medical management of secondary MR includes standard guideline-directed medical treatment (GDMT) of LV dysfunction. The guidelines indicate that mitral surgery or transcatheter repair should be contemplated only in patients with

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severe secondary MR who remain symptomatic despite optimal medical treatment.

Mitral surgery and CABG

Patients with secondary (ischaemic) MR require evaluation for CABG and if the MR is judged to be severe, attention can also be directed towards the mitral valve and potentially mitral surgery. Treatment directed at both coronary disease and MR would seem to be a logical approach. If the MR fundamentally contributes to the LV dysfunction, its correction should provide salutary clinical benefits.

Observational studies

A relatively large study of patients with moderate or severe MR indicated that mitral valve surgery 'may improve survival' in a subgroup undergoing the combined procedure.[10] In the per-protocol analysis, there were 22 deaths (52%) among 42 patients with CABG alone and 21 deaths (43%) among 49 patients who underwent CABG with mitral surgery; this difference became significant only after adjustment for other prognostic baseline variables. In another study of 119 symptomatic patients (most had moderate MR), those with CABG alone (n=51) and those with CABG plus mitral surgery (n=68) exhibited reductions in LV end-systolic volume (ESV) and increases in the EF.[11] However, there was no significant difference in the degree of improvement in the ESV or EF between the two groups. The group with the combined procedure had greater improvement in functional status and a reduction in hospitalisations, but there was no difference in survival between the two groups. Several other observational studies also failed to find a survival benefit of mitral surgery when combined with CABG.[12–14]

Randomised studies

The results of prospective randomised studies are summarised in box 1. In two relatively small studies of patients with moderate MR, there was a greater reduction in ESV and more symptomatic improvement in patients undergoing CABG with mitral surgery compared with those with CABG alone.[15 16] Neither of these studies reported a difference in survival between the two groups. A larger trial included 301 patients with moderate MR.[17 18] Both groups (CABG with mitral surgery and CABG alone) showed a decrease in ESV and an increase in EF, but the decrease in ESV (the primary end point) was not significantly different in the two groups. After 2 years, recurrent MR (moderate or severe) was seen in 11% of those with the combined procedure. Self-reported exercise capacity tended to be better with CABG plus mitral surgery, but other measures of quality of life were similar in the two groups. Survival after 2 years was virtually equal with CABG plus mitral surgery versus CABG alone (90% and 89%).

Comment

Mitral surgery in secondary MR can reduce the severity of regurgitation, but this ostensible benefit is not consistently associated with a reversal of the adverse LV remodelling, nor is it consistently associated with greater improvement in functional status. This might have been expected because most of the patients in these studies had less than severe MR. It should be acknowledged, however, that the study incorporating cardiac MRI and objective measures of functional impairment did uncover significant differences in remodelling and exercise capacity.[16] These methods are more reliable than those used in the other studies presented in box 1. Such methods should be applied in future studies that include only patients with severe

Box 1 Randomised studies of surgical intervention in secondary mitral regurgitation.

CABG alone versus CABG plus mitral surgery[15] (n=102, moderate MR

Primary end points

- NYHA class improved in both groups (more with CABG plus vs CABG alone).
- Reversal of the adverse LV remodelling was greater with CABG plus versus CABG alone.

Other results

- Survival similar in the two groups (98% CABG alone vs 96% with CABG plus).
- EF increased more with CABG plus versus CABG alone (6 vs 2 units).
- Persistent/recurrent MR more frequent with CABG alone versus CABG plus (60% vs 8%).

CABG alone versus CABG plus mitral surgery[16] (n=73, moderate MR)

Primary end point

- Peak VO_2 during exercise increased more with CABG plus versus CABG alone (22% vs 5%).

Other results

- Survival was similar in the two groups (95% with CABG alone vs 91% with CABG plus).
- ESV decreased more with CABG plus versus CABG alone (28% vs 6%).
- Persistent/recurrent MR more frequent with CABG alone (23% vs 7%).
- Regurgitant volume decreased more with CABG plus versus CABG alone (28 vs 9 mL).
- NYHA class improved more with CABG plus mitral surgery.

CABG alone versus CABG plus mitral surgery[17 18] (n=301, moderate MR)

Primary end point result

- ESV decreased in both groups (9 mL/m^2 at 1 year).

Other results

- Survival was equal in the two groups (92.7% with CABG alone vs 93.3% with CABG plus).
- EF increased similarly in both groups (4 vs 5 units).
- Persistent/recurrent MR more frequent with CABG alone (31% vs 11%).
- Quality of life was affected similarly in the two groups.

Choice of procedure (mitral repair vs replace)[21 22] (n=251, severe MR, 75% CABG)

Primary end point

- ESV decreased in both groups (7 mL/m^2).

Other results

- Survival was similar in the two groups (86% with repair vs 82% with replacement).
- EF unchanged in both groups (0 vs decrease two units).
- Recurrent MR more frequent with repair versus replacement (33 vs 2%).
- Quality of life (in patients without recurrent MR) was similar in the two groups.

One-year postoperative data are presented.

CABG, coronary artery bypass grafting; EF, ejection fraction; ESV, end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; VO_2, oxygen consumption.

MR (Regurant Fraction>50%) or at least moderate-to-severe MR (Regurgitant Fraction=40%–50%).

Surgical valve repair or replacement

When mitral valve surgery is planned in patients with secondary MR, the options of valve replacement or repair should be considered. Some observational studies suggest that survival might be better with valve repair.[19 20]

Randomised study

A trial in 251 patients with severe secondary (ischaemic) MR found no significant difference in survival between chordal sparing mitral valve replacement and mitral valve repair (77% vs 81% after 2 years).[21 22] In this study, CABG was performed in most patients. The recurrence of moderate or severe MR was more frequent in the repair group than in the replacement group (33% vs 2% after 1 year and 59% vs 4% after 2 years). The rate of hospital readmission for cardiovascular causes was higher in the group with mitral valve repair.

Comment

If recurrent MR and hospital readmissions are less frequent with valve replacement than with valve repair, it would seem that valve replacement should be the favoured procedure. Recognising that the life expectancy of most patients with secondary MR is shorter than the expected time to structural deterioration of a bioprosthetic valve, consideration should be given to a chordal sparing bioprosthetic valve replacement. Obviously, the choice of a prosthetic valve depends on consideration of many factors including of patient's age, comorbidities, the risks of anticoagulation and patient wishes.[7]

Normalised regurgitant volume

Recognising that the RegV is directly related to the end-diastolic volume (EDV),[23] the RegV was normalised for EDV,[6] and the normalised RegV (ie, the ratio of RegV to EDV) was examined in the three randomised studies that included ESV data. Two of these studies included patients with moderate MR[16 17]; the third incorporated patients with severe MR.[21] In all three studies, most patients had LV enlargement (average values ranged from 95 to 125 mL/m^2) and an EF of approximately 40%. Assuming that moderate MR implies a regurgitant fraction of 40% and that severe MR implies a regurgitant fraction of 50%, the estimated RegV in these studies was relatively low; the average values were approximately 18, 15 and 20 mL/m^2. The ratio of RegV to EDV in the three studies was 0.14, 0.16 and 0.21. As is shown in figure 1, these results are consonant with previously published data,[6] and they are associated with a blunted LV response to the correction of secondary MR.

This dimensionless ratio describes the impact of the RegV on the EDV and when expressed as a percentage it provides an estimate of the fractional change in EDV that might be expected after surgical correction of MR. In the two studies with postoperative EF data,[16 17] the ratio predicts a 16% and 21% decrease in EDV after correction of the MR. One year after surgery, the EDV actually declined only 9 and 11 mL/m^2 in the two studies. Thus, the change in EDV in these two studies was only about 10%. This is consistent with our prior suggestion that the ratio tends to overestimate the expected change in EDV after correction of secondary mitral MR when the adverse LV remodelling is irreversible and not amenable to substantial improvement.[6] Obviously, other factors determine the extent LV remodelling after correction of MR. For example, the presence of residual MR is associated with a blunted reverse remodelling.[24] The suggestion of overestimation of the expected change in EDV in secondary MR is in contrast to the underestimation that was seen late after correction of primary MR.[6] The clinical utility of the RegV/EDV ratio needs to be examined in primary and secondary MR using quantitative volumetric methods.

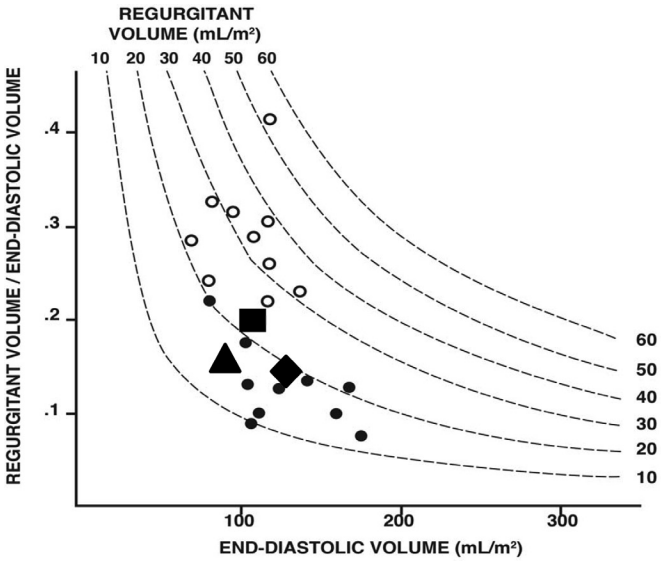

Figure 1 Schema illustrating the relation between the ratio of regurgitant volume to end-diastolic volume (RegV/EDV) and the EDV in patients with mitral regurgitation (MR); the isopleths of RegV are shown as a function of the two variables. Open circles represent average values taken from published studies of primary MR; closed circles represent average values taken from published studies of secondary MR.[6] The triangle, the square and the diamond each represent an average value from the three randomised studies of surgical results in secondary MR.[16 17 21] In these studies, the RegV/EDV is low (0.14, 0.16 and 0.21) and the absolute RegV is less than is seen in most of those with primary MR. This indicates that the effect of surgical correction of secondary MR on the remodelled ventricle would be less than that expected in primary MR.

Mitral surgery in non-ischaemic cardiomyopathy

Recognising that isolated mitral surgery does not directly address the LV dysfunction, it would seem reasonable to assume that isolated mitral surgery would be less likely to influence the LV dilatation and dysfunction than CABG with mitral surgery in patients with ischaemic cardiomyopathy. Unfortunately, there is relatively little experience with mitral surgery in the absence of coronary heart disease and there are no randomised trials in this population.

Observational studies

In an early report of mitral annuloplasty in nine patients with dilated cardiomyopathy and secondary MR, there were several encouraging results.[25] Four months after surgery the MR had decreased, there was a decrease in EDV, an increase in EF, an increase in cardiac output, as well as an improvement in symptoms and exercise tolerance. Other relatively small short-term studies had comparable results with modest improvements in haemodynamic parameters, and improvements in the symptoms of heart failure.[26 27] These observations were later expanded in a larger study of survival differences in 126 patients undergoing mitral annuloplasty versus 293 treated medically.[28] This study

included patients with secondary MR that was judged to be moderate to severe. The analysis included propensity scoring. During a 5-year follow-up period, survival was not significantly different in the medically and surgically treated patients.

Comment

Isolated mitral surgery in secondary MR can produce a significant decrease in regurgitant flow and symptomatic improvement, at least in some patients. In none of these studies was there a decline in the EF. However, there is no evidence that isolated mitral surgery can increase survival of patients with non-ischaemic cardiomyopathy. These results are similar to those seen with percutaneous valve repair (vide infra) in patients with ischaemic as well as non-ischaemic secondary MR.[29]

Transcatheter (surgical) valve implantation

The feasibility of transcatheter mitral valve implantation (via left lateral minithoracotomy and LV apical access) has been documented in 30 patients with grade 3 or 4 MR.[30] The study included high-risk patients with primary and secondary MR, but the predominant pathology was MR secondary to ischaemic LV remodelling. Overall, successful device implantation (free of cardiovascular death, stroke and device dysfunction at 30 days) was 87%. The MR was virtually abolished and there was a significant decrease in EDV, a decline in the EF, no significant change in the ESV, but functional class improved.

Comment

This procedure (currently in an investigational stage) has potential value, and should be studied in risk-stratified patients with quantitative volume data. The mean change in EDV was substantial (20% reduction), but it should be noted that there were relatively large changes in EDV in the individuals with the most dilated ventricles and little change in those with normal or near-normal EDV. The diagnosis of severe chronic MR should be questioned in patients with normal EDV.[6 7]

Transcatheter (percutaneous) mitral repair

Transcatheter correction of mitral regurgitant flow with the MitraClip device is approved by the US FDA for treatment of symptomatic patients with severe or moderate-to-severe primary MR. In Europe, the MitraClip and the CARILLON mitral annuloplasty device have CE Mark approval. A variety of other native valve repair and prosthetic valve insertion techniques are under development and evaluation.[31] There is an extensive literature on the transcatheter repair of secondary MR, and there are several ongoing prospective randomised trials comparing GDMT plus Mitraclip with GDMT alone in patients with secondary MR.[32]

Valve repair

Early clinical investigation with the Mitraclip device confirmed the feasibility of the percutaneous technique.[33] This study is the only randomised study with the Mitraclip. Other studies were also encouraging. For example, an observational study with the Mitraclip device incorporated data from 51 patients with moderate-to-severe secondary MR.[34] After 1 year, there were reductions in the EDV and ESV, a small increase in the EF and a significant symptomatic improvement. A larger study, EVEREST II (Endovascular Valve Edge-to-Edge Repair Study), incorporated data from two registries. There were 327 symptomatic patients with grade 3 to 4+ MR; the majority had secondary MR.[35] Early after repair there was a reduction in the severity of MR, and after 12 months there was a reduction in EDV and ESV, no change in the EF, and an improvement in functional class and quality of life.

Comment

The EVEREST II study included a minority of patients with primary MR, but virtually all of the published studies confirm a significant reduction in the severity of MR with the Mitraclip. Obviously, this is not truly a valve repair, but rather an edge to edge approximation that effectively reduces the severity of MR. Symptomatic improvement is commonly reported. As with mitral surgery, the transcatheter procedure is followed by a reduction in LV chamber size in some patients. The reduction in EDV tends to be most prominent in patients with the largest ventricles and presumably the largest regurgitant volumes. However, persistent LV enlargement is seen in many if not most patients. The transcatheter repair has not been shown to be followed by a survival benefit.

The results of the transcatheter procedures for secondary MR (and those of mitral surgery) are limited largely by their observational design. Most studies use semiquantitative methods and many include patients with less than severe MR. Some do not exclude patients with primary MR. Others do not consider the impact of recurrent MR. Such problematic protocols should be avoided in future studies. In an attempt to identify patients who are most likely to show survival and other salutary results, risk stratification should be incorporated in study design.[36] Future studies should utilise methods that are more reliable than the semiquantitative methods employed in the studies reviewed herein.

Volume imaging in MR

It has long been known that the 'regurgitant volume is generally small' in secondary MR,[37] and more recently the dependence of the RegV on EDV has been emphasised.[23] It has become increasingly apparent that accurate measurement of RegV is necessary to adequately define the severity of chronic MR. Cardiac MRI appears to be the most accurate and reproducible method to determine the absolute volumes (EDV, ESV, RegV) and the normalised parameters (EF, regurgitant fraction, RegV/EDV).[38–41] Most published MRI data come from studies of primary MR; studies of secondary MR are sorely needed. Such studies must specify the specific modality and quantification method,[42] as well as information on whether the papillary muscles (and trabeculae) are included in the LV cavity volume or in the LV wall volume.[43] Future studies, both surgical and percutaneous, should include only patients with severe MR (regurgitant fraction >50%) or at least moderate-to-severe MR (regurgitant fraction=40%–50%).

SUMMARY AND CONCLUSIONS

Currently, the treatment of patients with secondary MR is based on observational data and a few randomised trials. Most clinical investigation has relied on semiquantitative echocardiographic estimates of severity; many studies include patients with only moderate MR; some include both primary and secondary MR. Recognising these and other limitations, and the mixed results of the published studies, it is difficult to make firm conclusions about the benefits of treating secondary MR with mitral surgery or transcatheter repair. Management of secondary MR is still in a state of evolution

Surgical or transcatheter repair results in a substantial reduction in the RegV, but valve replacement abolishes the regurgitation and reduces the likelihood of recurrence. Unfortunately, the potential benefit of a reduction in the RegV does not consistently

lead to reversal of the adverse LV remodelling. In most observational studies, these valve interventions are followed by an improvement in symptoms of heart failure, but the results of randomised studies are mixed. Such uncertainties, especially when coupled with a lack of a survival benefit, diminish enthusiasm for mitral valve surgery or transcatheter repair in patients with secondary MR.

These issues can only be clarified by randomised trials that recruit patients who are most likely to show a benefit, for example, those with the most severe MR. It is essential to obtain quantitative volume data; cardiac MRI appears to be more accurate and reliable than echocardiography for this purpose. It is also important to obtain objective measures of functional improvement, not merely patient-reported symptoms. A reasonable study population, or clinical phenotype, would include symptomatic patients with secondary MR, LV enlargement, an EF between 20% and 40%, a regurgitant fraction >40%,and a RegV/EDV ratio <20%. Until prospective randomised trials prove beneficial effects, it is most prudent for clinicians to apply a conservative approach as is outlined in the ACC/AHA and ESC guidelines.

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