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ORIGINAL RESEARCH

Repair of Aortic Regurgitation in Young Adults: Sooner Rather Than Later

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BACKGROUND: Establishing surgical criteria for aortic valve replacement (AVR) in severe aortic regurgitation in young adults is challenging due to the lack of evidence-based recommendations. We studied indications for AVR in young adults with severe aortic regurgitation and their outcomes, as well as the relationship between presurgical echocardiographic parameters and postoperative left ventricular (LV) size, function, clinical events, and valve-related complications.

METHODS AND RESULTS: Data were collected retrospectively on 172 consecutive adult patients who underwent AVR or repair for severe aortic regurgitation between 2005 and 2019 in a tertiary cardiac center (age at surgery 29 [22–41] years, 81% male). One-third underwent surgery before meeting guideline indications. Postsurgery, 65% achieved LV size and function normalization. LV ejection fraction showed no significant change from baseline. A higher presurgical LV end-systolic diameter correlated with a lack of LV normalization (odds ratio per 1-cm increase 2.81, $P<0.01$). The baseline LV end-systolic diameter cut-off for predicting lack of LV normalization was 43 mm. Pre- and postoperative LV dimensions and postoperative LV ejection fraction predicted clinical events during follow-up. Prosthetic valve-related complications occurred in 20.3% during an average 5.6-year follow-up. Freedom from aortic reintervention was 98%, 96.5%, and 85.4% at 1, 5, and 10 years, respectively.

CONCLUSIONS: Young adult patients with increased baseline LV end-systolic diameter or prior cardiac surgery are less likely to achieve LV normalization after AVR. Clinicians should carefully balance the long-term benefits of AVR against procedural risks and future interventions, especially in younger patients. Evidence-based criteria for AVR in severe aortic regurgitation in young adults are crucial to improve outcomes.

Key Words: aortic regurgitation ■ aortic valve ■ congenital heart disease ■ outcomes ■ surgery ■ young

Aortic valve abnormalities are one of the most frequent congenital cardiac conditions and often result in severe aortic regurgitation (AR), which causes left ventricular (LV) volume overload, dilatation and, if left unrepaired, LV dysfunction.[1] Establishing the surgical timing and indications for aortic valve replacement (AVR) or repair in the setting of severe AR is challenging, especially for young adults. Current European and American guidelines recommend intervention based on the presence of symptoms, LV dysfunction, or severe chamber dilatation.[2,3] These indications have been validated on survival analyses performed mainly in older adults with aortic valve degeneration and a higher prevalence of comorbidities, hence a higher perioperative risk.[4–7]

AR in younger adults is typically due to congenital heart disease (CHD), and the clinical presentation and natural history can differ from that of older individuals with acquired aortic valve disease. Patients with CHD tend to adapt their lifestyle to their limitations and may

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CLINICAL PERSPECTIVE

What Is New?

- Young adults with severe aortic regurgitation tend to undergo aortic valve replacement or repair before fulfilling standard criteria from clinical practice guidelines; more than one-third of the cohort did not normalize their left ventricular (LV) diameters or function after surgery.
- Young patients who fulfilled the guideline-based criteria for surgery in terms of LV size or function were less likely to fully normalize their left ventricle postoperatively.
- Postoperative LV diameters and ejection fraction were predictors of clinical events (death or heart failure) during follow-up; prosthetic valve complications, such as valve degeneration and infective endocarditis, are frequent during follow-up, especially in younger individuals.

What Are the Clinical Implications?

- In young adults with previous cardiac surgery or raised LV end-systolic diameters preoperatively, normalization of LV size and function is less likely to occur after aortic valve replacement; a lower threshold for valve replacement may, thus, be reasonable in this young cohort with the aim to protect the left ventricle.
- Early intervention for aortic regurgitation should, however, be weighed against the medium-to-long-term risk of prosthesis-related complications, which are frequent in young adults.

Nonstandard Abbreviations and Acronyms

AR	aortic regurgitation
AVR	aortic valve replacement
BNP	pro-b-type natriuretic peptide
EATCS	European Association for Cardio-Thoracic Surgery
EDD	end-diastolic diameter
IE	infective endocarditis

not report symptoms even in the presence of objective exercise limitation (eg, an abnormal cardiopulmonary exercise test).[8] Moreover, despite the low prevalence of comorbidity when compared with older cohorts, young patients with CHD have often undergone previous surgical and percutaneous interventions. When considering surgery for young adults, the timing of intervention is critical, not only to avoid long-term sequelae but also to minimize the number of surgeries across their lifespan.

In this study, our primary goal was to analyze the surgical indications and interventional thresholds in a cohort of young adults with significant AR managed through multidisciplinary decision-making in a tertiary CHD center, with a focus on perioperative LV characteristics. We also investigated the relation between presurgical echocardiographic parameters and LV remodeling during follow-up, with the aim of identifying parameters that may assist cardiologists in deciding on the best timing for surgery. Finally, we assessed the relation between pre- and postsurgical LV characteristics and adverse clinical events after AVR.

METHODS

Population

We conducted a retrospective review of all adults (age ≥16 years) who underwent AVR or repair for AR at a tertiary center in the United Kingdom between 2005 and 2019. Patients were included if they had at least moderate AR on the presurgical echocardiogram. They were excluded if they had concomitant severe valvular, sub- or supravalvular stenosis, univentricular physiology, systemic right ventricle, or a prosthetic aortic valve (except autografts). Patients with concurrent mitral valve disease or significant shunts were also excluded. Demographic, clinical, and imaging data were retrospectively collected. Echocardiographic information was collected at 3 time points: before surgery (baseline), before hospital discharge after surgery (immediately postoperative), and at least 6 months after surgery (follow-up). Clinical events and prosthetic valve complications were collected up to April 2021. The study was approved by the UK Health Research Authority and the Centre Ethics Committee, and informed consent was waived due to the retrospective nature of the data.

Imaging

All transthoracic echocardiography studies were performed and reported by expert cardiac sonographers and reviewed by a CHD imaging cardiologist. LV dimensions were measured using the approach recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging Chamber Quantification guidelines.[9,10] LV ejection fraction (EF) was assessed using the 2D biplane method of disks (modified Simpson's method). The measurements were retrieved from the original transthoracic echocardiography reports. In a small number of cases (n=5), the reports were incomplete, but images were available and the data were retrieved by a cardiologist certified in adult transthoracic echocardiography. AR severity (mild, moderate, or severe) was graded by combining semiquantitative and quantitative measures: vena contracta size, pressure

half-time, end-diastolic velocity, proximal iso-velocity surface area–derived regurgitant volume and effective regurgitant orifice area and flow reversal in the descending aorta.[11] Symptoms were recorded according to the New York Heart Association functional class classification.

Outcome Definition

The primary composite outcome was normalization of the LV in terms of LV size (assessed by echocardiographic diameters) and function (measured by EF) at least 6 months postsurgery (ie, on the follow-up echocardiogram). For men, normal LVEF was considered ≥52%, normal LV end-diastolic diameter (LVEDD) <58 mm, and LV end-systolic diameter (LVESD) <40 mm. For women, normal LVEF was considered ≥54%, LVEDD <52 mm, and normal LVESD <35 mm.[9] LV diameters rather than volumes were used to define the outcome of LV normalization due to the greater availability of data. Normal and abnormal cut-offs for LV size and function were based on current American Society of Echocardiography/European Association of Cardiovascular Imaging echocardiography guidelines.[9]

The secondary outcome of this study was a composite of major adverse clinical events that occurred after surgery. Major adverse clinical events were defined as either death or new-onset heart failure, indicated by a new clinical diagnosis or hospitalization due to heart failure, as per current recommendations.[12] Tachyarrhythmias requiring intervention (ablation or direct current cardioversion) were considered secondary minor cardiac events. Valve longevity and complications associated with AVR or repair were also collected (ie, prosthetic valve degeneration, infective endocarditis [IE], prosthetic valve–associated stroke and patient–prosthesis mismatch), all defined according to international standards.[13,14] Surgical failure was defined as significant AR immediately after surgery requiring reoperation.

Statistical Analysis

All values are presented as mean with SD or median with interquartile range (IQR), as appropriate. The Wilcoxon signed-rank test was used for paired comparisons of continuous and ordinal variables. The association between the baseline clinical and echocardiographic parameters, and LV non-normalization on the follow-up echocardiogram was assessed using univariable and multivariable logistic regression analysis, with backward stepwise selection (minimization of the Akaike Information Criterion). Receiver-operating characteristic curves were drawn for echocardiographic continuous parameters that were included in the final multivariable logistic regression model, identifying the cut-off that maximizes sensitivity and specificity for LV non-normalization at follow-up. The continuous covariates were checked for nonlinearity using visual scatter plots displaying the relation between covariates and the outcome variable.

We performed a sensitivity analysis using purposeful variable selection for the multivariable logistic regression model. Initially, all the significant parameters in the univariable analysis (with a flexible P value of <0.25) were included in the multivariable model but, to avoid overfitting, the maximum number of predictors never exceeded 4. To ensure that the parsimonious model fit as well as the new models, they were compared using a partial likelihood ratio test. Finally, the coefficients of the variables included in the parsimonious model were compared with the other models for effect changes exceeding 20%.

Freedom from reintervention was analyzed using Kaplan–Meier survival curves, and the log-rank test was used for group comparisons. Univariable Cox proportional hazards regression was used to identify predictors of clinical events after surgery, with the date of the follow-up echocardiogram as "start time."

A 2-sided P value <0.05 was considered statistically significant. R software version 4.1.1 (R Core Team, Austria, 2021) was used for all statistical analyses.

Data Availability

Requests for access to the data set may be directed to the corresponding author. Given the sensitive nature of the data gathered for this study, each request will be assessed on a case-by-case basis.

RESULTS

Baseline Characteristics

From 2005 to 2019, a total of 172 patients had AVR for at least moderate AR. The median age at surgery was 29.0 years (IQR, 22.0–41.0), and the majority (80.8%) were male (Table 1).

The cohort was mainly composed of patients with CHD (99.4%), with a bicuspid aortic valve in 77.3%. Of the latter, 23 (13.4%) had associated coarctation of the aorta. Other diagnostic groups included ventricular septal defects and repaired tetralogy of Fallot (Table 1). A minority had complex anatomy (double outlet right ventricles, Fallot-type, repaired in early childhood), and 1 had rheumatic valve disease (with prior Ross procedure). More than half (52.7%) had at least 1 previous sternotomy, and 10.5% a previous thoracotomy. Almost one-third (32.0%) of the cohort had a prior aortic valve intervention.

Surgical Indication

Most patients had chronic AR at the time of the surgery (92.5%), with a minority (7.6%) presenting with acute AR due to IE. At the time of the operation, most patients had severe AR (88.4%). In patients with chronic

Table 1. Clinical Background and Demographic Characteristics

	N=172
Male sex (n, %)	139 (80.8%)
Age at surgery, y (median, IQR)	29.0 (22.0–41.0)
Height, cm (median, IQR)	178.0 (172.0–182.2)
Weight, kg (median, IQR)	75.0 (64.1–90.0)
BMI, kg/m^2 (median, IQR)	24.5 (21.6–28.0)
BSA, m^2 (mean±SD)	1.9±0.2
Main diagnosis (n, %)	
Isolated BAV	110 (64.0%)
BAV and aortic coarctation	23 (13.4%)
Perimembranous ventricular septal defect	18 (10.5%)
D-TGA arterial switch	5 (2.9%)
Double-outlet right ventricle	5 (2.9%)
Truncus arteriosus	3 (1.7%)
Subaortic membrane	3 (1.7%)
Repaired tetralogy of Fallot	2 (1.2%)
Dilated aortic root or ascending aorta	2 (1.2%)
Rheumatic valve disease	1 (0.6%)
Previous aortic valve intervention (n, %)	
None	112 (65.1%)
Only surgical	45 (26.2%)
Only percutaneous	8 (4.7%)
Surgical and percutaneous	7 (4.1%)
Type of prior surgery on the aortic valve or root (n, %)	
None	117 (68.0%)
Surgical valve repair	35 (20.4%)
Ross procedure	17 (9.9%)
David procedure	3 (1.7%)
Number of previous surgeries (n, %)	
None	83 (48.3%)
1	64 (37.2%)
≥2	25 (14.5%)
Number of previous sternotomies (n, %)	
None	94 (54.7%)
1	57 (33.1%)
≥2	21 (12.2%)
Number of previous thoracotomies (n, %)	
None	154 (89.5%)
1	18 (10.5%)
Previous percutaneous procedures (n, %)	
None	146 (84.9%)
Aortic balloon valvuloplasty	15 (8.7%)
Coarctation dilatation/stent implantation	8 (4.7%)
VSD closure	3 (1.7%)
Comorbidities (n, %)	
None	109 (63.4%)
Hypertension	20 (11.6%)
Obesity	10 (5.8%)
Asthma	7 (4.1%)
Smoker/former smoker	8 (4.7%)
Atrial tachycardias	12 (7.0%)
Permanent pacemaker	5 (2.9%)
Implantable cardioverter defibrillator	2 (1.2%)
Cardiac resynchronization therapy	1 (0.6%)
Liver disease (cirrhosis)	1 (0.6%)
Chronic kidney disease	1 (0.6%)
Diabetes	1 (0.6%)
Previous stroke	1 (0.6%)
Down syndrome	1 (0.6%)

BAV indicates bicuspid aortic valve; BMI, body mass index; BSA, body surface area; D-TGA, dextro-transposition of the great arteries; IQR, interquartile range; and VSD, ventricular septal defect.

AR, the main surgical indication was progressive LV dilatation and/or dysfunction (92.4%), with 7.6% operated on due to dilatation of the ascending aorta in the presence of at least moderate AR (Table 2).

Baseline Ventricular Parameters

Even though LV dilatation or dysfunction was the most common indication for surgery in patients with chronic AR, over one-third (35.8%) were operated on before fulfilling the 2021 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guideline recommendations for surgery, while 27% did not satisfy the 2020 American College of Cardiology/American Heart Association guideline indications (Figure 1A and 1B). Indeed, the vast majority (91.2%) underwent surgery with an LVESD ≤50 mm (the mean LVESD was 42.0±7.5 mm) and 80.5% with an LVEF >50%. There was no significant difference in LVEF between patients with and without previous surgery (LVEF 57.6±10.0% versus LVEF 59.9±7.8%, respectively, P=0.055).

At the time of surgery, fewer than half of the patients (45.3%) were symptomatic, and only 23 (13.4%) had significant symptoms (New York Heart Association class III or IV) (Table S1). Only a minority of patients with chronic AR were severely symptomatic (6.3%) compared with the acute AR group, which were all severely symptomatic (100%). A preoperative cardiopulmonary exercise test was available in 78 (45.3%) patients: the mean percent-predicted peak oxygen consumption was 80.1±22.9%; one-quarter (24.4%) had a peak oxygen consumption <60% predicted.

Table 2. Surgical Indications, Presence of Aortopathy at Baseline, and Surgical Procedures

	N=172
Indication for surgery according to MDT (n, %)	
Chronic AR with LV dilatation or dysfunction	147 (85.5%)
Chronic AR with dilatation of the ascending aorta	12 (7.0%)
Acute AR due to infective endocarditis	13 (7.6%)
Ascending aorta diameter presurgery, mm (median, IQR)	39 (35.0–46.0)
Aortic regurgitation presurgery (n, %)	
Severe	152 (88.4%)
Moderate	20 (11.6%)
Type of surgery (n, %)	
Biological AVR	101 (58.7%)
Mechanical AVR	41 (23.8%)
Autograft/Ross procedure	22 (12.8%)
Aortic valve repair	4 (2.3%)
Homograft	4 (2.3%)
Ascending aorta replacement surgery (n, %)	
None	96 (55.8%)
Gelseal/Gelweave/Hemashield/Intergard graft	39 (22.7%)
St Jude Composite	10 (5.8%)
Freestyle AVR & root	10 (5.8%)
Biovalsalva conduit	4 (2.3%)
Homograft replacement	4 (2.3%)
Patch augmentation of the aorta	4 (2.3%)
Ascending aorta plication	3 (1.7%)
Hemiarch repair	2 (1.2%)
Valve type (n, %)	
Perimount	60 (34.9%)
St Jude	39 (22.7%)
Autograft (Ross procedure)	19 (11.0%)
Mosaic	18 (10.5%)
Medtronic Freestyle	16 (9.3%)
Biovalsalva	4 (2.3%)
Carbomedics	4 (2.3%)
Homograft	4 (2.3%)
Valve repair	4 (2.3%)
Hancock	1 (0.6%)
Inspiris	1 (0.6%)
On-X	1 (0.6%)
Sorin	1 (0.6%)
Valve size (median, IQR)	27.0 (25.0–29.0)
Surgical timing (n, %)	
Elective	159 (92.4%)
Urgent	13 (7.6%)
Cardiopulmonary bypass used (n, %)	172 (100.0%)
Length of hospital stay for surgery, d (median, IQR)	8.0 (7.0–12.0)
Immediate complications postsurgery (n, %)	
Postoperative AT/AF	11 (6.4%)
Pericardial effusion requiring drainage	5 (2.9%)
Complete AV block requiring PPM	4 (2.3%)
Temporary mechanical circulatory support	1 (0.6%)
Perioperative stroke	1 (0.6%)
Acute kidney injury requiring dialysis	1 (0.6%)
Early prosthetic valve infection requiring surgery	1 (0.6%)

AF indicates atrial fibrillation; AR, aortic regurgitation; AT, atrial tachycardia; AV, atrioventricular; AVR, aortic valve replacement; IQR, interquartile range; LV, left ventricle; MDT, multidisciplinary team; and PPM, permanent pacemaker.

Surgical Characteristics and Perioperative Complications

Prosthetic valve characteristics, length of hospital stay, and immediate postoperative complications are shown in Table 2. The majority of patients received a biological prosthesis (58.7%), followed by a mechanical prosthesis (23.8%) and an autograft with pulmonary valve replacement (Ross procedure, 12.8%). Patients who received an autograft were younger (mean age 21.6±6.4 years) than the ones who received a biological (32.5±2.4 years) or a mechanical prosthesis (35.5±9.1 years, $P<0.001$). There was no significant difference regarding the type of prosthesis used between men and women ($P=0.073$).

No patient died in the perioperative period; 1 required temporary mechanical circulatory support as a bridge to recovery due to severe LV dysfunction. One patient had a perioperative stroke, whereas another presented with IE <15 days after the procedure, requiring reoperation and prolonged antibiotic therapy.

Echocardiographic and Symptomatic Changes Postsurgery

A significant reduction in LV size occurred in the immediate postoperative period (median 5 days after surgery, IQR, 4–7), particularly in terms of end-diastolic parameters (Figure 2). The median change in the LVEDD was –10.0 mm (–14.0 to –6.0) immediately after surgery, with a further –2.4 mm (–6.8 to 2.0) reduction on the follow-up echocardiogram ($P<0.001$ for both), performed at a median of 15.1 months after surgery (IQR, 10.8–21.3) (Table S1). The reduction in LVESD occurred more evenly throughout the follow-up: immediately postsurgery –3.3 mm (–8.0 to 0.0) and a further –4.0 mm (–8.0 to 1.0) after the first 6 months ($P<0.001$ for both). A significant drop in LVEF of –7.0% (–14.5 to 0.0, $P<0.001$) was observed immediately after surgery, with a +5.9% improvement on follow-up (0.0–12.0,

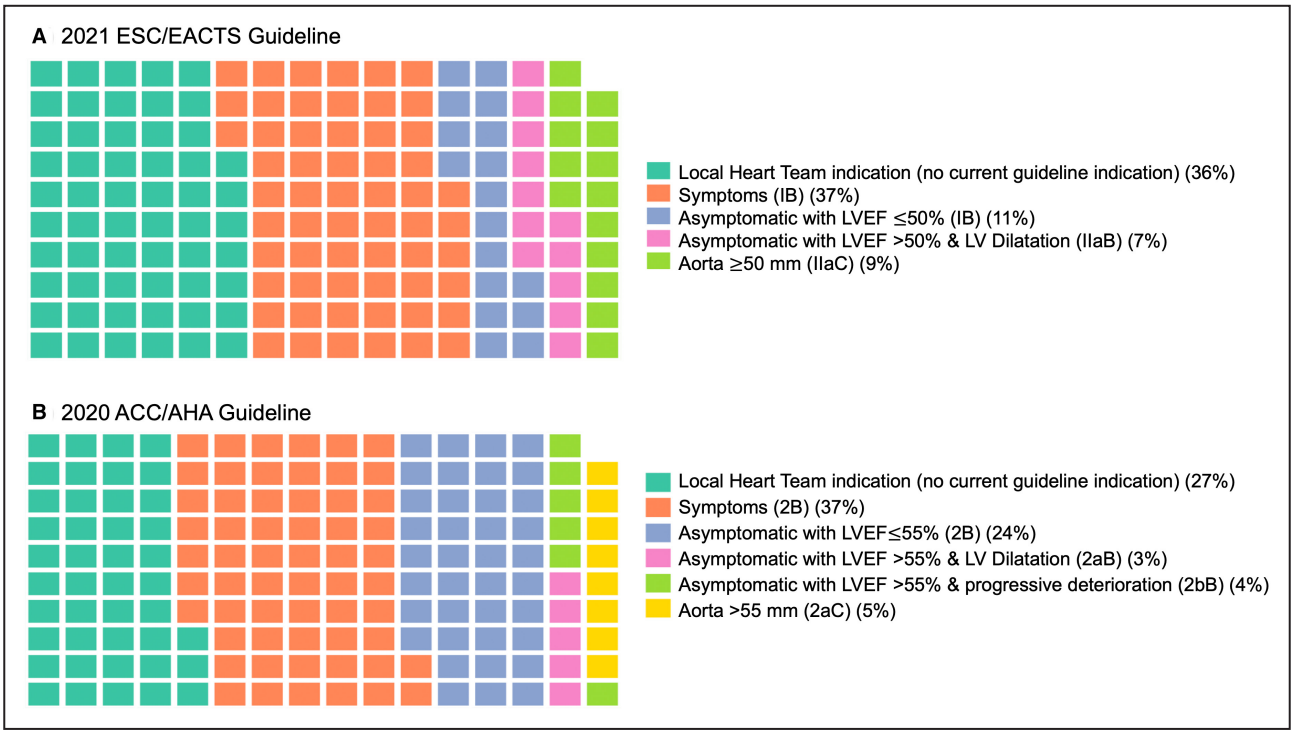

Figure 1. Patients with chronic AR stratified by the type of guideline indication ([A] 2021 ESC/EATS; [B] 2020 ACC/AHA) for aortic valve surgery present at the time of the surgery.
ACC indicates American College of Cardiology; AHA, American Heart Association; AR, aortic regurgitation; EATCS, European Association for Cardio-Thoracic Surgery; ESC, European Society of Cardiology; LV, left ventricle; and LVEF, left ventricular ejection fraction.

P<0.001); as a result, there was no significant overall change in LVEF from baseline to the latest follow-up (overall difference 0%, IQR, –7.6 to 5.0, *P*=0.084). More than one-third of the cohort (35.5%), however, had not normalized their LV size and function by the time of the follow-up echocardiogram. The LVEF remained impaired in 22.5%, in most to a mild degree (90.3%).

Symptoms improved significantly after surgery (*P*=0.001), with only 9.3% experiencing residual symptoms, mostly mild (98.1%). The few patients in New York Heart Association class III postoperatively belonged to the group in whom the LV had not normalized on the follow-up echocardiogram. A postoperative cardiopulmonary exercise test was available in 62 patients, performed at a median 2.9 years (IQR, 1.7–4.5) after surgery. There was no significant difference in peak O_2 consumption between patients with and without LV normalization on the follow-up echocardiogram (85.3±18.7% versus 80.5±20.1%, *P*=0.46).

Predictors of LV Non-Normalization

The following echocardiographic parameters were associated with the risk of LV non-normalization on univariable logistic regression analysis: LVEF and LV end-systolic (LVES) parameters (OR per 10% increase in LVEF, 0.50 [95% CI, 0.31–0.75], *P*=0.002; OR per 1-cm increase in LVESD, 2.49 [95% CI, 1.43–4.69], *P*=0.003; OR per 10-mL increase in LVES volume, 1.11 [95% CI, 1.01–1.24], *P*=0.042, respectively) (Table S2). Univariable analysis using demographic and clinical variables (age, sex, body mass index, symptoms, BNP [pro-b-type natriuretic peptide], number of previous surgeries, and acute/chronic AR) only identified previous surgery as a predictor of LV non-normalization. When the echocardiographic and clinical variables significant on univariable analysis were included in a multivariable model, baseline LVESD (OR, 2.81 [95% CI, 1.54–5.56], *P*=0.002) and previous surgery (OR, 3.46 [95% CI, 1.57–8.14], *P*=0.003) remained in the model. Additionally, utilizing purposeful variable selection with all parameters that achieved *P*<0.25 in the univariable analysis (including sex, baseline LVEDD, LVESD, LVEF, and previous surgery), the multivariable model obtained was identical to the one obtained from backwards variable selection.

On receiver-operating characteristic analysis, the cut-off for baseline LVESD that maximizes sensitivity and specificity was 43 mm (Figure 3). Based on the logistic regression, the predicted probability of LV non-normalization with a baseline LVESD of 43 mm was 35.7% (Figure S1). In our cohort, patients who

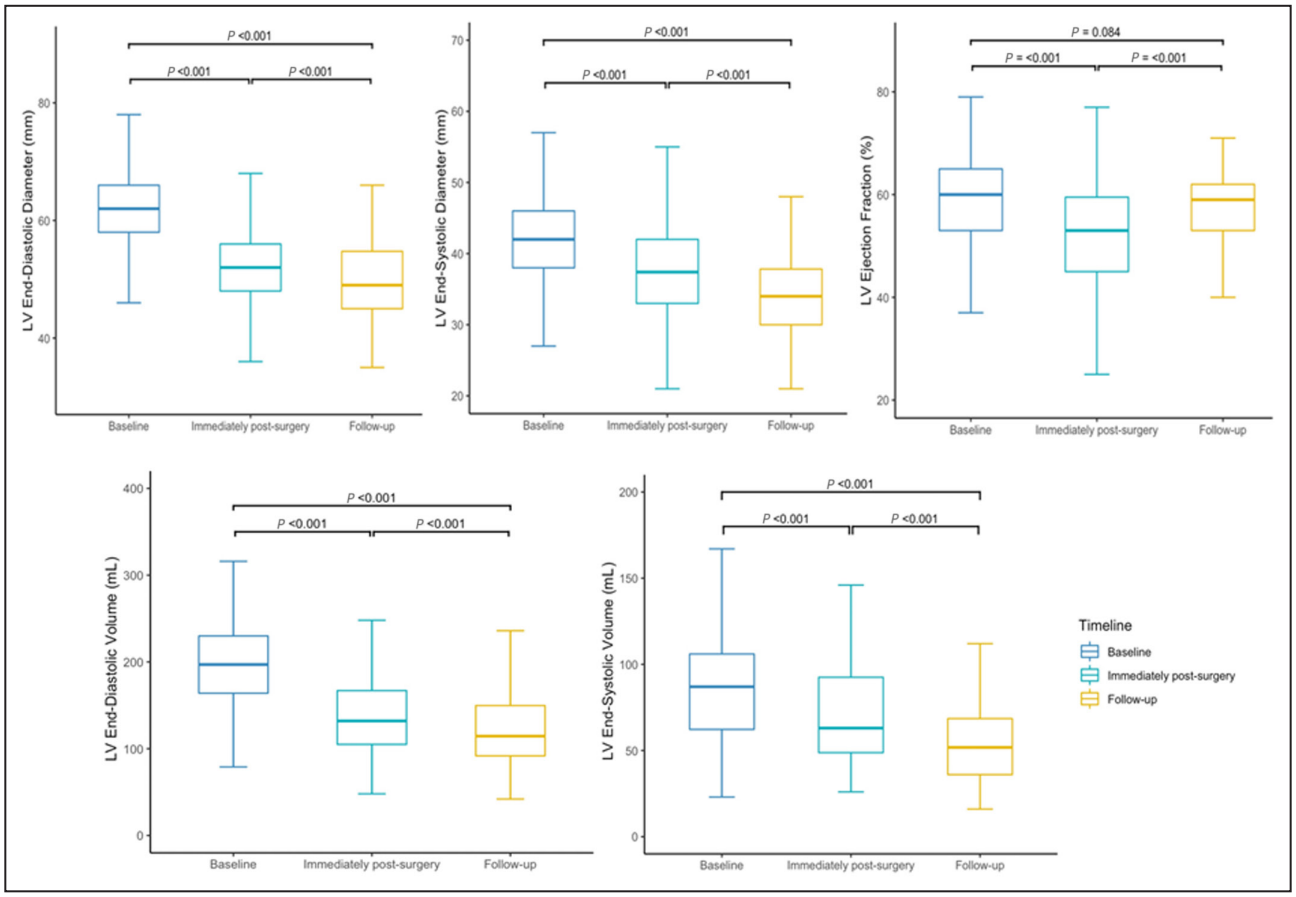

Figure 2. LV parameters (end-diastolic diameter, end-systolic diameter, ejection fraction, end-diastolic volume, and end-systolic volume) measured by transthoracic echocardiogram before, immediately after surgery, and at least 6 months postprocedure.
LV indicates left ventricle/ventricular.

fulfilled the European Society of Cardiology/European Association for Cardio-Thoracic Surgery or American College of Cardiology/American Heart Association guideline criteria for AR surgery were less likely to normalize their LV postoperatively (OR, 2.97 [95% CI, 1.45–6.21], *P*=0.003 and OR, 2.90 [95% CI, 1.41–6.13], *P*=0.004, respectively).

Follow-Up and Clinical Events

Patients were followed for a median of 5.6 years (IQR, 2.6–9.2) after surgery. At least 1 major clinical event was recorded in 22.1% of the cohort and ≥1 minor event in 1.7%. During follow-up, 5 patients (2.9%) died: 1 patient died of an unknown cause 5 months after the intervention (aged 34 years), 1 of heart failure (8.7 years after surgery) and 3 due to heart failure secondary to valve degeneration (8.8, 10.4, and 11.0 years after surgery).

During follow-up, 10 (5.8%) patients presented with heart failure, of whom 6 (3.5%) required cardiac resynchronization therapy or implantable cardioverter defibrillator (Table 3). One patient was referred for heart transplantation.

Echocardiographic parameters associated with the clinical outcome of death or new-onset heart failure (11 events) on univariable Cox regression analysis were baseline LVEDD (hazard ratio [HR] per 1-cm increase, 2.15 [95% CI, 1.27–3.61], *P*=0.004) and LVESD (HR per 1-cm increase, 1.75 [95% CI, 1.16–2.63], *P*=0.007), but not LVEF (Table S3). Clinical variables, such as age, sex, body mass index, symptomatic status, previous surgery, treatment with an angiotensin-converting enzyme inhibitor, and BNP concentration before surgery were not associated with the clinical end point. When using data from the postoperative transthoracic echocardiography (n=136), LVEDD and LVESD were predictors of the clinical end point: (HR, 2.23 [95% CI, 1.21–4.10], *P*=0.010; HR, 2.41 [95% CI, 1.40–4.14], *P*=0.006, per 1-cm increase, respectively). Moreover, a higher postoperative LVEF was protective of clinical events (HR for 10% increase, 0.32 [95% CI, 0.17–0.61], *P*<0.001) during follow-up.

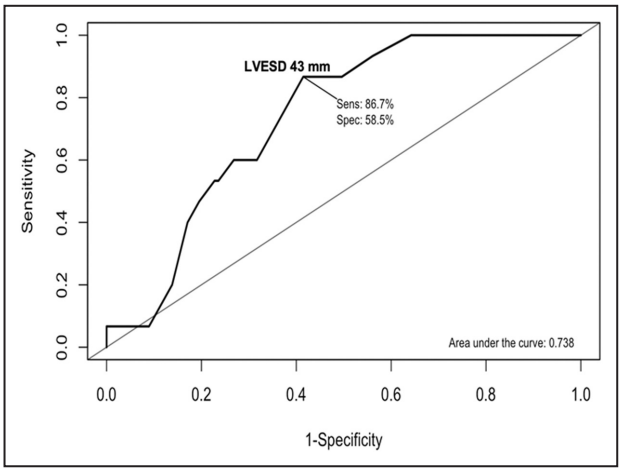

Figure 3. ROC curve displaying the sensitivity and specificity of the preoperative LVESD in predicting LVESD normalization after surgery.
The sensitivity and specificity for the optimal cut-off points are also shown. LVESD indicates left ventricular end-systolic diameter; ROC, receiver operating characteristic; Sens, sensitivity; and Spec, specificity.

Prosthetic Valve Complications

During follow-up, valve-related complications were recorded in 20.3% of patients (n=35): 9.3% experienced valve degeneration, 6.4% had IE, and 2.9% developed significant AR (Table 4). Other valve-related events included prosthesis-related strokes in 4 patients (2.3%), 2 of whom were in the context of IE. Of note, 5 out of 11 cases of IE happened in the first year after surgery, and the remainder occurred at least 4 years thereafter.

Of those with valve-related complications, approximately half (51.4%) underwent redo aortic valve surgery, whereas 3 (8.6%) patients died. The overall freedom from aortic valve reintervention (Figure 4) was 98%, 96.5%, 85.4%, at 1, 5, and 10 years, respectively. There were no significant differences in freedom from reintervention according to the surgical procedure/type of valve implanted (P=0.490) (Figure S2).

DISCUSSION

Our data show that a significant proportion of our young cohort underwent surgery for AR before fulfilling standard guideline surgical indications. Yet over one-third did not experience complete normalization of LV function or size after surgery. Pre- and postsurgical LV size and function parameters were associated with the likelihood of clinical events (death or new-onset heart failure) during follow-up.

Operating on patients with significant AR earlier than the current guidelines recommend has the obvious benefit of protecting the LV from long-standing dysfunction and adverse clinical events.[15–18] Indeed, the most recent American guidelines have raised the threshold for recommending surgery.[3] In our cohort, patients who fulfilled guideline criteria were less likely to normalize their LV postoperatively. This suggests that operating on these patients earlier than current guidelines recommend may be of benefit. These observations have clinical implications, because postoperative LV characteristics were strongly associated with the risk of death or heart failure during follow-up.

Table 3. Clinical Status and Events During Follow-Up

Clinical status at the end of follow-up (n, %)	N=172
Alive with heart failure	9 (5.2%)
With CRT, P	2 (1.16%)
With CRT, D	3 (1.74%)
With ICD	1 (0.58%)
Dead	5 (2.9%)
Clinical end point: death or heart failure on follow-up (n, %)	
Yes	11 (6.40%)

CRT-D indicates cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; and ICD, implantable cardioverter defibrillator.

In our cohort, end-diastolic parameters returned to normal earlier than end-systolic parameters after AVR, as has been reported by other groups.[19,20] While end-diastolic parameters are heavily influenced by chronic volume overload and are faster to normalize once the hemodynamic burden is relieved, the end-systolic parameters reflect myocardial contractility, which appears to recover more slowly and, often, not fully. Despite the significant volume overload to the LV preoperatively, LV systolic function could not be described as "hyperdynamic" in most patients (mean LVEF 58.7±9.1%). LV dimensions decreased in the immediate postoperative period, with a greater reduction observed in end-diastolic rather than end-systolic dimensions, while LVEF at the follow-up echocardiogram was comparable to the preoperative LVEF. This appears to support our early intervention approach.

Prosthetic valve-related complications were common after surgery. Our data clearly show that early intervention should be weighed against the medium-to-long-term risks of prosthesis-related complications, which affected >20% of our cohort. Freedom from aortic valve reintervention at 10 years was 85%, which is in line with previous reports in young adults.[21,22] The longevity of a valve prosthesis is related to the type of valve chosen[21]; despite metallic prostheses being considerably more durable, most young patients in our cohort (58.7%) opted for bioprosthetic valves. Indeed, young individuals who want to remain active or become pregnant often choose biological prostheses. The Ross procedure, which uses an autograft in the aortic position, is a valid alternative for young patients who want to avoid life-long anticoagulation. However,

Table 4. Prosthetic Valve Complications During Follow-Up

	N=172
Prosthetic valve complications (n, %)	
Valve degeneration	16 (9.3%)
Infective endocarditis	11 (6.4%)
Surgical failure/residual significant AR	5 (2.9%)
Stroke	4 (2.3%)
Death attributed to valve degeneration/IE	3 (1.7%)
Other complications (patient–prosthesis mismatch)	1 (0.6%)
Aortic valve reintervention (n, %)	
Completed	18 (10.4%)
Pending surgery	6 (3.4%)
Other reinterventions (n, %)	
Aortic root replacement (dilatation)	1 (0.6%)
Ascending aorta replacement (abscess)	1 (0.6%)
Augmentation of main pulmonary artery	1 (0.6%)
Pulmonary valve replacement (due to IE)	1 (0.6%)

AR indicates aortic regurgitation; and IE, infective endocarditis.

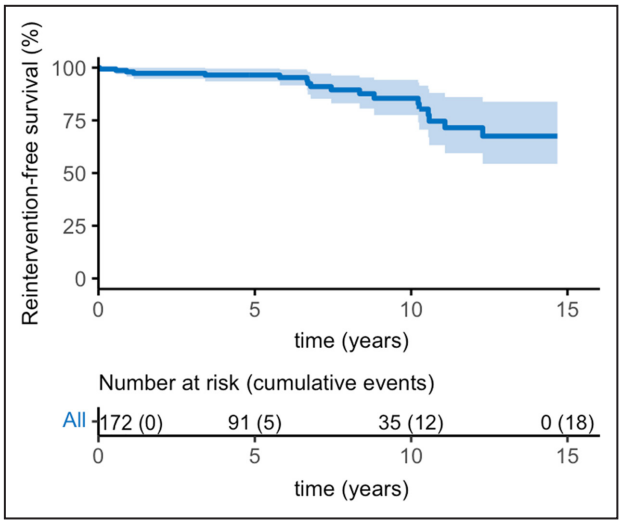

Figure 4. Kaplan–Meier curve presenting freedom from aortic valve reintervention with 95% CIs.

the presence of AR and dilatation of the aortic root or ascending aorta are considered by many to be a contraindication for the Ross procedure.[23–26]

Freedom of reintervention is also linked to prosthesis-related infections. Indeed, 6.4% of our cohort had at least 1 episode of IE during follow-up; in almost half, infection occurred within the first year of the index operation. IE is a devastating complication, with a high mortality and morbidity, especially when involving prosthetic material in the aortic or mitral position.[27] However, patients with a bicuspid aortic valve, especially those with significant ongoing hemodynamic lesions, are also at significant risk of IE.[1]

One of the major challenges for physicians caring for patients with AR is optimizing long-term outcomes while minimizing the number of interventions throughout the patients' lifetime, especially surgeries involving cardiopulmonary bypass. Our short- and long-term postoperative event rate was not insignificant and was similar to previous reports.[16,28] A recent German study of 289 patients operated on for AR (median age 57 years) reported a freedom from severe valve deterioration at 10 years of 73.3% and rate of IE at 10 years of 6.2%.[28] Moreover, the overall freedom from aortic reintervention was 87.4% at 10 years, although no patients older than 60 years were reoperated. These data support our results and highlight the fact that younger patients are more likely to experience prosthetic valve degeneration and need additional interventions; this should be considered when deciding on the timing of intervention in patients with AR.

Recently published data suggest that previous cardiac surgery is a risk factor for surgical mortality in adults with CHD.[29–31] In our study, previous cardiac surgery was associated with a lower likelihood of LV normalization on follow-up. Despite major advances in percutaneous interventions in the past decades, these are largely avoided in young individuals with AR due to technical (small aortic annulus, lack of calcification and associated aortopathy, etc) and possible valve durability issues, hence are reserved for older patients in whom the surgical risk is significant.[32,33]

Our work has important limitations. It is retrospective in nature, using data available from clinical records. One of the main limitations is a relatively small sample size, and larger studies are warranted to potentially detect further significant variables for the main outcome. Of the 172 patients initially included, only 138 had an echocardiogram in the follow-up visit within the timelines defined in this study; therefore, all our multivariable models included 138 patients. While this number is lower than the overall sample size, it provided sufficient power for our analyses, but further larger studies are needed to confirm our findings. Moreover, while cardiovascular magnetic resonance (CMR) is currently often used for LV assessment and quantification of AR, data in this study were collected starting from 2005; therefore, CMR measurements were unavailable for many patients in our cohort. For this reason, echocardiography measurements were used instead for the analysis. Recent studies have highlighted that CMR is more accurate than echocardiography in determining the severity of AR, with CMR measurements more strongly related to clinical outcomes.[34–38] Moreover, CMR-derived parameters combined with BNP were superior to individual parameters in identifying asymptomatic patients with severe AR at risk of clinical decompensation.[36] While CMR is becoming the gold-standard for the evaluation of regurgitant lesions, validated CMR-derived thresholds for determining the timing of surgery in AR are still lacking.

Multivariable analysis using clinical end points was not performed due to the low event rate. Current literature describes an association between higher preoperative LV function and lower LVESD with adverse clinical events during follow-up.[15,16] We were unable to confirm the association between baseline LVEF and adverse outcomes in our cohort, possibly due to the limited number of events in our study. Additionally, LV diameters can be measured with greater accuracy on echocardiography than LVEF. Notably, Yang et al also found that preoperative indexed LVESD, rather than LVEF, was the only LV parameter independently associated with all-cause mortality, providing support for the routine reporting and use of LVESD when determining the optimal timing of surgery for AR.[16]

Further studies are needed to identify the optimal time for aortic valve surgery, ideally in the form of a validated risk score, incorporating the benefits of early intervention, the risks of surgery itself, and the likelihood of short- and longer-term complications, such as IE, valve degeneration, and the risk of redo surgery. Because younger patients tend to prefer biological valves due to lifestyle considerations, vigilance is required to promptly detect and manage prosthetic valve complications. The new and evolving era of transcatheter aortic valve implantation might present an alternative strategy for patients requiring redo surgery following conventional aortic valve replacement in the future.

CONCLUSIONS

In our young cohort of adults with AR, preoperative LV characteristics were predictive of the likelihood of postoperative LV normalization. Patients who were operated on fulfilling current guideline criteria were less likely to normalize their LV compared with patients undergoing an earlier operation. Pre- and postoperative LV characteristics were predictive of death or new-onset heart failure in the years after surgery. AR remains a major challenge for physicians caring for these patients, because there is a need to balance the short- and long-term benefits of surgery against the potential perioperative and long-term complications, as well as a need to minimize the number of surgeries that a patient undergoes throughout their lifetime.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3
Figures S1–S2

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