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Prognostic impact of left ventricular reverse remodeling after surgical aortic valve replacement in severe aortic stenosis

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Surgical aortic valve replacement (SAVR) is the treatment of choice for young patients with severe aortic stenosis (AS). Left ventricular (LV) reverse remodeling (RR) after surgery is expected to occur, even though its definition is largely heterogenous and ill-defined. However, LV RR not always occurs following afterload relief, and such may impact the prognosis. Single-centre prospective study including patients referred for SAVR due to severe symptomatic AS, with no previous history of ischemic cardiomyopathy. Both pre- and post-operative transthoracic echocardiographic (TTE) and cardiac magnetic resonance (CMR) study (at the 3rd to 6th month after SAVR) were performed. LV RR was defined when in presence of at least one of the imaging criteria: >15% decrease in end-diastolic volume (CMR); >15% decrease in LV indexed mass (CMR); >10% decrease in geometric remodeling (LV mass/EDV ratio) by CMR; >10% increase in LV ejection fraction (CMR); >50% increase on global longitudinal strain (TTE). We assess the prognostic value of RR definitions for the outcome after SAVR using Cox regression and Kaplan-Meier analysis. The primary endpoint was defined as all-cause mortality, heart failure (HF) hospitalization or worsening HF. We enrolled 140 patients – mean age 71 ± 9 years-old, 49% male, predominantly high-gradient-normal flow AS submitted to SAVR. At a mean follow-up of 34 ± 12 months, 16% patients met the primary endpoint, with an overall mortality rate of 6%. Twelve patients (9%) were admitted for HF and 7 (5%) had at least one episode of worsening HF. 118 patients had complete pre and post-surgery imaging study (mean follow-up: 36 ± 10 months): 103 patients (87%) met at least one RR parameter. Post-operative RR was not independently associated with the primary endpoint. LV mass regression was the sole predictor of the outcome. LV RR after SAVR is highly prevalent in a cohort of patients with classical severe symptomatic AS. However, only LV mass regression independently predicts the clinical outcome after surgery. LV structural remodeling, rather than functional improvement after surgery, may better define the prognosis after pressure overload relief.

Keywords Left ventricle reverse remodeling, Severe aortic stenosis, Cardiac magnetic resonance, Left ventricle hypertrophy

Abbreviations

AS	Aortic stenosis
AVAi	Indexed aortic valve area

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CABG	Coronary artery bypass graft
CMR	Cardiac magnetic resonance
ECV	Extracellular volume
EDV	End–diastolic volume
EF	Ejection fraction
EMB	Endomyocardial biopsy
GLS	Global longitudinal strain
HF	Heart failure
LGE	Late gadolinium enhancement
LV	Left ventricle
LVMi	LV indexed mass
MF	Myocardial fibrosis
ROC	Receiver Operating Characteristic
RR	Reverse remodeling
SAVR	Surgical aortic valve replacement
TTE	Transthoracic echocardiography

Degenerative aortic stenosis (AS) is the most common valvular heart disease, characterized by the progressive narrowing of the aortic valve, leading to left ventricular (LV) remodeling[1], a morphofunctional adaptation to chronic pressure overload[2]. This is initially compensatory, but eventually becomes maladaptive as cardiomyocyte apoptosis and fibrosis ensue with progressive impairment of diastolic relaxation and systolic contractile function[3]. LV hypertrophy is part of this adaptation, being an independent predictor of cardiac mortality[4], as in other clinical contexts[5].

Ultrastructural myocardial remodeling is an early process occurring for less than severe stages of the disease and it may include a variable degree of myocardial fibrosis (MF), a key independent marker of LV decompensation[6].

Left ventricular reverse remodeling (LV RR) is characterized as a decrease in chamber volume and normalization of its shape associated with improvement in both systolic and diastolic function[7]. LV RR might occur spontaneously or more often in response to therapeutic interventions that either remove the initial stressor or alleviate some of the mechanisms that contribute to further deterioration of the failing heart[7], such as aortic valve replacement (AVR) in patients with severe AS. There are various definitions of LV RR, depending on which imaging technique is used, yet no consensus has been reached on which one is most effective for predicting prognosis. More recently, novel machine-learning tools have showed to accurately predict myocardial architectonical properties using routinely available cardiac imaging and hemodynamic measures[8,9].

Contrary to ancillary echocardiographic studies relying on M-mode measurements and geometric assumptions, the estimation of LV mass and geometry by cardiac magnetic resonance (CMR) more accurately reflects both structural and geometrical LV changes[10]. CMR is currently the imaging modality of choice for the non-invasive assessment of LV remodeling. Besides, it may also provide the detection and quantification of LV fibrosis, a recognized prognostic marker in a wide range of clinical scenarios, including AS[6].

Surgical aortic valve replacement (SAVR) is the treatment of choice for symptomatic patients with severe AS, aged below 75 years-old and with low surgical risk[11]. The efficacy and safety of SAVR is well established, although recent data suggest that patients with LV hypertrophy have worse perioperative outcomes[3]. In retrospective studies, elevated LV mass index on preoperative echocardiography was associated with post-surgical complications, increased intensive care unit length of stay and in-hospital mortality[12,13]. The timing of AVR hinges significantly on the belief that intervention may fully reverse cardiac remodeling. However, recent knowledge on structural myocardial adaptation indicates the persistence of maladaptive changes following pressure overload relief from SAVR[3]. These negatively affect clinical outcomes, including heart failure (HF) symptoms maintenance and anticipated cardiovascular death[14].

Our primary aim was to assess the prognostic effect of distinct definitions of LV reverse remodeling, based on transthoracic echocardiography (TTE) and CMR, in the long-term outcome of patients with severe symptomatic AS who underwent SAVR.

Additionally, we assessed whether combinations of LV reverse remodeling criteria were associated with the primary endpoint, aiming to capture broader patterns of structural recovery. This approach was intended to move beyond the limitations of isolated LV RR parameters, which may conflate minor, potentially insignificant changes with meaningful cardiac remodeling.

Methods

Study population

This single-center prospective study included a cohort of 140 consecutive patients with severe symptomatic AS who were referred for SAVR at our tertiary center between April 2019 and January 2022. The study was conducted as part of a correlation research protocol, which involved comprehensive pre- and post-operative assessments of LV structure and function using multimodal imaging, as well as myocardial histopathological analysis through endomyocardial biopsy (EMB). A particular focus was placed on cardiomyocyte adaptation, extracellular matrix remodeling, and fibrosis. The definition of AS followed the European guidelines on valvular heart disease[11]. Study approval was granted by the ethical committee of Nova Medical School University (number 61/2018/CEFCM). The study was performed conforming to the principles of the Helsinki Declaration. All participants gave written informed consent before inclusion. Exclusion criteria are detailed at Supplementary Material – Detailed Methods.

Clinical data and study design

At study inclusion, prior to SAVR, clinical parameters—including demographic data, major cardiovascular risk factors, and symptomatic status—were recorded, along with a 12-lead ECG and transthoracic echocardiography (TTE). Cardiac magnetic resonance (CMR) imaging was conducted within two weeks of inclusion, accompanied by blood sample analysis for hematocrit (Htc), creatinine, high-sensitivity cardiac troponin I (hsTnI), and N-terminal pro B-type natriuretic peptide (NT-proBNP). Both TTE and CMR assessments were performed within six months before and after SAVR. When clinically indicated for the exclusion of coronary artery disease, patients underwent coronary angiography, with coronary revascularization performed alongside SAVR if necessary. Additionally, surgical myectomy was carried out either if pre-planned due to asymmetric septal hypertrophy or at the surgeon's discretion during the procedure.

Standard echocardiographic study – evaluation for aortic valve stenosis

All patients underwent a comprehensive TTE by experienced cardiologists before AVR, using commercially available ultrasound systems (Vivid E9; GE Healthcare, Chicago, IL, USA) with a 4D probe (3.5-MHz 2D phased array transducer), in accordance with current guidelines[1,15,16]. Imaging analysis and measurements were performed on image data stored in the regional image vault and re-examined using EchoPAC version 202 for PC (GE Healthcare, Milwaukee, WI, USA) (Supplementary Material – Detailed Methods).

Cardiac magnetic resonance

CMR study was performed at 1.5T equipment (*Magnetom Avanto*; Siemens Medical Solutions, Erlangen, Germany) using a clinical scan protocol, as previously published[17]. Methods for image acquisition, pre- and post-contrast tissue characterization, post-processing and quantification, are detailed in Supplementary Material – Detailed Methods.

Myocardial Fibrosis Quantification at Histopathology

EMB samples were collected either through an intraoperative septal biopsy, as outlined in the study protocol (harvested with a scalpel from the basal interventricular septum, ideally including the endocardium), or from an additional septal myectomy performed by the surgical team during SAVR. Technical details addressing the quantification algorithm and *QuPath* platform are specified in Supplementary Material – Methods.

Definitions of left ventricular reverse remodeling

Left ventricle RR was considered when in presence of at least one of the following criteria: >15% decrease in LV end-diastolic volume (EDV) ($\Delta LVEDV^{CMR}$)[18], > 15% decrease in LV indexed mass ($\Delta LVMi^{CMR}$), > 10% decrease in geometric remodeling (LV mass/EDV ratio) ($\Delta Geometric\ remodeling^{CMR}$), > 10% increase in LV ejection fraction ($\Delta LVEF^{CMR}$)[18,19], > 50% increase on global longitudinal strain (ΔGLS^{TTE}). EDV, LVEF, and LV mass were derived from CMR studies, as CMR provides more reproducible measurements and is considered the gold standard for quantifying cardiac mass and volumes. The only echocardiographic parameter used to assess LV reverse remodeling was myocardial deformation, measured by GLS.

All patients with complete pre and post-operatory TTE and CMR were included in the analysis.

Primary endpoint was defined as all-cause mortality, HF hospitalization or worsening HF, the latter defined as episodes of decompensated HF with therapeutic adjustment and no need for hospitalization[20].

Statistical analysis Categorical variables were reported as numbers and percentages, and continuous variables as mean±standard deviations (normal distribution), or as median and interquartile range for variables with skewed distributions. Normal distribution was checked using Shapiro-Wilk test or skewness and kurtosis, as appropriate. Clinical characteristics of the subgroups of interest were compared using the $\chi 2$-test and Fisher's exact test (when applicable) for dichotomous variables; and the student's t-test or Mann-Whitney U test (when applicable) for continuous variables. Categorical variables were compared by two-tailed chi-square. Paired samples *t* test was used to assess differences of LV RR parameters before and after SAVR. The prognostic value of LV RR definitions for the outcome after SAVR was assessed using Cox regression and Kaplan–Meier analysis. Kaplan–Meier analysis was used to analyse survival data. After univariate analysis, we performed Bonferroni correction to further adjust for multiple comparisons and reduce the risk of type I error when evaluating the significance of multiple remodeling parameters.

A two-sided p-value < 0.05 was considered statistically significant. The statistical analysis was performed with IBM SPSS Statistics 26.0 (IBM Corp, Armonk, NY, USA).

Results

Cohort characterization

A total of 140 patients (mean age of 71 ± 9 years-old, 49% male) with severe AS undergoing SAVR were included. Clinical and laboratory data are summarized in Table 1. These were all ambulatory symptomatic patients, mostly with exertional dyspnoea or functional impairment on daily activities.

Patients had predominant high gradient, normal flow, preserved EF AS (only 14 patients with LVEF < 50%). LV concentric remodeling and hypertrophy were the predominant patterns of adaptation as determined by CMR (from LV mass, volumes, and geometric remodeling) (Table 1). At baseline, there was a statistically significant positive correlation between LVMi and mean aortic gradient ($r = 0.222$, $p = 0.016$). None of the patients had ischemic scar at pre-operative CMR study (90 [64%] patients with non-ischemic late gadolinium enhancement (LGE), with a median LGE mass of 2.8 [0.0–7.8] gr/%LGE mass of 1.9 [0.0–6.0] %).

Most patients received a bioprosthesis implantation ($n = 130$, 93%), and 79 (56%) underwent concomitant surgical myectomy. At surgical report there was no reference to the extension of myectomy, namely in what

Clinical data	Number of patients ($n = 140$)
Length of follow-up, in months	34.1 ± 12.3
Age, years	70.9 ± 8.5
Male sex, n (%)	69 (49.3)
Body mass index, kg/m^2	27.7 (25.5–31.1)
Arterial hypertension, n (%)	115 (82.1)
Diabetes, n (%)	36 (25.7)
Atrial fibrillation, n (%)	12 (8.6)
Chronic kidney disease, n (%)	5 (3.6)
Coronary artery disease, n (%)	27 (19.3)
CABG, n (%)	23 (16.4)
NYHA functional class	
I, n (%)	7 (5.0)
II, n (%)	103 (73.6)
III, n (%)	30 (21.4)
Anginal symptoms, n (%)	40 (28.6)
Syncope, n (%)	32 (22.9)
Laboratory results	
NT-proBNP, pg/mL	577.0 (40.0–22664.0)
Troponin I, ng/L	12.0 (9.0–20.0)
Creatinine, mg/dL	0.9 (0.4–2.6)

Table 1. Baseline clinical and laboratory data. Values are median (interquartile range); n (%); mean ± standard deviation. CABG, Coronary artery bypass graft; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; Htc, haematocrit.

Echocardiographic data	
Aortic valve area, cm^2	0.7 ± 0.2
Maximum aortic valve gradient, mmHg	98.9 ± 27.4
Mean aortic valve gradient, mmHg	62.2 ± 17.7
Stroke volume index, mL/m^2	47.2 ± 10.6
LV indexed mass, g/m^2	151.5 (123.5–183.3)
Maximum septal thickness, mm	15.9 ± 2.5
LV ejection fraction, %	58.3 ± 9.1
Global longitudinal strain, %	14.9 ± 3.6
Cardiac Magnetic Resonance	
LV indexed mass, g/m^2	79.9 ± 26.5
LVEDV, mL	145.0 (122.3–177.0)
Geometric remodeling, g/mL	0.95 ± 0.19
LVEF, %	59.8 ± 10.1
Number of patients with LGE, n (%)	90 (64)
Absolute LGE, g	2.8 (0.0–7.8)
LGE, % of mass	1.9 (0.0–6.0)
Global native T1, ms	1050.8 ± 36.8
Global ECV, %	24.0 (21.0–27.0)
Histopathology at EMB	
Myocardial Fibrosis, % (CVF)	11.9 (6.3–20.5)

Table 2. Pre-operative imaging and histopathology data. Values are median (interquartile range); mean ± standard deviation, CVF, collagen volume fraction; ECV, extra-cellular volume; EDV, end-diastolic volume; EF, ejection fraction; EMB, endomyocardial biopsy; LGE, Late gadolinium enhancement; LV, left ventricle.

concerned the dimension of the excised sample on the interventricular septum. Concomitant surgical coronary revascularization was performed in 23 (16%) patients.

Left ventricle reverse remodeling

A total of 118 patients had complete pre and post imaging study with both TTE and CMR at 3–6 months. Within this sub-group of patients, 15 (12.7%) did not show LV RR after SAVR according to any of the definitions used (Fig. 1a–b). LVMi regression ($\Delta LVMi^{CMR}$) was the most frequently observed criterion of structural reverse remodeling, identified in 77 patients (65.3%) (Fig. 1b). All parameters used to define LV reverse remodeling showed statistically significant improvement from pre- to post-SAVR, except $\Delta LVEF^{CMR}$ (**Supplementary Tables** 1 and **Supplementary Fig. 1**).

Patients with pre-operative arterial hypertension were less likely to exhibit LV RR, as defined by LVMi regression ($\Delta LVMi^{CMR}$). However, there were no significant differences in the clinical features of patients with LV RR (Table 1). Patients who experienced LVMi regression had higher baseline NT-proBNP values and a higher reduction at follow-up (Table 1). LV RR and mass regression ($\Delta LVMi^{CMR}$) occurred in patients with more severe indexes of AV stenosis (Table 1 and **Supplementary Fig. 2c-d**). Neither non-invasive myocardial tissue characterization nor invasive quantification of MF at EMB differed in patients with LV RR (Table 1).

Primary endpoint analysis

At a mean follow-up of 34 ± 12 months, 23 (16%) patients met the primary endpoint: 5 patients (4%) died immediately after surgery; three patients died at the follow-up (overall mortality rate of 6%). Overall, 12 patients (9%) were admitted for HF and 7 (5%) had at least one episode of worsening HF.

LV reverse remodeling was not associated with improved outcome (Fig. 2a). However, when examining each LV RR definition separately, at univariate analysis, LVMi regression ($\Delta LVMi^{CMR}$) had an independent association with our primary endpoint (HR 0.118 [0.033–0.420]; $p = 0.001$), even after Bonferroni correction (adjusted $p = 0.005$) (**Supplementary Table 2a**) (Fig. 2b-f). Interestingly, LVMi regression remained an independent predictor of our primary endpoint even after adjusting for surgical revascularization (HR 0.114 [0.032–0.406]; $p = 0.001$), myectomy (HR 0.110 [0.031–0.396]; $p = 0.001$) and AS severity indexes based on mean aortic gradient and AVAi (**Supplementary Table 2b**).

Given that the $\Delta LVMi^{CMR}$ cut-off used to define LV RR was initially derived by extrapolating it from reverse remodeling criteria on heart failure patients undergoing cardiac resynchronization therapy[21,22] or percutaneous mitral valve repair[23], we conducted additional analyses to enhance the scientific robustness of our study. We conducted a ROC curve analysis using the percentage change in LVMi as a continuous variable. The optimal cut-off point was determined based on the highest area under the curve (AUC), which was 0.874 [95% CI: 0.799–

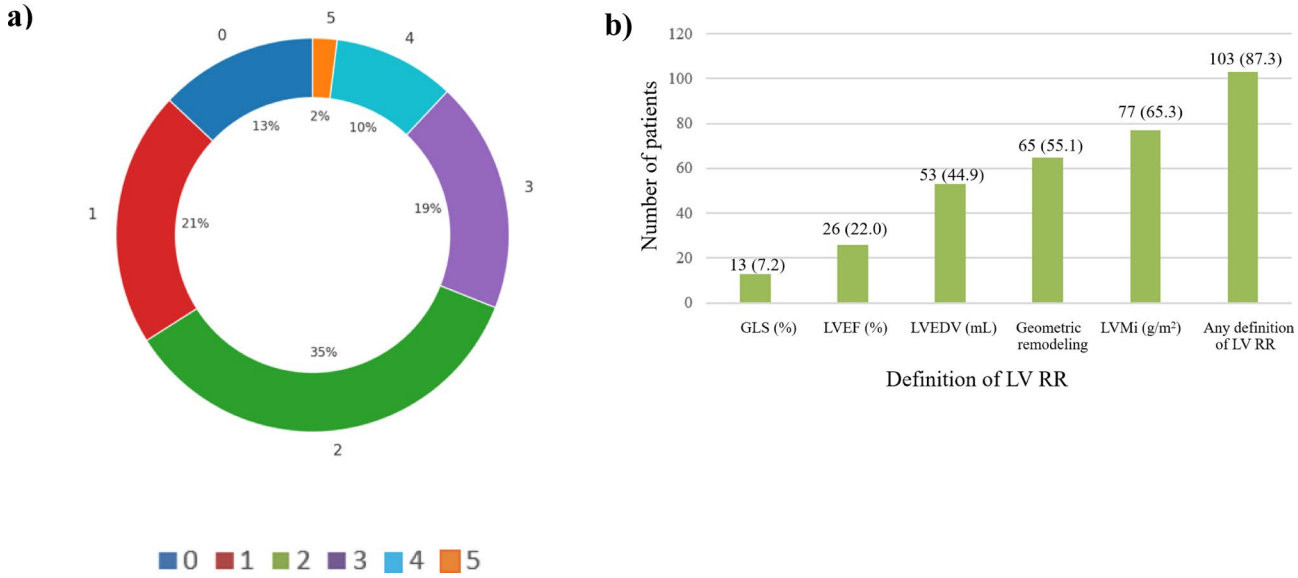

Fig. 1. Distribution of patients according to the number of LV RR definitions met (**a**) and according to the LV RR definition (**b**). (**a**) The numbers 0 to 5 represent how many LV RR criteria were met. Specifically, 13% of patients met none of the criteria, 21% met one, 35% met two, 19% met three, 10% met four, and 2% met all five criteria as defined in the Methods section. Overall, 87% of patient met at least one LV RR criterion. (**b**) Regression in LVMi ($\Delta LVMi^{CMR}$) was the most commonly observed indicator of structural reverse remodeling, present in 77 patients (65.3%). In contrast, ΔGLS^{TTE} was the least frequently observed criterion, which was anticipated given the wide variability in GLS changes (50%). This is consistent with our cohort, which predominantly comprises patients with high-gradient/high-flow aortic stenosis and preserved LVEF, where large GLS variations are not to be expected. GLS, global longitudinal strain; LV, left ventricle; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVMi, LV indexed mass; RR, reverse remodeling

	LV RR + ($n=103$)	LV RR – ($n=15$)	Mean difference	p-value
Clinical variables				
Age, years (median [IQR])	72 (68–77)	72 ± 7		0.824
Male sex, n (%)	51 (49.5)	5 (33)		0.341
Arterial hypertension, n (%)	83 (64)	14 (93)		0.159
Diabetes mellitus, n (%)	25 (24)	2 (13)		0.826
Creatinine, mg/dL (median [IQR])	0.9 (0.8–1.1)	0.8 ± 0.2		0.060
hs-TnI, ng/L (median [IQR])	13 (9–21)	10 (8–14)		0.058
Baseline NTpro-BNP, pg/mL (median [IQR])	571 (244–1483)	274 (116–519)		**0.016**
NT-proBNP reduction at FUP, pg/mL (median [IQR])	−120 [−701–91]	−83 [−155–115]		0.361
AS severity				
Mean aortic gradient, mmHg (mean ± SD)	63.1 ± 17.9	52.5 ± 17.3	−10.5 [−20.3– −0.8]	**0.035**
AVAi, cm^2/m^2 (mean ± SD)	0.4 ± 0.08	0.5 ± 0.09	0.07 [0.02–0.12]	**0.006**
Imaging variables				
LGE, n (%)	73 (71)	7 (47)		0.533
LGE mass, g (median [IQR])	3 (0–8)	2 (0–6)		0.525
Native T1 mapping, ms (median [IQR])	1053 (1031–1072)	1040 (1000–1065)		0.100
ECV, % (median [IQR])	24 (21–28)	24 ± 4		0.846
Histologic variable				
CVF, % (median [IQR])	12.6 (7.3–21.3)	14.9 (7.1–25.5)		0.839
	LV RR defined by LVMi + ($n=77$)	**LV RR defined by LVMi – 0($n=41$)**	**Mean difference**	***p*-value**
Clinical variables				
Age, years (median [IQR])	71 (67–77)	73 ± 6		0.078
Male sex, n (%)	40 (52)	17 (41)		0.278
Arterial hypertension, n (%)	59 (77)	38 (93)		**0.036**
Diabetes mellitus, n (%)	18 (23)	9 (22)		0.692
Creatinine, mg/dL (median [IQR])	0.9 (0.8–1.1)	0.9 (0.7–1.1)		0.982
hs-TnI, ng/L (median [IQR])	13 (11–22)	10 (8–15)		**0.016**
Baseline NTpro-BNP, pg/mL (median [IQR])	645 (255–2015)	340 (168–1059)		**0.022**
NT-proBNP reduction at FUP, pg/mL (median [IQR])	−371 (−930 – −22)	−30 (−159–344)		**0.015**
AS severity				
Mean aortic gradient, mmHg (median [IQR])	62.0 [51.4–81.0]	50.8 [44.0–61.7]		**< 0.001**
AVAi, cm^2/m^2 (mean ± SD)	0.38 ± 0.09	0.42 ± 0.08	0.04 [0.004–0.07]	**0.027**
Imaging variables				
LGE, n (%)	56 (73)	24 (59)		0.587
LGE mass, g (median [IQR])	3 (0–6)	2 (0–6)		0.269
T1 mapping, ms (median [IQR])	1053 (1033–1072)	1044 (1011–1071)		0.112
ECV, % (median [IQR])	24 (20–27)	24 (21–28)		0.577
Histologic variable				
CVF, % (median [IQR])	15.1 (0.2–22.2)	10.2 (4.9–17.3)		0.054

Table 3. Relationship between clinical and imaging variables and LV Reverse Remodeling. Values are median (interquartile range); mean ± standard deviation, AS, aortic stenosis, AVAi, indexed aortic valve area, CVF, collagen volume fraction; ECV, extracellular volume; FUP, follow-up; hs-TnI, high-sensitivity troponin I, LGE, late gadolinium enhancement, LV, left ventricle; LVMi, Left ventricle indexed mass.

0.949], $p < 0.001$. Using the Youden Index, the most predictive cut-off for the primary endpoint was identified as a 19.8% reduction in LVMi (absolute value − 19.8%).

Following analysis of multiple LV RR criterion combinations, only the pair $\Delta LVMi^{CMR} + \Delta$Geometric remodeling^{CMR} was associated with outcome (HR 0.078 [0.010–0.597]; $p = 0.014$) (**Supplementary Table 1**). However, this association did not remain statistically significant after applying Bonferroni correction for multiple comparisons (**Supplementary Table 1**).

Discussion

The main findings of this study were that: (a) LV reverse remodeling after SAVR is highly prevalent in a cohort of patients with severe AS, present in almost 90% of patients; (b) there was a statistically significant improvement of LV structural parameters, using different definitions of RR, following afterload relief, as provided by SAVR; (c) despite the evidence of LV RR, this was not correlated with the overall survival at the 2.5 years of follow-up;

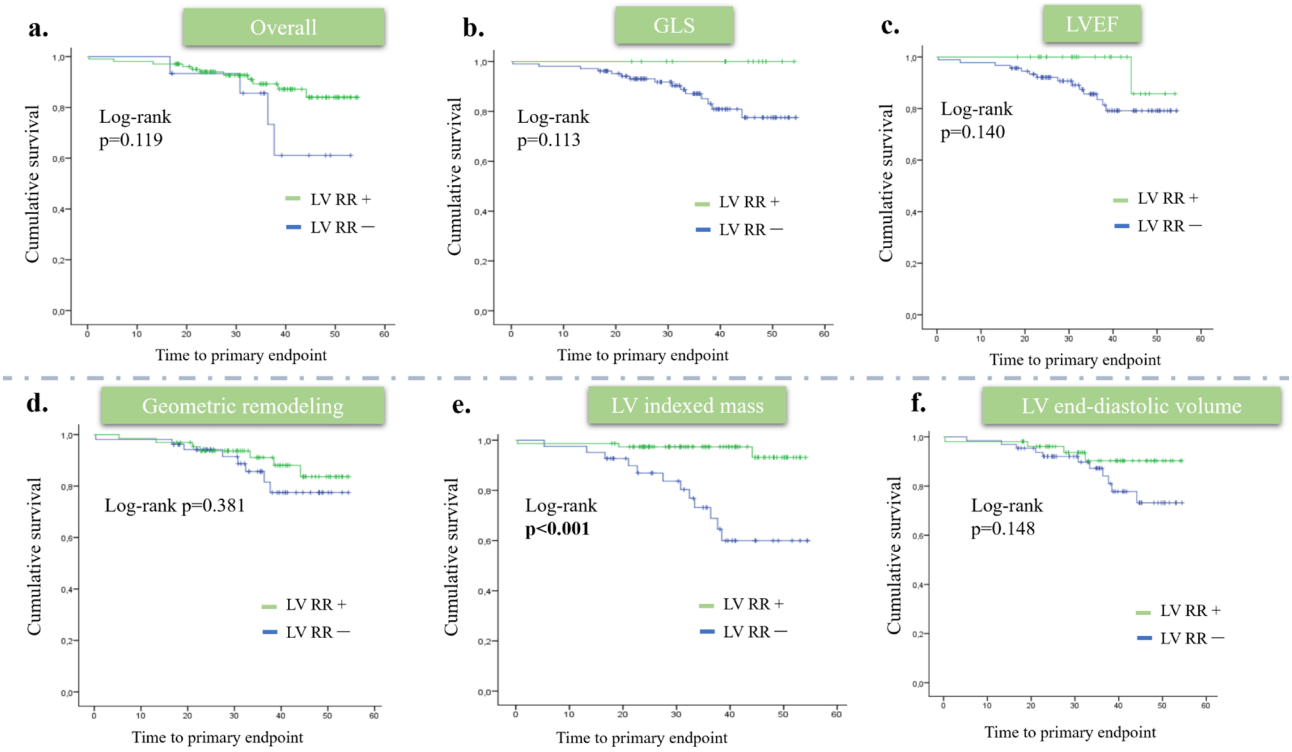

Fig. 2. Kaplan-Meier survival curves regarding different left ventricular reverse remodeling parameters (**a**-**f**). In the Kaplan-Meier survival analysis, overall LV reverse remodeling was not associated with improved outcomes (**a**). However, when evaluating each criterion individually, LVMi regression ($\Delta LVMi^{CMR}$) demonstrated an independent association with a better survival (**e**). For this analysis, we used a single predefined threshold (delta) for each LV RR criterion, as described in the Methods section. LV, left ventricular, LV RR, Left ventricular reverse remodeling.

(d) only LV mass regression, as a measure of LV RR, was protective of the primary endpoint and associated with a better survival after surgery.

Generally speaking, left ventricle reverse remodeling is characterized by LV volumes reduction, combined with an improvement in systolic function, after interventions targeting LV loading[24]. However, several definitions of reverse remodeling in several clinical settings were used throughout the years, using distinct criteria, including EMB, to assess the regression of both myocardial hypertrophy and fibrosis after AVR, and its correlation with outcomes[25,26]. Most studies rely on echocardiographic variables to define LV RR, namely for cohorts of patients with ischemic and non-ischemic cardiomyopathy[7]. Indeed, our initial $\Delta LVMi^{CMR}$ cut-off as one of the LV RR criteria — defined as a reduction greater than 15% — was derived from previous studies conducted in cohorts of heart failure patients, as previously explained[21–23]. However, recognizing the need for a data-driven approach specific to our study population, we performed a ROC curve analysis to identify the most accurate threshold for predicting our primary endpoint. This analysis revealed that a 19.8% reduction in LVMi was the optimal cut-off, which is not far-off from the initial 15%. These findings support the robustness of our results and confirm that the association between LVMi reduction and clinical outcomes holds true even when applying a data-driven, population-specific threshold rather than an extrapolated value.

The prognostic impact of LV RR echo-derived parameters such as LVEF normalization, LV volumetric changes, GLS improvement and LVMi regression ($\Delta LVMi^{CMR}$) has been extensively studied[14,27–29]. However, no single criterion is universally recognized as the best indicator of remodeling after intervention in patients with severe AS. In our cohort, among the various definitions of LV RR, only LV mass regression predicted patients' outcomes at univariate analysis, even after cut-off adjustment for our cohort. The inclusion of both functional and structural comprehensive criteria for the definition of LV RR might explain its high prevalence following SAVR, even at the 3rd to 6th month after intervention. Additionally, there were few events at a relative short period of follow-up. This would be expected to occur considering not only the low risk of a surgical cohort, but also the predominant phenotype of high gradient, normal flow, preserved LV EF AS. These together may stand behind the lack of association between LV RR criteria and prognosis.

Except for GLS, we resort to CMR to define LV RR criteria, in trying to overcome echocardiographic limitations in the estimation of LV volumes, ejection fraction and particularly LV mass[30]. Our LVMi assessment used CMR, which is more accurate than TTE's M-mode measurements, as the latter can overestimate LVMi reduction post-SAVR due to reliance on the LV end-diastolic diameter and limited 2D measurement[30]. As we previously showed[10], LV remodeling in this setting, as assessed by CMR, is diverse, and asymmetric LV hypertrophy is a common finding. These prove the limitations of bidimensional echocardiography in the estimation of LV mass.

Our study is one of the few studies with a surgical cohort of patients with severe AS and CMR evaluation of pre- and postoperative LV remodeling. As demonstrated by Biederman et al.[31], we could confirm that LV RR is highly prevalent and occurs early after SAVR. We found an absolute 22% reduction of LV mass post-SAVR which, individually, correlated with improved survival at the follow-up.

There were no significant clinical differences in patients exhibiting LV RR after SAVR, except for the presence of pre-operative high blood pressure. As our cohort was mostly homogeneous in what concerns clinical comorbidities, we assume that the presence of post-operative hypertension in these patients might affect LV mass regression, as previously described[32]. Unfortunately, we were unable to assess blood pressure control after surgery. This finding leads us to believe that hypertension becomes an important factor in determining global LV afterload after SAVR. This even considering that relative valve load is probably the predominant factor of the afterload before surgery, affecting LV remodeling, in this group of patients with a classical phenotype[33,34]. Largest absolute regression of LV mass in patients with both higher AV gradients and smaller valve orifices comes in the same line, as surgery corrects the main obstacle to the LV systolic work.

Previous evidence showed that severe LV hypertrophy and residual LV hypertrophy post-AVR are linked to worse outcomes[30,35], while LV mass regression is associated with improved prognosis in this setting[36,37]. In line with this, the regression of LV mass served as a predictor for our primary outcome, with patients maintaining similar degree of LV hypertrophy after surgery showing lower survival rates and increased risk of HF symptoms and hospitalizations during follow-up. Importantly, regression of LV mass ($\Delta LVMi^{CMR}$) remained an independent predictor of the primary endpoint, even after adjusting for surgical revascularization, concomitant myectomy, and baseline aortic stenosis severity. Functional LV parameters instead, including GLS (ΔGLS^{TTE}), were unrelated to the defined outcome. This could be related to the abrupt change in LV afterload conditions mediated by SAVR, and its impact on systolic volumes and LVEF, increased stroke volume and lower subendocardial pressure affecting longitudinal deformation. The regression of LV mass, a change of a structural parameter, is probably determined by the previous level of myocardial damage and this could be assessed either invasively or at pre-operative CMR. As previously demonstrated, both LGE, a marker of irreversible myocardial replacement fibrosis, and extracellular volume (ECV), are independent predictors of the outcome of patients with severe AS[5,29,38,39]. This last marker owing its interest to the ability to reflect the reversibility potential and the response of distinct myocardial compartments to SAVR. Indeed, we could confirm that patients with either absence of LV reverse remodeling or increase LV mass had higher degrees of MF, albeit non-significant, at both CMR and EMB. Our purpose was not to find tissue characterization markers of the outcome but to assess morphofunctional predictors at both echo and CMR studies.

In a secondary analysis using combinations of LV reverse remodeling criteria, we found that the combination of LV mass regression and reverse geometric remodeling was associated with a reduced risk of the primary endpoint. However, this association lost statistical significance after adjustment for multiple comparisons. This finding is not unexpected, as the calculation of geometric remodeling inherently includes LV mass, leading to potential overlap between the two measures.

In clinical terms, our study showed that no single LV RR parameter, mostly defined at peri-operative CMR studies, was able to define patients´ prognosis after SAVR. Patients with the same clinical indication and AS phenotype are probably being referred for AV intervention with distinct grades of myocardial damage. In this way, further investigations should be able to investigate the clinical impact of the use of pre-operative myocardial tissue characterization, namely with CMR, on patient´s outcomes and appropriate timing of intervention.

Limitations

This study has some limitations. There is no consensus regarding LV RR definition, which is arbitrary, and current evidence is conflicting regarding its prognostic role, with recent reports suggesting that faster improvements of the LVMi is paradoxically linked to a higher 30-day mortality[32].

There was complete imaging re-evaluation in 118 patients (84% of total cohort), all performed in less than 6 months after surgery, which may have hindered our results, regarding evidence of LV RR defined by functional parameters, as previously explained. Nonetheless, there is evidence that the majority (>80%) of volumetric and geometric LV changes have already occurred at this time point[31]. Also, mean follow-up time was relatively short (less than 3-years). Some factors that may impact LV RR were not evaluated, such as blood pressure control, ongoing medications, and post-operative renal function.

Conclusion

LV reverse remodeling after SAVR is highly prevalent in a cohort of patients with classical severe symptomatic AS. However, only LVMi regression independently predicted the clinical outcome at follow-up. This may stand the greater importance of early structural reverse remodeling, rather than LV functional improvement, in the early phase after pressure overload relief.

Data availability

All data exposed in this case report was acquired from our institution, after obtaining informed consent from the patients. The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author contributions

All authors have contributed to this manuscript, reviewed, and approved the current form of the manuscript. RL and JA were specifically responsible for manuscript conceptualization. RL, JA, SM, RRS and PL were responsible for data collection, analysis and first manuscript edition. RL and PL were specifically responsible for statistical analysis. KS, RR and MJA specifically made the first revision and editing. All authors have contributed to this manuscript, reviewed, and approved the current and final form of the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

Study approval was granted by the ethical committee of Nova Medical School University (number 61/2018/CEFCM) conforming to the principles of the Helsinki declaration.

Consent to participate

All participants gave written informed consent before inclusion.

Consent to publish

Written informed consent was obtained from patients for publication of this article.

Additional information

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