Impact of residual regurgitation after aortic valve replacement†

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Abstract

OBJECTIVES: Mild-to-moderate aortic regurgitation (AR) is not infrequently encountered after standard aortic valve replacement, and reportedly more often following transcatheter aortic valve implantation. Patients are usually managed by observational follow-up, but the clinical significance and natural history of residual AR are unknown. The goal of this study was to determine its impact on the outcome of these patients.

METHODS: Between 1992 and 2011, 3201 consecutive patients underwent isolated standard aortic valve replacement in our institution. Of these, 135 patients (4.2%) were found to have paravalvular leak >1/4. Clinical, intraoperative as well as early and late postoperative outcome variables were studied. Factors associated with residual AR and their impact on survival were assessed by multivariate analysis.

RESULTS: Mean follow-up was 4.5 ± 3.4 years. The use of a bioprosthesis, longer cardiopulmonary bypass duration and preoperative atrial fibrillation were associated with a higher risk of presenting residual AR. Survival was negatively affected by commonly identified comorbidities (diabetes, stroke, pulmonary disease, renal failure, peripheral vascular disease) but also by the presence of >1/4 residual AR. Survival in the latter group was lower than for patients with ≤1/4 AR at all time points: 91.4 vs 96.7%, 77.5 vs 82.4% and 44.1 vs 54.5% at 1, 5 and 10 years, respectively (P < 0.01).

CONCLUSIONS: Postoperative residual AR >1/4 is an independent predictor of postoperative mortality and should be considered in the selection of surgical approach and management strategy for patients in need of standard and transcatheter aortic valve replacement.

Keywords: Perivalvular leak • Aortic valve replacement • Aortic regurgitation

INTRODUCTION

The incidence of prosthetic residual aortic regurgitation (AR) identified early after surgery has varied widely from 1 to 17% [1, 2]. Some studies have suggested that patients with mild regurgitation had a benign course during follow-up, but they were limited by small sample size, variation in the time interval between valve surgery and detection of the paravalvular leak, and the duration of follow-up [1–3]. There is a resurgent interest in the impact of residual AR with the advent of minimally invasive procedures associated with a higher incidence of this complication: two-thirds of patients treated with transcatheter aortic valve implantation have residual AR, which is generally considered tolerable, and 12% of patients have a moderate or severe prosthetic valve regurgitation [4]. Consequently, the purpose of our study was to assess the natural history of prosthetic valve regurgitation detected early after aortic valve replacement (AVR).

METHODS

Between January 1992 and March 2011, 6769 patients were treated with AVR at the Quebec Heart and Lung University Institute.

Patients with combined valvular surgery (mitral and/or tricuspid) (n = 775), redo operations (n = 1023), AVR with stentless valves (n = 579), homografts (n = 96), Ross procedure (n = 217), Bentall (n = 413), aortic valve repair (n = 169), transcatheter aortic valve implantation (n = 198), patients who died before hospital discharge (n = 162) and patients who had no echographic evaluation before discharge (n = 553) were excluded from the study.

The study population was composed of 3201 patients treated with AVR with or without coronary artery bypass grafting (CABG) by standard sternotomy.

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The vast majority of stented aortic prostheses were implanted using double-mattress non-evertting 2-0 braided pledgeted sutures, with extensive decalcification of the annulus. All clinical, echocardiographic, procedural and post-procedural data were prospectively collected and entered into the Cardiac Surgery Database.

All patients enrolled underwent a transthoracic Doppler echocardiography at hospital discharge. Patients followed in our institution had a follow-up echo at 6 months and annually thereafter, whereas results from other patients were collected from the institutions where they were followed.

Echocardiographic parameters considered to follow left ventricular function, and dimensions were left ventricular ejection fraction, left ventricular end-diastolic volume, septal and posterior wall thickness and aortic valve performance.

The severity of residual AR was assessed semi-quantitatively using visual estimation. Additional parameters taken into account to assess the regurgitation severity were the diastolic slope of AR detected by continuous-wave Doppler and the degree of diastolic flow reversal by pulsed Doppler at the arch or abdominal aorta and ratio of jet/outflow tract [5–12].

Patients were divided into two groups: patients having residual AR ≤1/4 (Group 1) and those having residual AR >1/4 (Group 2).

We reviewed the videotapes of echocardiograms of the 131 patients (97%) classified in our database as having residual AR >1 and followed in our hospital after 2001 to be confirmed as having that degree of leak and that mechanism of residual AR (central or perivalvular). Regurgitation was considered periprosthetic if the jet of regurgitation was identified as originating between the prosthetic valve sewing ring and the native valve annulus.

Clinical follow-up data were obtained from cardiac surgery database to find patients with haemolysis. Data concerning the date of death was obtained from the Quebec Civil Registry.

Statistical analysis

Qualitative data are presented as percentages; quantitative data are given as mean ± SD or median (25–75% interquartile range). Differences between patients with AR ≤1/4 classification and >1/4 regarding baseline characteristics were analysed using an unpaired Student's t-test, Wilcoxon rank sum test or Fisher's exact test according to the distribution variables. A logistic regression approach was performed to model patients with AR >1/4. Candidate variables for the multivariate model building were selected from univariate tests with P-values <0.20. To obtain the correct relationship in the model, continuous variables were checked for the assumption of linearity in the logit. First, for each continuous variable, quartiles of the distribution were obtained and a new 4-level categorial variable was created. Second, a multivariate logistic regressions model was built with three design variables associated with the 4-level categorial variable using the first quartile as the reference value. Third, the scatter plot of the estimated coefficients vs the midpoints of the quartiles q2, q3 and q4 was created. In addition, a coefficient equal to zero was associated with the midpoint of q1. For all continuous variables, the graphical representations suggested linear relationships with the logit. The selection variables were performed using two statistical approaches. First, the stepwise and backward variable selections were used in the logistic regression model. Both approaches gave similar results. An alternative procedure to select variables was to use the best subset selection containing three to nine variables. The same approach was used for stepwise selection of interactions with main effects forced into the initial model. Using the 0.05% level of significance, no interaction effect was added to the model. To assess the goodness-of-fit of the model, the Hosmer–Lemeshow decile of risk test was performed, and the value of the statistic indicated that the final model fitted quite well.

Death-estimated survival functions vs time were constructed with the use of product-limit method. Death at follow-up was analysed with a Cox regression analysis. A multivariate Cox regression analysis was used to determine the variables predictive of cumulative death at follow-up for patients with AR ≤1 with >1, including all variables with values of P ≤0.20 in univariate Cox analysis. The selection variable with interaction terms was performed using a forward approach. The Akaike’s information criterion and Schwarz’s Bayesian criterion were used to compare candidate models. After model building, the adequacy of the proportional hazards assumption was checked.

Measurements from echocardiography were analysed using a repeated mixed model with adjustment for the time course. The univariate normality assumptions were verified with the Shapiro–Wilks tests. The multivariate normality assumptions were verified with the Shapiro–Wilks tests after a Cholesky factorization. The Brown and Forsythe’s variation of Levene’s test statistic will be used to verify the homogeneity of variances. The results were considered significant with P-values ≤0.05.

The data were analysed using the statistical package program SAS v 9.1.3 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Of the 3201 patients who underwent AVR in our institution, 3066 (96%) patients had residual AR ≤1/4 (Group 1) and 135 patients (4%) had residual AR >1/4 (Group 2). Preoperative data of both the groups are shown in Table 1.

There were no statistical differences between Group 1 and Group 2 regarding the mean age (69.7 ± 9.9 vs 70.2 ± 10.9, P = 0.6), sex distribution (male, 64.5 vs 63.7%), surgical risk (logistic EuroSCORE, 8.0 ± 8.1 vs 8.8 ± 9.2, P = 0.3) and major comorbidities. The body mass index was significantly higher in Group 1 (27.9 ± 5 vs 26.7 ± 4.4, P = 0.01), while the prevalence of preoperative atrial fibrillation was significantly higher in Group 2 (12.2 vs 14.1%, P = 0.02).

There was a similar distribution of primary causes for AVR: rheumatic valve disease (1.8 vs 1.5%), degenerative disease (71.5 vs 69.2%), bicuspid aortic valve (22.1 vs 24.8%), infective endocarditis (11.1 vs 8.0%), other (3.5 vs 3.7%) (P = 0.4).

The main indication for AVR was aortic stenosis in 2911 patients in Group 1 (95.7%) and in 128 patients in Group 2 (94.8%). The rest of the patients were operated for prevalent AR (P = 0.64).

Mechanical valves were used in 503 patients (16.4%) in Group 1 (St Jude, n = 225; Carbomedics, n = 69; MCRI, n = 100; Medtronic, n = 109) and in 37 patients (28.4%) in Group 2 (St Jude, n = 23; Carbomedics, n = 4; MCRI, n = 6; Medtronic, n = 4). Bioprostheses were used in 2563 patients (84.6%) in Group 1 (Carpentier–Edwards, n = 1342; Medtronic, n = 812; Mitroflow, n = 237; St Jude Biocor, n = 172) and in 98 patients (72.6%) in Group 2 (Carpentier–Edwards, n = 43; Medtronic, n = 46; Mitroflow, n = 4; St Jude Biocor, n = 5) (P < 0.01).
Prosthesis mean size was 23.2 ± 2.2 in Group 1 vs 23.2 ± 2.3 in Group 2 (P = 0.78). Combined procedures (AVR + CABG) were performed in 47.9% of patients in Group 1 and in 44.4% of patients in Group 2 (P = 0.43).

Mean cardiopulmonary bypass time was lower in Group 1 (105.1 ± 34.4 vs 115.2 ± 42.9 min, P = 0.01). Mean clamping time was also lower in Group 1 (79.8 ± 26.8 vs 86.6 ± 33.1 min, P < 0.02).

There was no difference regarding all other postoperative complications (Table 2), except for renal failure, with 9.4% of patients in Group 2 experiencing a 100 mg/dl increase or more in creatinine levels, compared with 4% of patients in Group 1 (P = 0.05).

### Long-term survival

The median clinical follow-up was 4 years (1.8–6.8 years) and data about survival were obtained in 3106 patients (97%) in Group 1 and in all patients in Group 2. Patients from Group 1 demonstrated a better survival at all time points (Fig. 1): at 1 year, 96.7% vs 90.4%; at 5 years, 82.4% vs 77.5%; at 8 years, 66.3% vs 57.5% and at 12 years, 43.4% vs 30.9% [hazard ratio (HR) = 1.7, 1.2–2.3, P = 0.01].

By univariate analysis, the risk factors for long-term mortality were: residual AR >1 [HR = 1.6, 1.1–2.2, P = 0.01], use of a bioprosthesis (HR = 2.0, 1.5–2.6, P < 0.01), age (HR = 1.1, 1.0–1.1, P = 0.01), combined AVR + CABG surgery (HR = 1.2, 1.0–1.4, P = 0.01), pre-operative stroke (HR = 1.7, 1.4–2.2, P < 0.01), diabetes (HR = 1.5, 1.3–1.8, P < 0.01), systemic arterial hypertension (HR = 1.2, 1.1–1.5, P < 0.01), chronic obstructive pulmonary disease (HR = 2.4, 2.0–2.8, P < 0.01), pre-operative renal failure (HR = 2.6, 2.1–3.2, P < 0.01), peripheral vascular disease (HR = 1.8, 1.5–2.2, P < 0.01), pre-operative atrial fibrillation (HR = 1.7, 1.3–2.1, P < 0.01), coronary artery disease (HR = 1.5, 1.3–1.7, P < 0.01), post-operative neurological complications (HR = 2.2, 1.8–2.6, P < 0.01), post-operative sepsis (HR = 2.8, 1.8–4.5, P < 0.01), mediastinitis (HR = 1.9, 1.1–3.3, P = 0.03), post-operative atrial fibrillation

### Table 1: Preoperative data

<table>
<thead>
<tr>
<th></th>
<th>Residual AR ≤1 (N = 3066)</th>
<th>Residual AR &gt;1 (N = 135)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>69.7 ± 9.9</td>
<td>70.2 ± 10.9</td>
<td>0.58</td>
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<tr>
<td>Male sex (%)</td>
<td>64.5</td>
<td>63.7</td>
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<td>NYHA class ≥3 (%)</td>
<td>48.0</td>
<td>53.3</td>
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<td>Body mass index</td>
<td>27.9 ± 5.0</td>
<td>26.7 ± 4.4</td>
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<tr>
<td>Hypertension (%)</td>
<td>64.5</td>
<td>61.5</td>
<td>0.48</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>6.9</td>
<td>8.9</td>
<td>0.36</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>24.6</td>
<td>23.9</td>
<td>0.72</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>14.9</td>
<td>17.8</td>
<td>0.36</td>
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<td>Active smokers (%)</td>
<td>12.0</td>
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<td>0.50</td>
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<tr>
<td>Renal failure (%)</td>
<td>6.2</td>
<td>3.7</td>
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<tr>
<td>Dialysis (%)</td>
<td>0.5</td>
<td>0.9</td>
<td>0.53</td>
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<tr>
<td>Peripheral vascular disease (%)</td>
<td>12.9</td>
<td>14.1</td>
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</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>12.2</td>
<td>18.5</td>
<td>0.02</td>
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<tr>
<td>Myocardial infarction (%)</td>
<td>19.5</td>
<td>21.5</td>
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<td>Endocarditis (%)</td>
<td>1.5</td>
<td>0.7</td>
<td>0.47</td>
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<td>Logistic EuroSCORE (%)</td>
<td>5.62 (3.08–9.52)</td>
<td>6.32 (3.98–10.66)</td>
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<tr>
<td>LVEF (%)</td>
<td>58.9 ± 13.2</td>
<td>59.2 ± 13.8</td>
<td>0.74</td>
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<tr>
<td>Aortic valve area (cm²)</td>
<td>0.8 ± 0.3</td>
<td>0.8 ± 0.4</td>
<td>0.61</td>
</tr>
<tr>
<td>Peak gradient (mmHg)</td>
<td>68.5 ± 26.3</td>
<td>68.5 ± 27.5</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
<td>41.8 ± 17.9</td>
<td>42.1 ± 17.5</td>
<td>0.86</td>
</tr>
<tr>
<td>Mitral valve regurgitation ≥2 (%)</td>
<td>26.2</td>
<td>30.8</td>
<td>0.24</td>
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</tbody>
</table>

### Table 2: Surgical data and outcome

<table>
<thead>
<tr>
<th></th>
<th>Residual AR ≤1 (N = 3066)</th>
<th>Residual AR &gt;1 (N = 135)</th>
<th>P-value</th>
</tr>
</thead>
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<tr>
<td>Elective surgery (%)</td>
<td>90.3</td>
<td>94.1</td>
<td>0.26</td>
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<tr>
<td>Mechanical valves (%)</td>
<td>16.4</td>
<td>27.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Prosthesis mean size (mm)</td>
<td>23.2 ± 2.2</td>
<td>23.2 ± 2.3</td>
<td>0.77</td>
</tr>
<tr>
<td>AVR + CABG (%)</td>
<td>47.9</td>
<td>44.4</td>
<td>0.43</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>105.1 ± 34.4</td>
<td>115.2 ± 42.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Clamping time (min) (median)</td>
<td>79.8 ± 26.8</td>
<td>86.6 ± 33.1</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Neurological complications (%)</td>
<td>16.7</td>
<td>17.8</td>
<td>0.91</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>3.2</td>
<td>5.2</td>
<td>0.20</td>
</tr>
<tr>
<td>Sepsis (%)</td>
<td>1.5</td>
<td>0.7</td>
<td>0.46</td>
</tr>
<tr>
<td>Mediastinitis (%)</td>
<td>1.5</td>
<td>0.7</td>
<td>0.49</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>1.5</td>
<td>0.7</td>
<td>0.17</td>
</tr>
<tr>
<td>Creatinine &gt;100 mg/dl (%)</td>
<td>4.0</td>
<td>9.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Surgical bleeding (%)</td>
<td>7.5</td>
<td>9.6</td>
<td>0.36</td>
</tr>
<tr>
<td>Intubation &gt;48 h (%)</td>
<td>4.1</td>
<td>5.9</td>
<td>0.31</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>7 (6–10)</td>
<td>7 (6–10)</td>
<td>0.16</td>
</tr>
<tr>
<td>LVSEF (%)</td>
<td>57.3 ± 17.2</td>
<td>56.6 ± 12.1</td>
<td>0.66</td>
</tr>
<tr>
<td>Aortic valve area (cm²)</td>
<td>1.4 ± 0.4</td>
<td>1.4 ± 0.4</td>
<td>0.68</td>
</tr>
<tr>
<td>Peak aortic gradient (mmHg)</td>
<td>26.6 ± 10.2</td>
<td>29.3 ± 12.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean aortic gradient (mmHg)</td>
<td>14.6 ± 5.8</td>
<td>16.2 ± 7.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mitral regurgitation ≥2 (%)</td>
<td>24.9</td>
<td>33.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Reintervention (%)</td>
<td>1.9</td>
<td>6.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Delay of reintervention (years)</td>
<td>3.8 (0.69–8.09)</td>
<td>3.8 (0.69–8.09)</td>
<td>0.18</td>
</tr>
<tr>
<td>Reintervention for perivalvular leak (%)</td>
<td>0.2 %</td>
<td>4.4%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Relevant haemolysis (%)</td>
<td>2.1</td>
<td>0.9</td>
<td>0.72</td>
</tr>
</tbody>
</table>
(HR = 1.4, 1.2–1.7, P < 0.01), post-operative renal failure (HR = 2.6, 2.2–3.1, P < 0.01), creatinine increase >100 mg/dl (HR = 3.0, 2.0–4.4, P < 0.01), dialysis (HR = 3.0, 1.9–4.7, P < 0.01), post-operative myocardial infarction (HR = 1.5, 1.2–1.8, P < 0.01) and logistic EuroSCORE (HR = 1.2, 1.1–1.12, P < 0.01).

By multivariate analysis, risk factors of long-term mortality were: residual AR >1 (HR = 1.7, 1.2–2.3, P < 0.01), age (HR = 1.1, 1.1–1.1, P < 0.01), previous cerebral ischaemia (HR = 1.4, 1.1–1.8, P < 0.01), diabetes (HR = 1.4, 1.2–1.7, P < 0.01), COPD (HR = 1.7, 1.5–2.1, P < 0.01), renal failure (HR = 1.4, 1.1–1.8, P < 0.01), peripheral vascular disease (HR = 1.3, 1.0–1.5, P = 0.02), coronary disease (HR = 1.2, 1.0–1.4, P = 0.02), post-operative renal failure (HR = 1.6, 1.3–2.0, P < 0.01), post-operative neurological complications (HR = 1.4, 1.9–1.8, P < 0.01). During follow-up, there was a statistically significant lower rate of reoperation in Group 1 (1.9 vs 6.7% (OR 2.1, 1.2–3.4, P = 0.01)) after a mean time of 4.4 ± 4.0 vs 2.4 ± 4.2 years (P = 1.83). Reintervention for perivalvular leak was necessary in nine patients (0.2%) in Group 1 and in six patients (4.4%) in Group 2 (P < 0.01). Perivalvular leak was the cause of reintervention in 13.2% of patients in Group 1 and in 66.7% in Group 2 (P < 0.01). The main causes of reintervention are reported in Fig. 2.

Haemolysis was reported in 2.1% in Group 1 and in 0.9% in Group 2 (P = 0.72). No patient needed reintervention because of haemolysis.

**Predictive factors for residual AR**

Univariate analysis was used to determine the clinical and surgical characteristics that were correlated to residual AR (Tables 1 and 2). Variables found to be significantly associated with residual AR >1 on univariate analysis included employment of mechanical valves (P < 0.001), lower body mass index (P = 0.01), preoperative atrial fibrillation (P = 0.03), cardiopulmonary bypass time (P = 0.01), clamping time (P = 0.02), post-operative creatinine increase >100 mg/dl (P = 0.06), post-operative mean aortic gradient (P = 0.01), post-operative peak aortic gradient (P = 0.01) and mitral regurgitation >2/4 (P = 0.04).

These variables were then used in a multivariate model. On multivariate analysis, risk factors for AR were the use of a mechanical valve (OR 1.97, 1.26–3.09, P = 0.01), preoperative atrial fibrillation (OR 2.0, 1.2–3.3, P = 0.01), cardiopulmonary bypass time (OR 1.1, 1.0–1.0, P = 0.01), post-operative mean aortic gradient (OR 1.1, 1.0–1.1, P < 0.01) and post-operative creatinine increase >100 mg/dl (OR 2.6, 1.2–5.3, P = 0.01).

**Echocardiographic follow-up**

The natural history of residual AR was evaluated by echocardiography. Transthoracic echocardiograms were obtained at discharge in all patients, and during follow-up in 1660 patients (54.1%) in Group 1 and in 131 patients in Group 2 (97%). Median echocardiographic follow-up was 2.9 years (1.3–7.5) in Group 1 and 2.5 years (1.1–6.3) in Group 2. In Group 1, 73 patients developed an AR >1 during follow-up.

In Group 2, 35 patients reduced their residual AR to ≤1, while 11 patients progressed from residual AR 2/4 to 3/4 (nine patients) or 4/4 (two patients). In the rest of the patients, the degree of regurgitation remained unchanged. To assess the haemodynamic consequences of paravalvular leaks, left ventricular dimensions and function within and between the subgroups of patients with and without paravalvular AR were compared during follow-up. Left ventricular ejection fraction increased in both groups, from 57.7 ± 12.5 to 60 ± 12% (P = 0.01) in Group 1 and from 56.7 ± 11 to 61 ± 10% (P < 0.01) in Group 2 (P < 0.01), but there were no differences between the two groups. Left ventricular mass, thickness of the left ventricle posterior wall and ventricular septum as well as end-diastolic left ventricular volume did not change in either group.

**DISCUSSION**

Although prosthesis design and surgical techniques have improved over the past decades, residual AR continues to complicate the postoperative course of some patients submitted to AVR. The problem is of particular interest with the advent and increasing use of minimally invasive techniques that have been associated with a higher incidence of residual AR. Despite
considered an acceptable trade-off in this patient population, the impact and significance of residual AR has thus far been poorly studied and may be underestimated. In our study, the incidence of residual AR >1 was 4.2%, which was associated with an increased risk of need for reoperation as well as an increased risk of mortality at all time points during follow-up.

Perivalvular leak

Some degree of physiologic transvalvular regurgitation has been demonstrated in many valves [10, 13–15]. In mechanical valves, it may occur during valve closure (backward flow) or after the valve has closed (leakage backward flow), but it rarely exceeds 10% of the forward flow [16]. In general, central residual ARs are narrow, have a low-velocity, consist of laminar jets of short duration (<1.5 cm) [17] and are considered of no haemodynamic significance. In contrast, paraprosthetic jets have a high velocity, are turbulent, have their origin outside the sewing ring and are considered more dangerous.

More recent data from transcatheter aortic valve implantation experience underline the importance of the degree of residual AR, independently from the mechanism of regurgitation (central or perivalvular) [18]. Results from the German transcatheter aortic valve interventions registry reveal that significant AR after transcatheter aortic valve implantation is common and is associated with increased in-hospital mortality [19].

For this reason, we divided our patient population between patients with a residual AR ≤1 (Group 1), considered as those with physiologic or at least not haemodynamically significant residual regurgitation, and patients with significant residual leaks (residual AR >1, Group 2).

The origin of the jet was not codified in our database for 48% of patients from Group 1. In the remaining 52%, residual AR was defined as perivalvular in 74.7% of patients. In Group 2, after all echocardiograms had been reassessed, residual AR was found to be at least in part periprosthetic in 97.1% of patients. Our experience corroborates previously cited results, suggesting that the impact of residual AR on clinical outcomes is not dependent on its mechanism (central or perivalvular) as it is on its degree. We found no difference in survival and in reoperation rates in patients with residual AR 0/4 and those with residual AR 1/4, while residual AR ≥2/4 was the minimal degree with an impact on outcomes, regardless of its origin.

Long-term survival

We found that the presence of a residual AR >1 is associated with a statistically significant increased risk of mortality at all time points (graphic 1) with an HR of 1.7. Observed survival rates at 5 and 10 years are similar to those previously reported in the literature [20–22]. However, our results regarding the impact of residual AR differ from previous experiences from other groups [1–3]. Literature on the impact of perivalvular leak is scarce. Moderate or severe residual ARs are generally corrected during the surgery, and less severe residual ARs are often judged acceptable and expected to improve over time, but their long-term impact is not well documented [1, 2].

O’Rourke et al. [1], in a group of 608 patients operated for mitral and AVR, studied 113 patients with trivial/mild residual AR and concluded that the clinical significance and the natural history of residual AR is benign in most cases, with no increase in mortality at 6 weeks.

Rallidis et al. [2] studied 40 patients initially identified as having a small aortic periprosthetic leak and reported no death during 5 years of follow-up, with unchanged echocardiographic parameters over time and no differences compared with the group without residual AR.

Recently, the interest in residual AR increased due to the high rate of both central and perivalvular regurgitation after transcatheter aortic valve implantation. Two-thirds of patients reveal a postoperative residual AR and 12% have a moderate-to-severe residual AR whose impact is not yet well established [4]. A study recently presented by Abdel-Wahab et al. [19] suggested that paravalvular leak >1 is associated with a significantly increased risk of in-hospital mortality. Tamburino et al. [18] in another study did not confirm an increased in-hospital mortality but identified residual AR >1 as an independent predictor of mortality between 30 days and 1 year, thus highlighting a role for suboptimal procedural results leading to haemodynamic instability in affecting midterm clinical outcomes.

We believe that previous papers on paravalvular leaks after surgical AVR underestimate the prognostic value of residual AR because of the reduced number of patients, the short follow-up and the misleading effect of considering mitral and aortic valves and trivial and mild regurgitation.

By multivariate analysis, survival was also negatively affected by commonly identified comorbidities (age, previous cerebral ischaemia, diabetes, COPD, renal failure, peripheral vascular disease, coronary disease) and postoperative factors (postoperative renal failure, postoperative neurological complications and length of hospital).

It should also be noted that in our experience, patients with residual AR >1 were statistically significantly more reinterventions, in particular, for perivalvular leaks (Fig. 2).

Since AR increases long-term mortality and the need for reinterventions, we suggest to repair paravalvular leaks >1 when they are found at intraoperative TEE after careful consideration of all other clinical data: the age of the patient, the presence of annulus calcification, the tissue fragility and the presence of possible technical mistakes.

Predictors of paravalvular leak

The main factors proposed as predictors of periprosthetic leak are the presence of endocarditis and severe calcification of the annulus [2, 3]. In active aortic endocarditis, the presence of abscesses and fragile inflammatory tissue may cause leakage that progresses with time. Calcium may prevent solid apposition and cause small crevices or suture breakage.

O’Rourke et al. [1] found that smaller body size and a bioprosthetic valve are significantly associated with residual AR. Miller et al. [3] analysing 1743 patients who underwent AVR found no clinical factors that could distinguish the 30 patients who developed residual AR. Engleberg et al. [23] found that the use of Silzone cuff is a risk factor for residual AR, while the use of pledges has a protective effect against paravalvular leak.

In our multivariate analysis, residual AR was associated with the use of a mechanical valve, the presence of preoperative atrial fibrillation, longer cardiopulmonary bypass time, higher
post-operative mean aortic gradient and post-operative creatinine increase.

Mechanical valves are more rigid and more difficult to adapt to the annulus in the case of severe aortic calcification increasing the risk of paravalvular leak. The other preoperative and postoperative data associated with residual AR cannot be considered as risk factors but in some cases they reflect the increased complexity of the operation. For instance, long cardiopulmonary bypass can be linked to the fragility of the tissues, to calcifications or to a small annulus and higher post-operative gradients can be explained by subvalvular calcifications or smaller annulus.

Echocardiographic follow-up

An important and unexpected finding in our study was the inability to predict the progression of the residual AR and to correlate the evolution of ventricular dimensions and function with survival. During follow-up, some patients from Group 1 developed residual AR > 2, while some patients from Group 2 experienced resolution of the leak and others worsened their regurgitation to a moderate-to-severe degree. In all cases, the evolution was not predictable. Most of the previous papers describe a favourable evolution of residual AR [1] even if some cases of new residual AR during follow-up are described [3].

Similarly, we have not been able to demonstrate a deterioration of left ventricular dimensions or function during follow-up in patients with a residual AR > 1. Conversely, the majority of patients showed a sustained improvement of left ventricular ejection fraction compared with the discharge studies. A similar favourable behaviour of left ventricular function in both groups of patients with and without residual AR had been described by Rallidis et al. [2], who also found a reduction in wall thickness that was not observed in our study.

Study limitations

First, this is a retrospective study even if data were prospectively collected. Second, specific causes of mortality are not available and only all-cause mortality could be assessed. However, cardiovascular deaths should easily be distributed among the two groups. Third, echocardiographic follow-up was not complete in Group 1, as many of the patients with uneventful initial follow-up were lost. As all patients undergo echocardiographic prosthesis evaluation before discharge in our institution, none of these patients had immediate postoperative residual AR.

CONCLUSIONS

Residual AR > 1 should be considered a risk factor of mortality and reoperation after AVR. Our data support a more aggressive treatment of residual AR when discovered at transoesophageal echocardiography after AVR, and caution in selecting AVR strategies, especially with regard to the use of transcatheter valve implantation which is associated with higher rates of residual AR.

Conflict of interest: none declared.

REFERENCES


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APPENDIX. CONFERENCE DISCUSSION

**Dr W. Gomes** (São Paulo, Brazil): I would like to commend you for all of this information; it is a lot of work to collect all this data, and to bring forward these important implications for this emerging technology, TAVI. I have a couple of remarks and questions as well.

From the table you showed there are some important differences. Patients in Group 2 seemed a bit sicker than patients in Group 1. Do you think it made any important difference to the results obtained from analysing and comparing these two groups? Also in Group 2 you have patients with higher than 1+ regurg, and you have analysed Group 2 as a whole. But there is a subgroup of patients where regurg remained unchanged throughout the follow-up, and another group of patients where regurg reduced or slightly progressed. Do you see any difference regarding prognosis between patients with unchanged regurg and those whose regurgitation progressed?

And stemming from your conclusions, conclusion number one is that the data support a more aggressive treatment of regurg. In your view, what would be a more aggressive treatment for this type of complication, a redo operation or perhaps a transcatheter approach with this new dedicated device just for that? Your second conclusion advises caution in selecting patients for TAVI. In your view, what type of patients should be referred for TAVI in order to minimize the chance of this complication?

**Dr Sponga**: I believe that a more aggressive approach means that when you discover residual aortic regurgitation >1 in the operating room, you should go back onto CPB and correct it. But it depends on the clinical situation of the patient. If you have a very old patient, 90 years old, with very fragile tissues, maybe it is not a good idea to go back to correct it, but if you have a young patient, in whom you suspect a technical error, you should go back and correct it.

This is a single retrospective study, and so I believe that we cannot change our practice because of the findings. However, it gives new information, because previous studies suggest there is no difference in patients that have residual aortic regurgitation and those who do not. And so I believe that this study may stimulate a surgeon to be more prone to repair a paravalve leak in the operating room.

Concerning TAVI, for sure it is an optimal treatment for a higher risk or an inoperable patient. But now the trend is to expand the indications, and, for sure, in this way we will have more residual aortic regurgitation with TAVI. And so if the patient has no specific indication for TAVI, the residual aortic regurgitation can have an impact on the decision to do or not to do a TAVI.

Concerning the evolution, certainly patients in whom there was evolution of the regurgitation performed worse than the others and required more operations. We had 35 patients in the group with residual aortic regurgitation >1 who improved their residual aortic regurgitation, passing from residual aortic regurgitation 2 or 3 to residual aortic regurgitation 1 or 0. In the other group, there were 11 patients in whom aortic regurgitation increased from ≤1 to 3 or 4, and for sure these patients performed worse. But it is difficult to predict which patients evolve and which ones do not; we have no predictive data about that. Even previous studies from the literature failed to show echocardiographic parameters able to predict that.

Concerning the differences between the two groups, we didn’t find a clear difference: the age, the EuroSCORE are the same. Certainly there are differences, but they were not statistically significant even though the population of patients considered is very large. I don’t know exactly why there were more deaths and complications in these patients with residual regurgitation.

**Dr A. Haverich** (Hannover, Germany): I think this is a very important contribution with a huge number of patients, and I think large centres are in a position to present a data set like this. I am still very interested from our daily practice that complications other than the death of the patients come into play in relation to complications of paravalvular leakage, one being haemolysis, and all of us have been in situations where we did actually reoperate on patients for haemolysis where transfusion is mandatory. Did you observe this in your patient population? Also the question of endocarditis comes up. Is there an increased risk of endocarditis in those patients who have paravalvular leakage and was that a common cause for reoperation in this series?

**Dr Sponga**: When we analysed the data, it was a surprise for me to discover that haemolysis was not a problem. It was reported only in a few patients. Regurgitation 2 and 3 doesn’t increase the risk of haemolysis. But it was not really a problem and not very frequent.

The risk of endocarditis was not increased in these patients. We had some endocarditis in patients with residual aortic regurgitation less than 1 and no endocarditis in patients with residual aortic regurgitation more than 1. It was surprising, but these were our results.

**Dr C. Alhan** (Istanbul, Turkey): Do you use preoperative transoesophageal echocardiography routinely? If not, do you think that it will improve the results?

**Dr Sponga**: Yes, we routinely do transoesophageal echocardiography in the operating room. I believe that gives us a lot of data to decide what to do and how to manage the patient, of course.

**Dr G. Lutter** (Kiel, Germany): Yes, very important, so it is mandatory.