Review

Aortic valve replacement for aortic stenosis in patients with concomitant mitral regurgitation: should the mitral valve be dealt with?

Leanne Harling *, Srdjan Saso, Omar A. Jarral, Antonios Kourliouros, Emaddin Kidher, Thanos Athanasiou

Department of Surgery and Cancer, Imperial College London, London, UK

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Summary

Co-existent mitral regurgitation may adversely influence both morbidity and mortality in patients undergoing aortic valve replacement for severe aortic stenosis. Whilst it is accepted that concomitant mitral intervention is required in severe, symptomatic mitral regurgitation, in cases of mild–moderate non-structural mitral regurgitation, improvement may be seen following aortic valve replacement alone, avoiding the increased risk of double-valve surgery. The exact benefit of such a conservative approach is, however, yet to be adequately quantified. We performed a systematic literature review identifying 17 studies incorporating 3053 patients undergoing aortic valve replacement for aortic stenosis with co-existing mitral regurgitation. These were meta-analysed using random effects modelling. Heterogeneity and subgroup analysis were assessed. Primary end points were change in mitral regurgitation severity and 30-day, 3-, 5- and 10-year mortality. Secondary end points were end-organ dysfunction (neurovascular, renal and respiratory), and the extent of ventricular remodelling following aortic valve replacement. Our results revealed improvement in the severity of mitral regurgitation following aortic valve replacement in 55.5% of patients, whereas 37.7% remained unchanged, and 6.8% worsened. No significant difference was seen between overall data and either the functional or moderate subgroups. The overall 30-day mortality following aortic valve replacement was 5%. This was significantly higher in moderate–severe mitral regurgitation than nil–mild mitral regurgitation both overall (p = 0.002) and in the functional subgroup (p = 0.004). Improved long-term survival was seen at 3, 5 and 10 years in nil–mild mitral regurgitation when compared with moderate–severe mitral regurgitation in all groups (overall p < 0.0001, p < 0.00001 and p = 0.02, respectively). The relative risk of respiratory, renal and neurovascular complications were 7%, 6% and 4%, respectively. Reverse remodelling was demonstrated by a significant reduction in left-ventricular end-diastolic diameter and left-ventricular mass (p = 0.0007 and 0.01, respectively), without significant heterogeneity. No significant change was seen in left-ventricular end-systolic diameter (p = 0.10), septal thickness (p = 0.17) or left atrial area (p = 0.23). We conclude that despite reverse remodelling, concomitant moderate–severe mitral regurgitation adversely affects both early and late mortality following aortic valve replacement. Concomitant mitral intervention should therefore be considered in the presence of moderate mitral regurgitation, independent of the aetiology.

Keywords: Aortic valve replacement; Mitral regurgitation; Aortic stenosis

1. Introduction

Aortic valve replacement (AVR) for acquired calcific aortic stenosis (AS) is the most commonly performed valvular procedure in adult cardiac surgery [1]. Mitral regurgitation (MR) frequently co-exists in these patients, and is often functional in origin without demonstrable structural abnormality, reflecting both the structural continuity and functional synchrony of the aortic and mitral annuli [2]. Initial chronic pressure overload occurring in longstanding AS produces concentric hypertrophy and an increased trans-mitral pressure gradient [3,4]. This, in turn, can either worsen existing structural MR or produce MR in the absence of structural abnormality. Progression to diastolic dysfunction with concomitant volume overload may then produce further functional deterioration.

Recent data from the Society for Thoracic Surgery (STS) database (2002–2006) reports an overall unadjusted mortality of 3.2% following AVR in a population of 67,292 patients at 809 centres worldwide [5]. Double valve replacement is, as expected, associated with a significantly higher operative risk with a postoperative mortality at 11–12% [6,7], emphasising that careful patient selection is imperative.

Current guidelines outlined by the American Heart Association (AHA) (2006) recommend combined AVR and MV repair or replacement in symptomatic patients with severe AS, severe MR and evidence of structural valve...
disease; however, the advice in lesser degrees of MR is less definitive. It is noted that the severity of MR may improve significantly following AVR, particularly in true functional MR where there is normal mitral valve morphology. Current advice is for intra-operative trans-oesophageal echocardiography (TOE) and visual inspection of the MV at the time of AVR to determine the necessity for MV repair or replacement in these patients [8]. However, variable loading conditions produced by positive pressure ventilation and the depth of anaesthesia may result in an underestimation of MR with pre-bypass TOE [9], and this strategy leads to uncertainty in preoperative planning, operative risk prediction and patient consent.

Whilst it is widely accepted that mild functional MR is likely to improve following AVR for AS, and severe MR is likely to require mitral valve repair or replacement, the evidence in moderate MR remains unclear. Previous reviews have provided a qualitative assessment of the literature; however, outcome-driven decision making is limited by a lack of quantitative analysis and no current consensus of opinion exists [10,11].

The objective of this study is, therefore, to provide recommendations on the optimal treatment strategy in patients with moderate MR in the absence of structural mitral valve disease, based on quantitative analysis of the available data. The primary end points of this review are the effect of AVR on MR severity, and the overall early and late mortality in patients undergoing AVR without concomitant MV surgery. Secondary end points include outcome data on end-organ dysfunction (neurovascular, renal and respiratory complications), and the extent of ventricular remodelling following AVR.

2. Methods

2.1. Literature search

A literature search was performed using PubMed, Ovid, Embase, Google Scholar and Cochrane databases. The ‘related articles’ function was used to broaden the search, and all abstracts, studies and citations were scanned and reviewed. Studies in all languages were sought. No date restrictions were placed on articles. The last date for this search was 1 January 2011.

The databases of peer-reviewed journals focussing on cardiac surgery were searched, including published conference proceedings. Previous reviews, including cross-references, were also searched. References of the acquired articles were searched manually to identify any further studies for inclusion.

2.2. Inclusion and exclusion criteria

All articles reporting patients undergoing isolated, first time, aortic valve replacement (AVR) with co-existing mitral regurgitation, as evidenced by preoperative transthoracic echocardiography (TTE) or TOE, were included in this review, regardless of the indication for AVR or the degree of MR. Studies reporting non-functional MR were also included in this review and subgroup analysis of functional MR performed where possible. All studies fulfilling these inclusion criteria were analysed in full, and divided into subgroups, depending on the degree of functional MR and the indication for AVR.

Studies were excluded from the review if: (1) inconsistency of data did not allow valid extraction; (2) data were duplicated; (3) the trial was carried out on animal models; and (4) studies included AVR for aortic regurgitation or mixed aortic valve disease, and data for AS alone did not permit independent analysis of this subgroup.

Based on these criteria, three reviewers (LH, SS and EK) independently selected studies for further examination by reading titles and abstracts of all identified citations. All potentially eligible studies were retrieved in full for further assessment. Any disagreement was resolved by discussion with the senior author (TA).

2.3. Data extraction

Three authors (LH, SS and EK) independently extracted the following data from each article: first author; year of publication; study type; number of subjects; study population demographics, type of aortic valve replacement, and pre- and postoperative echocardiogram parameters. All laboratory, physiological and clinical outcome measures used by the included studies were recorded. Specific outcome data were retrieved where possible for the following: (1) primary end points: change in MR severity and 30-day and long-term mortality; (2) secondary end points: end-organ dysfunction (stroke and neurological, respiratory and renal dysfunction) and echocardiographic parameters (left-ventricular (LV) mass, LV end-diastolic (LVED) and end-systolic diameter, LV ejection fraction (LVEF), septal thickness and left atrial area) following AVR.

Data extraction was carried out independently by the same authors, using a standardised Excel spreadsheet, any discrepancy between reviewers being addressed through consensus.

2.4. Data analysis

AVR was the sole intervention in this review. No control group was available for comparison. Meta-analysis was performed in line with recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUORUM) guidelines [12,13].

2.4.1. Echocardiographic data

Pre- and postoperative echocardiographic parameters were analysed using a random effects model, and reported as weighted mean difference (WMD), together with 95% confidence intervals. A positive WMD favoured a reduction in magnitude following AVR. The point estimate of the WMD was considered statistically significant at the p < 0.05 levels, if the 95% confidence interval did not include the value zero.

2.4.2. Clinical outcomes

Overall pooled estimates and 95% confidence intervals of clinical outcomes, and 30-day mortality were analysed using the risk ratio (RR) and its standard error (SE) via a random effects model. The inverse variance (IV) method was used. The summary point estimate was considered statistically
significant if $p < 0.05$ and the 95% confidence intervals did not include 1.

### 2.4.3. Long-term mortality

Long-term mortality data were estimated from Kaplan–Meier curves using the methods and spreadsheet produced by Tierney and colleagues [14]. Direct methods were used where data were available; whereas this was not possible, indirect methods were used, based on summary statistics.

### 2.4.4. Heterogeneity

Inter-study heterogeneity was explored using the chi$^2$ statistic, but the $I^2$ value was calculated to quantify the degree of heterogeneity across trials that were not attributable to chance alone. When $I^2$ was more than 50%, significant heterogeneity was considered to be present.

Analysis was conducted by use of Review Manager®, Version 5.0 for Windows (The Cochrane Collaboration, Software Update, Oxford, UK).

### 3. Results

#### 3.1. Eligible studies

Seventeen publications [15–31] were identified as fulfilling the inclusion criteria of this review, producing a pooled data set of 3053 patients. Of these, 10 studies included mitral valve disease of other than functional aetiology [16–18,20,21,23,25–27,31]. Three studies reported AVR for both mixed AV disease and AR [23,31,32]. Here, data were not reported as specific to the AS group were also excluded from analysis. Seven studies included patients with concomitant coronary artery disease (CAD) [18–20,22,25,27,28]. The characteristics of the included studies are shown in Table 1.

#### 3.2. Primary end points

### 3.2.1. Grading MR severity

Of the 17 studies included in this review, 15 used TTE in both pre- and postoperative assessment: one [25] used a combination of TOE and TTE, and one used TOE assessment alone [29]. Whilst inter-study variation was noted in the method and grading of MR severity, all methods used were in compliance with the 2003 American Society of Echocardiography recommendations. These are outlined in Table 1. Only one study [24] did not report the method of echocardiographic assessment.

Ten studies [16,18,19,21–23,28–31] ($n = 1000$) reported change in MR severity following AVR; of these, six [19,22,23,29–31] ($n = 807$) were specific for MR of functional aetiology. An overall improvement in postoperative MR was seen in 55.5% of patients following AVR, 37.7% remained unchanged and 6.8% worsened. Consideration of functional MR alone revealed an improvement in 60.8% and deterioration in 6.6%, with 32.7% remaining unchanged. Further subgroup analysis of patients with ‘only moderate’ preoperative MR (eight studies [16,18,21–23,28,29,31], $n = 266$) revealed improvement in 62.8%, no change in 34.2% and deterioration in 3.0%. When ‘only moderate preoperative and functional’ MR was considered (five studies [16,18,21,22,28], $n = 236$), improvement was seen in 63.1%, no change in 33.5% and deterioration in 3.4% (Fig. 1).

### 3.2.2. Mortality and long-term survival data

#### 3.2.2.1. 30-Day (early) mortality

Seven studies [15,17,19,20,29–31] reported overall 30-day mortality. Pooled analysis revealed a 5% relative risk of 30-day mortality following AVR. There was no significant heterogeneity between studies.

Three studies compared 30-day mortality moderate/severe MR to nil/mild MR. Combined analysis of these results showed a significant increase in 30-day mortality ($p = 0.002$) in the moderate–severe group when compared with the nil–mild group without significant inter-study heterogeneity. Subgroup analysis of only functional MR also revealed a significant increase in 30-day mortality in the moderate–severe group ($p = 0.004$) (Fig. 2).

#### 3.2.2.2. 3-, 5- and 10-Year survival data

Five studies [15,17,23,24,30] provided Kaplan–Meier estimates of long-term survival comparing nil–mild versus moderate–severe preoperative MR. Both 3- and 5-year pooled estimates showed a significantly improved long-term survival in patients with nil–mild MR when compared with the moderate–severe MR group (hazard ratio (HR) 0.49, $p < 0.0001$ and HR 0.46, $p < 0.00001$, respectively), without significant inter-study heterogeneity (Fig. 3). This remained true in subgroup analysis of functional MR at both 3 and 5 years ($p = 0.0005$ and $p < 0.00001$, respectively).

Four of these studies provided 10-year survival estimates [15,17,24,30]. A significantly improved long-term survival was again seen in the nil–mild group, although the effect was less marked (HR 0.61, $p = 0.02$) and significant heterogeneity ($p = 0.04$, chi$^2 = 8.53$, $I^2 = 65\%$) was found within the data. Interestingly, subgroup analysis focussing on functional MR alone did not reveal a significant difference in 10-year mortality between nil–mild and moderate–severe groups ($p = 0.15$) (Table 4).

### 3.3. Secondary end points

#### 3.3.1. Clinical outcomes

Respiratory, renal and neurovascular outcomes were analysed following AVR, across all groups. Overall, five studies [15,17,19,29,31] reported data suitable for analysis; this is shown in Table 2. The weighted average relative risk of respiratory, renal and neurovascular complications were 7%, 6% and 4%, respectively. No significant heterogeneity was present within these data. Subgroup analysis of functional MR did not change the relative risk of any of the aforementioned adverse outcomes.

#### 3.3.2. Structural myocardial remodelling

Analysis of pooled pre- and postoperative echocardiographic parameters is shown in Table 3. Evidence of structural remodelling following AVR is demonstrated by a significant reduction in LVED diameter and LV mass ($p = 0.0007$ and 0.01, respectively), without significant heterogeneity. No significant change was seen in LVES diameter ($p = 0.10$), septal thickness ($p = 0.17$) or LA area ($p = 0.23$). Echocardiographic data that focussed on func-
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Total n</th>
<th>MR aetiology</th>
<th>Groups</th>
<th>Inclusions</th>
<th>Exclusions</th>
<th>TOE/TTE Method of MR severity measurement</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absil and colleagues [15]</td>
<td>Retrospective</td>
<td>116</td>
<td>Functional</td>
<td>MR0—1: 58 MR2—3: 58</td>
<td>G</td>
<td>a, n, p</td>
<td>TTE Continuous wave and pulse wave doppler</td>
<td>74.7 ± 6.6</td>
</tr>
<tr>
<td>Adams and Otto [16]</td>
<td>Prospective cohort</td>
<td>56</td>
<td>36 Calcific</td>
<td>2 Rheumatic 18 Functional</td>
<td>C, K</td>
<td>-</td>
<td>TTE Doppler with measure of systolic flow disturbance in LA</td>
<td>74.8 ± 7.1</td>
</tr>
<tr>
<td>Barreiro and colleagues [17]</td>
<td>Retrospective</td>
<td>408</td>
<td>15 Functional</td>
<td>None-mild: 338 Moderate: 70</td>
<td>G</td>
<td>c, m, n</td>
<td>TTE Colour flow jet area Systolic flow reversal in PVs</td>
<td>77 ± 4.9</td>
</tr>
<tr>
<td>Brasch and colleagues [18]</td>
<td>Retrospective</td>
<td>27</td>
<td>26 Calcific</td>
<td>9 Thickened MV leaflets 4 Restricted MV leaflets</td>
<td>C</td>
<td>f, i</td>
<td>TTE Colour flow doppler Non-sig MR: 76 ± 9 Significant MR: 77 ± 17</td>
<td></td>
</tr>
<tr>
<td>Christenson and colleagues [20]</td>
<td>Prospective cohort</td>
<td>60</td>
<td>36 Potentially ischaemic with CAD</td>
<td>CAD: 36 No CAD: 24</td>
<td>A</td>
<td>a, q, m</td>
<td>TTE Colour flow doppler CAD: 64 ± 13.3 No CAD: 70.9 ± 9.2</td>
<td>68.3 ± 9.2</td>
</tr>
<tr>
<td>Cabarello-Borego and colleagues [19]</td>
<td>Retrospective</td>
<td>557</td>
<td>Functional</td>
<td>Mild—moderate MR: 153</td>
<td>C</td>
<td>a, c, d, f, g, h</td>
<td>TTE Regurgitant jet area Colour and pulsed doppler and PV flow.</td>
<td>63.3 ± 13.8</td>
</tr>
<tr>
<td>Goland and colleagues [21]</td>
<td>Prospective cohort</td>
<td>30</td>
<td>Calcific 13</td>
<td>Functional 17</td>
<td>B</td>
<td>a, c, g, l.</td>
<td>TTE Colour flow doppler: indexed maximal jet area Pulsed, continuous and colour flow doppler Indexed overall maximum jet area Colour flow doppler</td>
<td>72 ± 6.5</td>
</tr>
<tr>
<td>Harris and colleagues [22]</td>
<td>Retrospective</td>
<td>28</td>
<td>Functional</td>
<td>—</td>
<td>G</td>
<td>a, f, i</td>
<td>TTE Colour flow doppler</td>
<td>75 ± 8.0</td>
</tr>
<tr>
<td>Moazami and colleagues [23]</td>
<td>Retrospective</td>
<td>107</td>
<td>Functional</td>
<td>MR grade 1—2: 72 MR grade 3—4: 35 AR: 30; AS: 28 Mixed AVD: 49</td>
<td>B, G</td>
<td>a, d, f, o, i</td>
<td>TTE Colour flow doppler</td>
<td>67.1</td>
</tr>
<tr>
<td>Ruel and colleagues [24]</td>
<td>Retrospective with prospective follow up</td>
<td>848</td>
<td>Functional</td>
<td>FMR ≤ 1: 741 FMR ≥ 2: 107</td>
<td>D</td>
<td>a, c, j, k.</td>
<td>TTE Not described</td>
<td>FMR ≤ 1 63.3 ± 13.8 FMR ≥ 2 69.6 ± 11.6</td>
</tr>
<tr>
<td>Tassan-Mangina and colleagues [25]</td>
<td>Prospective observational</td>
<td>30</td>
<td>12 Calcific</td>
<td>2 Dystrophic 16 Functional</td>
<td>−</td>
<td>−</td>
<td>TOETTE Regurgitant jet area on TTE Maximum jet area and width at origin on TOE Pulsed and continuous wave doppler Vena contracta width</td>
<td>68 ± 8</td>
</tr>
<tr>
<td>Tunic and colleagues [26]</td>
<td>Prospective observational</td>
<td>44</td>
<td>23 Calcific</td>
<td>21 Functional</td>
<td>−</td>
<td>−</td>
<td>TTE Regurgitant jet area, vena contracta width, flow convergence on colour flow doppler Jet profile on continuous wave doppler</td>
<td>69 ± 12</td>
</tr>
<tr>
<td>Waisbren and colleagues [29]</td>
<td>Retrospective</td>
<td>227</td>
<td>Functional</td>
<td>—</td>
<td>−</td>
<td>−</td>
<td>TOE Regurgitant jet area, vena contracta width, flow convergence on colour flow doppler</td>
<td>71 ± 11</td>
</tr>
<tr>
<td>Wan and colleagues [30]</td>
<td>Retrospective</td>
<td>190</td>
<td>Functional</td>
<td>AS: 158 AR: 25 Mixed: 7</td>
<td>H</td>
<td>a, c, d, o, p, q, t, u, v</td>
<td>TTE Flow quantitattion of pulsed doppler</td>
<td>74 ± 11</td>
</tr>
</tbody>
</table>
Table 1 (Continued).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Total n</th>
<th>MR aetiology</th>
<th>Exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Velden and colleagues [28]</td>
<td>prospective (multicentre)</td>
<td>52</td>
<td>myxomatous/MR</td>
<td>a: systolic anterior motion and dynamic left-ventricular outflow tract obstruction; b: mitral valve prolapse; c: combined procedures; d: endocarditis; e: right heart valve procedures; f: postoperative aortic valve replacement; g: preoperative aortic regurgitation; h: preoperative aortic stenosis; i: combined aortic valve disease; j: concomitant functional MR; k: prior transcatheter aortic valve implantation; l: prior surgical aortic valve replacement; m: preoperative aortic valve insufficiency; n: preoperative mitral valve insufficiency; o: preoperative aortic stenosis; p: preoperative mitral stenosis; q: preoperative atrioventricular valve abnormalities; r: preoperative aortic root replacement</td>
</tr>
</tbody>
</table>

MR: mitral regurgitation.}

4. Discussion

4.1. Structural reverse remodelling following AVR in the presence of concomitant MR

Our results quantitatively demonstrate that within this review, the structural remodelling resulting from sustained AS regresses following AVR, as demonstrated by a reduction in LV mass and LVED diameter. It is recognised that pressure overload in AS results in concentric hypertrophy as demonstrated by an increase in LV wall thickness [3,4]; when AS is severe and sustained, increased end-diastolic pressure may result in dilatation of the LV cavity. It therefore follows that coexistent pressure-induced concentric hypertrophy and LV diastolic dysfunction occurring in severe AS may result in both a significant increase in LV mass and LVED diameter. This has been further studied on a molecular level, and is thought to involve early activation of maladaptive cell-signalling pathways in which angiotensin II, tumour necrosis factor β (TNFβ) and changes in metalloproteinase activity may mediate myocyte degeneration and fibrosis [3]. Functional MR, developing in part as a consequence of this ventricular remodelling, may then result in further progression of this process secondary to volume overload. Whilst we cannot ascertain the exact aetiology of the regression of these changes from the data set available, we can conclude that AVR in the setting of severe AS with concomitant functional MR may reverse ventricular remodelling.

4.2. Does preoperative MR improve following AVR and what is the influence of MR severity and aetiology?

Our results show an improvement in preoperative MR in 55.5% of patients following AVR, deterioration in 6.8% and no change in the remaining 37.7%. Subgroup analysis of functional and moderate MR demonstrated an improvement in 60.8% and 62.8%, and deterioration in 6.6% and 3.0%,
respectively, although these differences were not statistically significant when compared with overall data. The mechanism of improvement in MR is likely to reflect a number of physiological changes following AVR. Early improvement in MR may result from a reduction in the trans-mitral pressure gradient due to reduced pressure loading of the LV following AVR [11]. In addition, as demonstrated in this data set, a degree of reverse remodelling occurs after AVR, leading to a regression of concentric hypertrophy and increase in LVED volume. Reverse remodelling may also play a further role in patients with evidence of LV dilatation, where mitral valve leaflet tethering occurs secondary to outward displacement of the papillary muscles [33]. A reduction in mitral tethering may consequently contribute to the improvement in MR in those patients with preoperative diastolic dysfunction. Several studies identify factors associated with evidence of ventricular remodelling, such as higher preoperative LV mass [18,27], larger LV diastolic diameter [18,30] and end-diastolic volume [27] to be independent predictors of improvement in MR following AVR. This suggests that, where there is potential for reverse remodelling to occur, a more significant improvement in MR will be seen following AVR.

Whilst 55–63% of these patients showed improvement in MR by one or more grades, 33–38% remained unchanged and
3–7% worsened. Neither consideration of moderate nor functional MR as separate subgroups revealed a statistically significant difference in the change in MR following AVR from the overall data set, suggesting that neither severity nor aetiology of preoperative MR had a significant effect on the improvement of MR postoperatively. Vanden Eynden and colleagues [28] do, however, report a significant correlation between aetiology of MR and improvement following AVR. Their results show ischaemic MR to correlate most strongly with improvement, followed by functional, rheumatic and myxomatous MR. It is likely, however, that these results are also a reflection of the concomitant coronary artery bypass

### Table 2. Outcomes following AVR.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>Overall effect</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Studies</td>
<td>Patients</td>
<td>Risk ratio</td>
</tr>
<tr>
<td>Respiratory complications</td>
<td>Overall/functional MR</td>
<td>3</td>
<td>900</td>
</tr>
<tr>
<td></td>
<td>Overall/functional MR</td>
<td>3</td>
<td>900</td>
</tr>
<tr>
<td>Renal complications</td>
<td>Overall/functional MR</td>
<td>4</td>
<td>1385</td>
</tr>
<tr>
<td></td>
<td>Functional</td>
<td>2</td>
<td>784</td>
</tr>
<tr>
<td>Stroke and neurovascular complications</td>
<td>Overall/functional MR</td>
<td>6</td>
<td>1558</td>
</tr>
<tr>
<td></td>
<td>Functional</td>
<td>4</td>
<td>1090</td>
</tr>
<tr>
<td>30-Day mortality</td>
<td>Overall/functional MR</td>
<td>3</td>
<td>Nil/mild: 815</td>
</tr>
<tr>
<td></td>
<td>Functional</td>
<td>2</td>
<td>Nil/mild: 477</td>
</tr>
</tbody>
</table>

* Denotes significance.
grafting (CABG) performed in 22 of the 26 patients presenting with ischaemic MR [28], and the improvement in MR following revascularisation.

4.3. What effect does preoperative MR have on postoperative early and late mortality in patients undergoing AVR?

Recent publication from the STS database reports the overall 30-day mortality to be 3.2% in patients undergoing AVR without concomitant mitral regurgitation [5]. Within this pooled data, the overall 30-day mortality in patients undergoing AVR with concomitant MR reaches 5%, suggesting relatively higher operative risk in these patients. Furthermore, consideration of functional MR as a subgroup reveals a 30-day mortality of 6%, close to double that seen in isolated AVR. Whilst this is undoubtedly of concern, it remains significantly lower than the operative mortality of a concomitant mitral repair/replacement and AVR at 11–12% [6,7]. Two studies identified severity of preoperative MR to be an independent predictor of mortality following AVR [17,23], although this is contradictory to the findings of other groups [15,24,30,31]. Our own analysis revealed a statistically significant increase in 30-day mortality in patients with moderate preoperative MR when compared with nil—mild preoperative MR (p = 0.002), as well as a significantly worse 3- and 5-year survival in those patients with moderate—severe mitral regurgitation undergoing AVR. This effect remained unchanged when moderate MR was considered separately, excluding all studies with preoperative MR. Interestingly, 10-year mortality was not significantly affected by preoperative MR severity when only functional MR was considered, although the presence of significant heterogeneity within these data is likely to reflect the relatively small number of studies included and further data are therefore required to demonstrate whether this is a true effect.

Several independent risk factors have been associated with mortality in these patients including age [24], diabetes mellitus [17], chronic lung disease [29], concomitant coronary artery disease [24], hypertension [31], poor LVEF [24,29], preoperative chronic renal failure and dialysis dependence [29,30], preoperative atrial arrhythmias or absence of sinus rhythm [24,30] and higher New York Heart Association (NYHA) functional status [17,30]. However, whether mortality directly correlates with improvement in MR severity following AVR remains unclear. Whilst several studies have observed a trend towards higher mortality rates in patients with no improvement in MR up to 5 years following AVR, none have demonstrated statistical significance [17,23,28].

4.4. What effect does preoperative MR have on postoperative clinical outcomes in patients undergoing AVR?

Consideration of postoperative morbidity and functional outcomes is also important in deciding whether concomitant mitral intervention is beneficial in these patients. Ruel and colleagues [24] highlighted an increase in the composite heart failure outcome (heart failure symptoms, death and the need for later mitral valve repair or replacement) in patients with moderate—severe preoperative MR undergoing AVR. Furthermore, Takeda and colleagues identified a significant difference in freedom from re-admission for heart failure in patients with mild—moderate compared with nil—trivial preoperative MR, favouring the nil—mild group (p = 0.002).
Results from our analysis show an overall 7% risk of respiratory complications, 6% risk of renal complications and 4% risk of stroke and neurovascular complications in these patients. Although notably, our data are independent of MR aetiology and severity, and limited by inter-study variation in defining outcomes, the 2002–2006 STS data in patients undergoing AVR without co-existing MR reports a much lower frequency of postoperative stroke and renal failure (1.5% and 4%, respectively).

4.5. Study limitations

A number of factors related to both study design and outcome reporting, influence the interpretation of these results. First, all of the studies included in this review are observational, and only one is prospective. No randomised controlled trials have been performed, and there is no control group available for comparison. Second, several aspects of inter-study variation may influence the results of pooled data. Diversity in both the aetiology of MR and concomitant procedures, such as CABGs, is likely to influence the overall data analysis. Structural MR of either myxomatous or calcific aetiology may not be expected to improve significantly following AVR. Whilst subgroup analysis has been performed in an attempt to independently examine functional MR, this is limited to only a small number of studies. The inclusion of severe MR may also negatively influence outcomes and mortality data, as it is generally recommended that these patients undergo concomitant mitral intervention [8]. Finally, the lack of a universal grading system has led to the use of a number of different echocardiographic parameters in grading the severity of preoperative MR (Table 1). Whilst remaining in accordance with the ASC guidelines, variation in both the technique and scale of MR grading limits direct comparison between studies.

5. Summary

Approximately 55–63% of all patients with preoperative MR improve following isolated AVR; however, almost half of them either remain unchanged or show some deterioration. The mechanism of improvement in non-structural MR is likely to relate to reverse remodelling, as demonstrated by a reduction in LV mass and LVED diameter within these data. Furthermore, the identification of both LV mass and LVED diameter as independent factors for improvement in MR following AVR suggests that where the potential for reverse remodelling to occur exists, a more significant improvement in MR may be seen.

Whether improvement in MR severity following AVR directly correlates with mortality does however remain unclear, as a number of studies have failed to demonstrate significance in multiple regression analyses. Our results demonstrate that co-existent moderate MR may increase both early and late mortality following AVR over patients with nil–mild MR, particularly in association with poor preoperative functional status, low LVEF, renal dysfunction, coronary artery and pulmonary disease.

Further research should focus on randomised controlled trials to assess the effect of mitral intervention versus no intervention in moderate MR, taking care to clearly define both MR aetiology and severity. Until such data are available, clinical decision making should be guided by a thorough assessment of the preoperative MR severity and aetiology, taking into account the presence of any of the aforementioned preoperative co-morbidities. Our results demonstrate that despite reverse remodelling, concomitant moderate–severe MR adversely affects both early and late mortality following AVR. As such, concomitant mitral intervention should therefore be considered in the presence of moderate MR, independent of aetiology.

References


