Vascular Health and Risk Management

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Ventricular Mechanics and Serum Biomarkers as Predictors of Aortic Valve Replacement in Severe Aortic Stenosis

Anna Gozdzik[1], Michał Czapla[2–4], Bożena Karolko[1], Marta Obremska[1]

[1]Institute of Heart Diseases, Faculty of Medicine, Wroclaw Medical University, Wroclaw, Poland; [2]Department of Emergency Medical Service, Faculty of Nursing and Midwifery, Wroclaw Medical University, Wroclaw, Poland; [3]Group of Research in Care (GRUPAC), Faculty of Health Sciences, University of La Rioja, Logroño, Spain; [4]Nursing Care and Education Research Group (GRIECE), Nursing Department, University of Valencia, Valencia, Spain

Correspondence: Michał Czapla, Department of Emergency Medical Service, Faculty of Nursing and Midwifery, Wroclaw Medical University, Wroclaw, Poland, Tel +48713468275, Email michal.czapla@umw.edu.pl

Purpose: Severe aortic stenosis (SAS) requires timely intervention to prevent irreversible myocardial damage. This study evaluated echocardiographic strain parameters and serum biomarkers in SAS patients and explored their value for qualifying patients for aortic valve replacement (AVR).

Patients and Methods: A total of 102 patients scheduled for surgical AVR were enrolled (symptomatic: n = 58; asymptomatic: n = 44). Echocardiography was used to measure left ventricular global longitudinal strain (LV GLS), peak atrial longitudinal strain (PALS), and left ventricular mass index (LVMI). Serum levels of osteoprotegerin (OPG), receptor activator of nuclear factor kappa B ligand (RANKL), and TNF-related apoptosis-inducing ligand (TRAIL) were assessed. Follow-up occurred six months postoperatively. Statistical analyses included Mann–Whitney U, Friedman ANOVA with post hoc testing, and logistic regression ($p < 0.05$).

Results: Symptomatic patients showed lower LV GLS (−15.2% vs −16.8%, $p = 0.016$) and PALS (21.8% vs 27.9%, $p < 0.001$) before surgery. Six months post-AVR, PALS (24.7% vs 28.6%, $p = 0.03$) and LVMI (108.1 vs 95.5 g/m^2, $p < 0.001$) remained worse in symptomatic patients. OPG levels were higher in SAS patients than in controls (6.90 vs 5.90 pmol/L, $p = 0.004$) but similar between symptomatic and asymptomatic subgroups.

Conclusion: LV GLS, PALS, and OPG levels are useful markers of myocardial dysfunction in SAS. Their persistence after AVR indicates ongoing structural remodeling and supports their use in preoperative evaluation beyond symptom-based assessment.

Keywords: aortic valve, biomarkers, echocardiography, cardiovascular diseases, hypertrophy, left ventricular

Introduction

Severe aortic stenosis (SAS) is a highly prevalent and life-threatening valve disease, particularly affecting the elderly.[1–5] Chronic pressure overload leads to compensatory left ventricular hypertrophy, which maintains wall stress and cardiac performance for many years.[6,7]

The current guidelines (ESC/EACTS and ACC/AHA) recommend a Class I indication for aortic valve intervention in symptomatic patients with severe aortic stenosis (SAS), defined by a mean gradient of ≥40 mmHg, a peak velocity of ≥4.0 m/s, or a valve area of ≤1.0 cm^2. Additionally, intervention is recommended in asymptomatic patients with markers of disease progression, such as reduced left ventricular ejection fraction, abnormal strain parameters (eg, LV GLS), or elevated biomarkers.[8,9] The symptoms occur well before the decrease in left ventricle ejection fraction (LVEF), which remains preserved for a long time.[10] Recent studies using cardiac magnetic resonance demonstrate that structural and functional abnormalities may be frequent despite an LVEF >50%.[11–13] This may be the reason for the reduced postoperative survival of patients with an LVEF of 50% to 60%.[14] Therefore, although current guidelines recognize

https://doi.org/10.2147/VHRM.S570954
Received: 28 September 2025
Accepted: 7 January 2026
Published: 3 February 2026

this issue, precise and validated criteria for early intervention in asymptomatic SAS patients remain lacking. Several studies highlight the need for better tools to detect subclinical myocardial dysfunction despite preserved LVEF.[15–18]

The impairment of LV longitudinal shortening is associated with myocardial fibrosis, which can be a potential prognostic marker in patients with SAS.[19–22] Left ventricular global longitudinal strain (LV GLS) by speckle tracking echocardiography (STE) could be a useful imaging marker of myocardial damage. More recently, measuring left atrial (LA) distension with STE makes it possible to assess the LA reservoir function by measuring the peak LA longitudinal strain (PALS) during the LV systole.

The Osteoprotegerin, Receptor activator of nuclear factor-kB ligand, TNF-related apoptosis-inducing ligand (OPG/RANKL/TRAIL system) which is known to play an important role in bone turnover and vascular calcification, has gained much interest in SAS.[23] In some studies, OPG levels were associated with AS severity.[24,25] In others, an elevated OPG was shown to indicate myocardial fibrosis, and therefore, might be a biomarker of heart failure.[26,27] Serum TRAIL was significantly higher in patients with calcific aortic valve stenosis.[28]

The aim of this study was to evaluate left ventricular and atrial remodeling, as well as myocardial mechanics, both before and six months after surgical aortic valve replacement. Additionally, we aimed to assess serum levels of OPG, RANKL, and TRAIL and investigate their relationship with structural and functional parameters of the left ventricle and atrium throughout the observation period. We hypothesized that echocardiographic strain parameters (LV GLS and PALS) and serum biomarkers (OPG, RANKL, and TRAIL) could serve as early indicators of myocardial dysfunction in patients with SAS, including those without symptoms. These markers may help refine qualification criteria for aortic valve replacement beyond traditional measures like ejection fraction or symptom presence.

Materials and Methods

Study Population

Between June 2018 and December 2020, we enrolled 112 patients with degenerative SAS scheduled for AVR in the Cardiac Surgery Department (Institute of Herat Disease, University Hospital in Wroclaw, Poland). This was a single-center, prospective observational study. The inclusion criteria were as follows: adult patients with SAS (aortic valve area < 1 cm^2, mean pressure gradient > 40mmHg, peak aortic jet velocity > 4m/s) without moderate or severe coexisting aortic regurgitation. Patients with irregular heart rhythm, pacemaker, severe renal impairment, diabetes mellitus, osteopenia and osteoporosis, significant coronary artery disease (>50% coronary artery stenosis), and other valve diseases were excluded. These exclusion criteria were applied to minimize confounding effects from comorbidities known to influence myocardial strain or biomarker levels. However, this may limit the generalizability of the results to broader SAS populations. The value of EF was above 45%.

A healthy control group suitable for age and sex without cardiac disease consisted of 28 people. A six-month follow-up was not performed in ten of them and for that reason, they were not included in the final analysis. All patients with SAS were divided based on typical aortic valve stenosis symptoms into two groups: symptomatic (Group 1) and asymptomatic with very severe aortic stenosis with maximum velocity (v. max)≥5 m/s (Group 2). The sample was based on a convenience cohort of eligible patients undergoing surgical AVR during the study period. The comprehensive assessment included blood sampling and clinical history. Patients were observed for six months after AVR.

Echocardiography

All patients underwent transthoracic echocardiography using the Vivid E9 ultrasound system (GE Vingmed, Milwaukee, WI, USA) equipped with an M3S transducer. The method of echocardiography and 2 D speckle tracking, as below, was described by the authors earlier.[29]

The echocardiograms were obtained according to the recommendations of the American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE) for the evaluation of cardiac chamber size, and function and the severity of native valve stenosis. All echocardiographic examinations were performed by the same experienced cardiologist using the same ultrasound device, and the analyses were conducted offline by two independent cardiologists blinded to patients' symptom status and biomarker results to minimize assessment bias.

2D Speckle Tracking Echocardiography

Apical four, two, and three chambers' views were used (4CH, 2CH, LAX) with 60–80 fps (frame per second) in 2D to calculate the LV GLS. Left ventricular strain quantification was then performed off-line using commercially available software (Echo PAC; GE Healthcare).

We also calculate left ventricular circumferential and radial strain (LV CS, LV RS).

To calculate the LA reservoir function, we used the QRS onset of the electrocardiogram as a reference point. We used the method proposed by E. Galli et al.[30] The LA endocardial surface was manually traced by a point-and-click approach in the apical two- and four-chamber views creating a region of interest that was manually adjusted to cover the full thickness of the myocardium with three consecutive heart cycles being recorded during breath-hold, and frame rate of 60–80 fps, as recommended. The peak atrial longitudinal strain (PALS) was calculated by averaging the peak values observed in all the LA segments (global PALS), and by separately averaging the peak values observed in the four- and two-chamber views.

The right ventricular (RV GLS) global longitudinal strain was obtained by averaging the strain of 3 segments of the free right ventricular wall. The RV peak global strain was defined as the peak negative value.

OPG Serum Level

Peripheral venous blood was drawn into EDTA tubes three times in the morning before and 3 and 6 months after surgery. Then, after waiting 30–90 minutes, the blood was centrifuged with a speed of 2000 rpm. Plasma samples were stored at −80 C. After collecting all samples, plasma levels were measured with an enzyme immunoassay (ELIZA) OPG and RANKL using the Biomedica Medizinproducte GmbH & Co KG 9 (Austria) and for the TRAIL, the eBioscience Bender MedSystems GmbH (Austria) analyzers.

Follow-Up

Follow up data were obtained by regular visits in our outpatient Cardiac Surgery Clinic or by telephone calls. The study endpoints were cardiac-related hospitalizations and mortality. Echocardiographic parameters and serum biomarkers were assessed at baseline, 3 months, and 6 months after AVR. No biomarker or strain measurements were performed beyond 6 months. Long-term clinical follow-up (median 31 months) included only mortality and cardiac-related hospitalizations.

Ethical Statement

The study was approved by the Local Bioethics Committee at Wroclaw Medical University (approval no. 633a/15, issued on December 22, 2016). All participants, including those in the control group, provided written informed consent prior to enrollment. The study was conducted in accordance with national regulations and the principles outlined in the Declaration of Helsinki (1975, and its later amendments). The research was supported by an institutional grant from Wroclaw Medical University (No. ST–933).

Statistical Analysis

The numerical data obtained during observation were collected and systematized using the Excel 2016 spreadsheet tools. These tools were also used to calculate the changes in the observed parameters over time. Quantitative research was carried out using the Statistica 13.1 PL package. The level of significance $p = 0.05$ was accepted for rejecting the null hypothesis. Due to the rejection by the Shapiro–Wilk test of the hypothesis about the normality of the distribution of the studied variables, nonparametric tests were used in the analysis. The Friedman ANOVA test with post hoc test, Mann–Whitney *U*-test, and nonparametric Spearman rank correlation were used, respectively. An attempt was also made to estimate logistic regression models for selected parameters. The distribution of qualitative variables was examined using multivariate tables (contingencies) and the chi-square test. For multivariable logistic regression, regression coefficients (β), odds ratios (OR) with 95% confidence intervals (95% CI) and p-values were reported. Model discrimination was assessed using the area under the ROC curve (AUC) and calibration with the Hosmer–Lemeshow goodness-of-fit test. No correction for multiple comparisons (eg, Bonferroni) was applied because all analyses were hypothesis-driven and pre-specified.

Results

Clinical Characteristics

One hundred and two patients (56% men) were included in the final analysis. The subjects were divided into two groups: symptomatic Group 1 n = 58 (62% men) and asymptomatic Group 2 n = 44 (48% men). The mean (SD) age was 65.4 (73.7), without differences between the groups. The groups were not different in respect to body surface area (BSA), body mass index (BMI), and the blood pressure values at rest. The clinical characteristics of the overall population, control group, and both groups are shown in Table 1.

Echocardiographic Characteristics at Baseline

Baseline echocardiographic and procedural characteristics of the total population, the control group, and both the symptomatic and asymptomatic groups are displayed in Table 2.

Table 1 Clinical Characteristics of the Studied Population with SAS and Divided into the Symptomatic Group (Group 1) and Asymptomatic Group (Group 2)

Variables	All Patients	Group 1	Group 2	p
	n = 102	n = 58	n = 44	
Age (y)	65.4	65.5	65.4	0.810
Men, n (%)	57 (50.9)	36 (62.0)	21 (47.7)	<0.001
BMI (kg/m^2)	28.9	29.4	28.2	0.288
BSA (m^2)	2.1	1.9	2.3	0.261
SBP (mmHg)	141.5	140.5	141.8	0.442
DBP (mmHg)	81.1	76.8	79.6	0.523
Dyslipidemia, n (%)	21 (20.5)	9 (20.4)	12 (20.6)	0.980
Hb (g/dL)	14.0	13.8	14.2	0.243
Smoking, n (%)	9 (8.8)	3 (5.1)	6 (13.6)	0.423
Statins, n (%)	20 (19.6)	12 (22)	8 (20)	0.342
ECC (min)	103.1	103.12	104.50	0.99
ACC (min)	74.6	74.10	75.32	0.91

Abbreviations: ACC, aortic cross clamp time; BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; ECC, extracorporeal circulation time; SBP, systolic blood pressure.

Table 2 Baseline Echocardiographic Characteristics of the Total Population, Control Group, and Both Symptomatic Group (Group 1) and Asymptomatic Group (Group 2)

Variables	Total	Control	p	Group 1	Group 2	p
	n = 102	n = 28		n = 58	n = 44	
LVDD (mm)	46.3	42.7	0.003	47.8	44.2	<0.001
LVEDV (mL)	85.6	68.1	0.008	87.9	82.6	0.400

(*Continued*)

Table 2 (Continued).

Variables	Total	Control	p	Group 1	Group 2	p
	n = 102	n = 28		n = 58	n = 44	
LAVI (mL/m^2)	28.3	18.2	<0.001	30.1	26.0	0.007
LVMI (g/m^2)	134.8	74.7	<0.001	146.4	119.7	<0.001
AVMG (mmHg)	58.7	2.6	<0.001	61.1	55.4	0.106
E/e'	10.4	6.2	<0.001	11.0	9.6	0.133
EF (%)	62.8	64.6	0.232	62.0	64.0	0.106
LVGLS (%)	−15.9	−21.8	<0.001	−15.2	−16.8	0.016
MAPSE (mm)	15.0	16.0	0.037	14.7	15.4	0.373
LVCS (%)	−11.6	−21.3	<0.001	−11.8	−11.4	0.257
LVRS (%)	31.7	41.2	<0.001	31.7	31.6	0.574
PALS (%)	24.4	40.6	<0.001	21.8	27.9	<0.001
RVGLS (%)	−22.8	−25.2	0.090	−22.5	−23.2	0.892

Abbreviations: AVMG, aortic mean gradient; E/e', E early mitral inflow and e' tissue doppler early mitral inflow ratio; EF, ejection fraction; LAVI, left atrium volume index; LVCS, left ventricular circumferential strain;LVDD, left ventricular diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVGLS, left ventricular global longitudinal strain; LVMI, left ventricular mass index; LVRS, left ventricular radial strain; MAPSE, mitral annular plane systolic excursion; PALS, peak atrial longitudinal strain; RVGLS, right ventricular global longitudinal strain.

Comparing Groups 1 and 2, we found that in Group 1, the patients had a larger left ventricular diastolic diameter (LVDD) and a bigger left ventricular mass index (LVMI). Also, the left atrial volume index (LAVI) was clearly bigger. Finally, the LV GLS and PALS were significantly lower. Both groups similarly showed a preserved LVEF. There were no differences in the RV GLS and the LV *RS* and LV CS. This supports the study aim of identifying early functional impairment in SAS patients using advanced strain parameters despite preserved ejection fraction.

OPG/RANKL/TRAIL Serum Levels at Baseline

Baseline levels of OPG in the total SAS group were significantly higher than in the control group (p = 0.004), whereas RANKL and TRAIL did not differ significantly. No differences in any biomarker were found between symptomatic and asymptomatic patients (Table 3). These results suggest that although OPG may reflect overall disease severity, its role in

Table 3 Baseline Serum Levels of OPG/RANK/TRAIL in Total Population, Control Group, and Both Symptomatic Group (Group 1) and Asymptomatic Group (Group 2)

Variable	Total	Control	p	Group 1	Group 2	p
	n = 102	n = 28		n = 58	n = 44	
OPG (pmol/l)	6.90	5.9	0.004	6.98	6.80	0.717
RANKL	262.1	220.5	0.582	259.6	265.4	0.865
TRAIL	952.2	874.2	0.311	914.8	1001.6	0.233

Abbreviations: OPG, osteoprotegerin; RANKL, soluble receptor activator nuclear factor kB ligand; TRAIL, TNF-related apoptosis inducing ligand.

differentiating clinical status is limited. This finding partially supports its utility as a general biomarker of SAS, as outlined in the study objectives.

Time Course of LV Remodeling, LV Mechanics, and OPG/RANKL/TRAIL Levels

Throughout follow-up, LV remodeling parameters (LVDD, LVMI, LAVI) and PALS remained significantly more abnormal in symptomatic patients compared to the asymptomatic group (Table 4). The persistence of these differences suggests that LV structural and functional abnormalities may remain despite AVR, reinforcing their potential as markers of disease progression.

The serum OPG level significantly increased during the observation time without differences between the groups. The same observations were found for the RANKL and TRAIL serum levels.

Multivariate Analysis of LV GLS < −15%

Multivariable logistic regression demonstrated that both LVMI and PALS were independent predictors of impaired LV GLS (≤–15%) at baseline and at 3 months after AVR. Higher LVMI was associated with increased odds of impaired GLS, while higher PALS showed a protective effect. Detailed effect sizes (β coefficients, ORs and 95% CIs) are presented in Table 5. These findings support the central.

Follow-up

Follow-up data were available for all patients. The median follows up was 31.05 months (range 14–56 months). Patients were regularly followed up at our outpatient Cardiac Surgery Clinic by both clinic visits and telephone calls. The study endpoints were cardiac-related hospitalization and mortality. Cardiac related mortality was observed in two patients (1.96%). A total of 14 (13.7%) patients underwent hospitalization during the observation period, and 7 (6.86%) were for cardiac reasons. Long-term follow-up (median 31 months) was used solely to evaluate clinical outcomes and was not linked to additional imaging or biomarker assessments.

Table 4 Echocardiographic Parameters at Baseline, 3 and 6 Months After Surgery in Patients Divided into the Symptomatic Group (gr1) and Asymptomatic (gr2) Group

Variable	Baseline		p	3 Months		p	6 Months		p
	gr1 (SD)	gr2 (SD)		gr1 (SD)	gr2 (SD)		gr1 (SD)	gr2 (SD)	
LVDD (mm)	47.8(6.2)	44.2(5.2)	0.00	46.7(5.3)	44.0(4.7)	0.00	44.2(6.2)	44.0(4.3)	0.90
LVEDV (mL)	87.9(33.9)	82.6(32.8)	0.40	78.2(29.7)	74.3(25.9)	0.57	77.1(25.8)	73.3(26.6)	0.37
LVMI (g/m^2)	146.4(34.4)	119.7(31.5)	0.00	120.2(36.1)	103.3(29.2)	0.01	108.1(30.7)	95.5(29.2)	0.00
LAVI (mL/m^2)	30.1(13.4)	26.0(11.3)	0.00	28.3(15.8)	22.2(7.8)	0.00	27.3(13.9)	24.1(8.5)	0.29
EF (%)	62.0(8.3)	64.0(8.5)	0.10	64.6(8.2)	65.7(7.6)	0.51	64.6(11.7)	66.8(8.5)	0.72
LV GLS (%)	−15.2(3.5)	−16.8(3.7)	0.01	−16.6(3.0)	−16.4(5.7)	0.47	−17.5(3.0)	−18.0(3.0)	0.56
LV CS (%)	−11.8(4.1)	−11.4(8.8)	0.25	−13.9(5.1)	−12.8(4.0)	0.19	−15.0(4.8)	−15.0(4.4)	0.49
LV *RS* (%)	31.7(13.5)	31.6(15.4)	0.57	32.7(12.9)	31.6(11.5)	0.98	35.6(14.7)	34.2(12.8)	0.73
RV LS (%)	−22.5(10.6)	−23.2(9.1)	0.89	−19.0(4.7)	−18.4(4.9)	0.23	−20.2(4.5)	−19.1(5.1)	0.24
MAPSE	14.7(3.4)	15.4(3.6)	0.37	17.3(3.3)	16.7(2.8)	0.31	17.6(3.4)	18.5(3.4)	0.14
PALS (%)	21.8(6.7)	27.9(8.0)	0.00	23.4(6.7)	26.6(10.7)	0.01	24.7(6.2)	28.6(7.6)	0.03

Note: Values are mean (SD).

Abbreviations: EF, ejection fraction; LAVI, left atrium volume index; LVCS, left ventricular circumferential strain; LVDD, left ventricular diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVGLS, left ventricular global longitudinal strain; LVMI, left ventricular mass index; LVRS, left ventricular radial strain; MAPSE, mitral annular plane systolic excursion; RVLS, right ventricular longitudinal strain; PALS, peak atrial longitudinal strain.

Table 5 Multivariable Logistic Regression for Impaired LV GLS (≤–15%) at Baseline and 3 Months

Time Point	Predictor	β	OR	95% CI	p-value
Baseline	LVMI	0.018	1.018	1.004–1.033	0.013
	PALS 4CH	–0.125	0.883	0.817–0.954	0.002
3 months	LVMI	0.018	1.018	1.004–1.032	0.011
	PALS 4CH	–0.080	0.923	0.863–0.987	0.019

Abbreviations: LAVI, left atrium volume index; PALS, peak atrial longitudinal strain.

Discussion

In this study, conducted on a cohort of 102 patients with SAS, we evaluated myocardial and atrial remodeling as well as functional parameters before and after SAVR. The findings indicate that symptomatic patients, despite a preserved mean EF of 62%, exhibited more advanced LV and LA remodeling and impaired longitudinal deformation compared to asymptomatic patients, both preoperatively and postoperatively.

Left Ventricular Remodeling and LVMI

The increased afterload imposed by the stenotic aortic valve leads to concentric left ventricular hypertrophy and progressive myocardial fibrosis, which may culminate in systolic dysfunction even before symptoms develop.[31,32] In our study, left ventricular mass regression was observed during the whole observation time. Nevertheless, six months after surgery, the left ventricular mass was still elevated in the symptomatic group suggesting persistent structural myocardial changes. The huge LV hypertrophy was removed from the guidelines for an indication of AVR, but still high LV mass (>110% of that expected for body size, sex, and wall stress) generates a significantly increased risk of mortality regardless of other risk factors.[33] LV mass regression after AVR seems critical for clinical improvement and long-term survival.[34] Several studies have described the time course of LV mass regression in SAS patients within 12 months after the intervention.[35,36] Daubert et al, in a report from the PARTNER I Trail, showed a sustained process of LV mass regression up to 5 years after surgical AVR. In turn, Une et al observed a steep decline in LVMI in AS during the first 24 months after surgery without any further significant reduction at longer-term follow up.[37]

Left Ventricular Systolic Function and GLS

The LVEF depends not only on the contractility of the LV but also on the loading conditions. Therefore, a reduced LVEF may be due to excessive afterload (high wall stress), reduced contractility, or a combination of both.[38] Even if the LVEF is preserved, LV systolic function is sometimes decreased.[32] Reduced LV GLS is an early marker of impaired contractile function despite preserved EF and is strongly associated with myocardial fibrosis. Impaired GLS has been consistently linked to adverse outcomes in SAS. A recent meta-analysis demonstrated that reduced GLS was significantly associated with major adverse cardiovascular events and an increased need for valve intervention, and patients with GLS <–14.7% had a 2.5-fold higher risk of mortality.[22,32,39]

In our study, the LV GLS was significantly impaired in both symptomatic and asymptomatic groups compared to the control group. However, the LV GLS was significantly worse in the symptomatic group. The values of LV myocardial deformation increased during the observation period in both groups, and six months after surgery, there were no significant differences between symptomatic and asymptomatic patients. The predictors of an impaired LV GLS < −15% (we take this threshold from the cardiac damage staging scheme proposed by Genereux et al) in our research were the LVMI and PALS.[40]

Atrial Mechanics and the Role of PALS

In the research of Galli et al, severe alterations of PALS were shown to be frequent in AS, and the cut-off value of 21% is predictive of Major Cardiac Events, MACEs.[30] The correlation between reduced PALS and LV function parameters

suggest that the PALS could be a barometer of global (systolic and diastolic) LV impairment in AS. Our observations showed that the PALS values were significantly worse in the symptomatic group before surgery and gradually improved but remained significantly low six months after surgery. These findings indicate sustained alterations in LA mechanics despite relief of valvular obstruction. Importantly, elevated LVMI and reduced PALS were identified as independent predictors of impaired LV GLS (≤−15%), highlighting the interplay between myocardial hypertrophy and atrial dysfunction in determining LV mechanics.

Biomarkers and Myocardial Fibrosis (OPG/RANKL/TRAIL)

The last point of our study was to observe the OPG serum level. Most studies have indicated a high serum OPG in AS and a correlation with global longitudinal strain, AS severity, pulmonary capillary wedge pressure, and NT-pro BNP levels. The presence of HF may be an important determinant of serum OPG in AS.[41–44] Elevated OPG levels could suggest underlying myocardial fibrosis, which drives the progression to HF.[41] In our study, the serum level of OPG was significantly elevated in patients with SAS compared to the control group. Symptomatic patients had significant serum OPG correlation with LV GLS. In summary, we can say that these results certainly confirm the unreliability of symptoms as a guide to the timing of surgery in patients with severe aortic stenosis. In our symptomatic group, structural and functional changes were so advanced that they remained until the end of the 6-month observation period. Finally, we suggest using the PALS parameter instead of the LAVI, LV GLS, and serum level of OPG, as a biomarker, when determining indications for valve replacement.

Clinical Implications

The persistence of impaired PALS and elevated LVMI despite surgical intervention suggests a need for closer post-operative structural monitoring in SAS patients. The findings also support incorporating LV GLS, PALS, and potentially OPG into pre-operative risk stratification tools, especially for asymptomatic individuals. These markers may enhance early identification of patients at risk of subclinical myocardial damage who could benefit from earlier intervention.

Study Limitations

This study has several important limitations. First, it was conducted in a single center with a relatively small sample size (n = 102), which limits the generalizability of the findings. The exclusion of patients with relevant comorbidities, including coronary artery disease, diabetes mellitus, atrial fibrillation, or significant arrhythmias, further restricts the applicability of the results to the broader population with severe aortic stenosis. Second, myocardial fibrosis was not assessed by cardiac magnetic resonance (CMR), the reference standard for tissue characterization; therefore, echocardiographic strain parameters and serum biomarkers served only as indirect markers of myocardial injury. Third, biomarker levels such as OPG, RANKL, and TRAIL may be influenced by unmeasured systemic factors, introducing potential variability in interpretation. Fourth, the postoperative follow-up period was limited to six months, allowing evaluation only of the early phase of reverse remodeling after AVR. Longer follow-up is necessary to determine whether the observed abnormalities in LVMI and PALS persist and whether they have prognostic significance. Despite these limitations, the study provides novel and clinically relevant insights into subclinical myocardial dysfunction in patients with severe aortic stenosis.

Conclusion

The assessment of left ventricular global longitudinal strain (LV GLS), peak atrial longitudinal strain (PALS), and left ventricular mass index (LVMI) provides important insights into myocardial remodeling in severe aortic stenosis and should be considered in preoperative qualification for aortic valve replacement. Despite surgical intervention, significant structural abnormalities in LVMI and PALS persist six months postoperatively, suggesting the need for closer long-term monitoring. Additionally, elevated osteoprotegerin (OPG) levels were observed in all patients with severe aortic stenosis (SAS), reinforcing its potential role as a biomarker of myocardial fibrosis. Future studies should include larger patient cohorts and longer postoperative follow-up to validate these findings and further clarify their predictive value for patient stratification and prognosis.

Author Contributions

Conceptualization, A.G.; Methodology: A.G. and M.O.; investigation, A.G., B.K., M.O.; formal analysis: A.G. and M. O. writing—original draft preparation, A.G., M.C., B.K., M.O.; writing—review and editing, A.G., M.C., B.K., M.O.; project administration: A.G.; supervision, A.G.; funding acquisition, A.G. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Strange G, Stewart S, Playford D, Strom JB. Risk for mortality with increasingly severe aortic stenosis: an international cohort study. *J Am Soc Echocardiogr*. 2023;36(1):60–68.e2. doi:10.1016/j.echo.2022.09.020
2. Ogata F, Hanatani S, Nakashima N, et al. Human epididymis protein 4 is a useful predictor of post-operative prognosis in patients with severe aortic stenosis. *ESC Heart Failure*. 2024;11(5):2924–2932. doi:10.1002/ehf2.14845
3. Adams HSL, Ashokkumar S, Newcomb A, MacIsaac AI, Whitbourn RJ, Palmer S. Contemporary review of severe aortic stenosis. *Internal Med J*. 2019;49(3):297–305. doi:10.1111/imj.14071
4. Suzuki W, Nakano Y, Ando H, et al. Association between coronary flow and aortic stenosis during transcatheter aortic valve implantation. *ESC Heart Failure*. 2023;10(3):2031–2041. doi:10.1002/ehf2.14316
5. Bociański M, Puślecki M, Ratajczak M, et al. Comparative study of quality of life after aortic valve replacement through partial upper ministernotomy versus full median sternotomy. *Adv Clin Exp Med*. 2025;34(6):895–900. doi:10.17219/acem/190454
6. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. *J Ame College Cardiol*. 2012;60 (19):1854–1863. doi:10.1016/j.jacc.2012.02.093
7. Hein S, Arnon E, Kostin S, et al. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart. *Circulation*. 2003;107(7):984–991. doi:10.1161/01.CIR.0000051865.66123.B7
8. Otto CM, Nishimura RA, Bonow RO, et al. ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *JACC*. 2021. doi:10.1016/j.jacc.2020.11.035
9. Vahanian A, Beyersdorf F, Praz F, et al. ESC/EACTS Guidelines for the management of valvular heart disease: developed by the task force for the management of valvular heart disease of the European society of cardiology (ESC) and the European association for cardio-thoracic surgery (EACTS). 2025. doi:10.1093/eurheartj/ehab395
10. Dahl JS, Eleid MF, Michelena HI, et al. Effect of left ventricular ejection fraction on postoperative outcome in patients with severe aortic stenosis undergoing aortic valve replacement. *Circulation Cardiovascular Imaging*. 2015;8(4):e002917. doi:10.1161/CIRCIMAGING.114.002917
11. Treibel TA, Kozor R, Schofield R, et al. Reverse myocardial remodeling following valve replacement in patients with aortic stenosis. *JACC*. 2018;71(8):860–871. doi:10.1016/j.jacc.2017.12.035
12. Dweck MR, Joshi S, Murigu T, et al. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. *J Ame College Cardiol*. 2011;58(12):1271–1279. doi:10.1016/j.jacc.2011.03.064
13. Chin CWL, Everett RJ, Kwiecinski J, et al. Myocardial fibrosis and cardiac decompensation in aortic stenosis. *JACC. Cardiovascular Imaging*. 2017;10(11):1320–1333. doi:10.1016/j.jcmg.2016.10.007
14. Ito S, Miranda WR, Nkomo VT, et al. Reduced left ventricular ejection fraction in patients with aortic stenosis. *J Ame College Cardiol*. 2018;71 (12):1313–1321. doi:10.1016/j.jacc.2018.01.045
15. Sciaccaluga C, Natali BM, Righini FM, et al. Heart Transplantation and Anti-HLA antibody: myocardial dysfunction and prognosis - heartlay study. *ESC Heart Failure*. 2023;10(5):2853–2864. doi:10.1002/ehf2.14442
16. De A. Left ventricular strain in systemic diseases. *J Indian Acad Echocardiograph Cardiovascu Imaging*. 2023;7(2):128–136. doi:10.4103/jiae.jiae_12_23
17. El-Menyar AA, Galzerano D, Asaad N, Al-Mulla A, Arafa SE, Al Suwaidi J. Detection of myocardial dysfunction in the presence of normal ejection fraction. *J Cardiovasc Med*. 2007;8(11):923–933. doi:10.2459/JCM.0b013e328014daf2
18. Wang T, Li L, Huang J, Fan L. Assessment of subclinical left ventricle myocardial dysfunction using global myocardial work in type 2 diabetes mellitus patients with preserved left ventricle ejection fraction. *Diabetol Metab Syndr*. 2022;14(1):17. doi:10.1186/s13098-021-00781-x
19. Weidemann F, Herrmann S, Störk S, et al. Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. *Circulation*. 2009;120 (7):577–584. doi:10.1161/CIRCULATIONAHA.108.847772
20. Azevedo CF, Nigri M, Higuchi ML, et al. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. *JACC*. 2010;56(4):278–287. doi:10.1016/j.jacc.2009.12.074
21. Cameli M, Lisi M, Focardi M, et al. Left atrial deformation analysis by speckle tracking echocardiography for prediction of cardiovascular outcomes. *Am J Cardiol*. 2012;110(2):264–269. doi:10.1016/j.amjcard.2012.03.022
22. Magne J, Cosyns B, Popescu BA, et al. Distribution and prognostic significance of left ventricular global longitudinal strain in asymptomatic significant aortic stenosis: an individual participant data meta-analysis. *JACC Cardiovascular Imaging*. 2019;12(1):84–92. doi:10.1016/j.jcmg.2018.11.005

23. Kaden JJ, Bickelhaupt S, Grobholz R, et al. Receptor activator of nuclear factor κB ligand and osteoprotegerin regulate aortic valve calcification. *J Mol Cell Cardiol*. 2004;36(1):57–66. doi:10.1016/j.yjmcc.2003.09.015
24. Ueland T, Aukrust P, Dahl CP, et al. Osteoprotegerin levels predict mortality in patients with symptomatic aortic stenosis. *J Internal Med*. 2011;270 (5):452–460. doi:10.1111/j.1365-2796.2011.02393.x
25. Dahl JS, Videbæk L, Poulsen MK, et al. Relation of osteoprotegerin in severe aortic valve stenosis to postoperative outcome and left ventricular function. *Am J Cardiol*. 2013;112(9):1433–1438. doi:10.1016/j.amjcard.2013.06.015
26. Ravassa S, López B, Treibel TA, et al. Cardiac Fibrosis in heart failure: focus on non-invasive diagnosis and emerging therapeutic strategies. *Mol Aspect Med*. 2023;93:101194. doi:10.1016/j.mam.2023.101194
27. Nezami Z, Holm H, Ohlsson M, et al. The impact of myocardial fibrosis biomarkers in a heart failure population with atrial fibrillation—The HARVEST-Malmö study. *Front cardiovasc med*. 2022;9:982871. doi:10.3389/fcvm.2022.982871
28. Galeone A, Brunetti G, Oranger A, et al. Aortic valvular interstitial cells apoptosis and calcification are mediated by TNF-related apoptosis-inducing ligand. *Int J Cardiol*. 2013;169(4):296–304. doi:10.1016/j.ijcard.2013.09.012
29. Gozdzik A, Letachowicz K, Grajek BB, et al. Application of strain and other echocardiographic parameters in the evaluation of early and long-term clinical outcomes after cardiac surgery revascularization. *BMC Cardiovascular Disorders*. 2019;19(1):189. doi:10.1186/s12872-019-1162-8
30. Galli E, Fournet M, Chabanne C, et al. Prognostic value of left atrial reservoir function in patients with severe aortic stenosis: a 2D speckle-tracking echocardiographic study. *Euro Heart J*. 2016;17(5):533–541. doi:10.1093/ehjci/jev230
31. Krayenbuehl HP, Hess OM, Monrad ES, Schneider J, Mall G, Turina M. Left ventricular myocardial structure in aortic valve disease before, intermediate, and late after aortic valve replacement. *Circulation*. 1989;79(4):744–755. doi:10.1161/01.CIR.79.4.744
32. Spilias N, Martyn T, Denby KJ, Harb SC, Popovic ZB, Kapadia SR. Left ventricular systolic dysfunction in aortic stenosis: pathophysiology, diagnosis, management, and future directions. *Struct Heart*. 2022;6(5):100089. doi:10.1016/j.shj.2022.100089
33. Cioffi G, Faggiano P, Vizzardi E, et al. Prognostic effect of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. *Heart*. 2011;97(4):301–307. doi:10.1136/hrt.2010.192997
34. Vollema EM, Singh GK, Prihadi EA, et al. Time course of left ventricular remodelling and mechanics after aortic valve surgery: aortic stenosis vs. aortic regurgitation. *Eur Heart J Cardiovasc Imaging*. 2019;20(10):1105–1111. doi:10.1093/ehjci/jez049
35. Ngo A, Hassager C, Thyregod HGH, et al. Differences in left ventricular remodelling in patients with aortic stenosis treated with transcatheter aortic valve replacement with corevalve prostheses compared to surgery with porcine or bovine biological prostheses. *Eur Heart J Cardiovasc Imaging*. 2018;19(1):39–46. doi:10.1093/ehjci/jew321
36. Lindman BR, Stewart WJ, Pibarot P, et al. Early regression of severe left ventricular hypertrophy after transcatheter aortic valve replacement is associated with decreased hospitalizations. *JACC Cardiovasc Interv*. 2014;7(6):662–673. doi:10.1016/j.jcin.2014.02.011
37. Daubert MA, Weissman NJ, Hahn RT, et al. Long-term valve performance of TAVR and SAVR: a report from the PARTNER I trial. *JACC Cardiovasc Imaging*. 2017;10(1):15–25. doi:10.1016/j.jcmg.2016.11.004
38. Ito S, Pislaru C, Miranda WR, et al. Left ventricular contractility and wall stress in patients with aortic stenosis with preserved or reduced ejection fraction. *JACC Cardiovascular Imaging*. 2020;13(2 Pt 1):357–369. doi:10.1016/j.jcmg.2019.01.009
39. Liao H, Yang S, Yu S, Hu X, Meng X, Wu K. Prognostic value of left ventricular global longitudinal strain for major adverse cardiovascular events in patients with aortic valve disease: a meta-analysis. *Cardiology*. 2024;149(3):277–285. doi:10.1159/000536331
40. Généreux P, Pibarot P, Redfors B, et al. Staging classification of aortic stenosis based on the extent of cardiac damage. *Eur Heart J*. 2017;38 (45):3351–3358. doi:10.1093/eurheartj/ehx381
41. Loudon BL, Ntatsaki E, Newsome S, et al. Osteoprotegerin and myocardial fibrosis in patients with aortic stenosis. *Sci Rep*. 2018;8(1):14550. doi:10.1038/s41598-018-32738-y
42. Barbas de Albuquerque F, Teixeira R, Pereira-da-Silva T, et al. Left ventricular global longitudinal strain is associated with filling pressure and cardiac output in an outpatient setting: insights from CardioMEMS™. *Revista Portuguesa de Cardiologia*. 2025;44(1):1–8. doi:10.1016/j.repc.2024.05.008
43. Kaler IGBPS, Wibhuti IBR, Wiryawan IN, Lestari AAW. Predischarge peak atrial longitudinal strain and plasma N-terminal pro-hormone brain natriuretic peptide as a predictor of short-term rehospitalization and cardiovascular mortality in patients with acute heart failure. *J Cardiovascu Echography*. 2024;34(2):63–71. doi:10.1111/imj.14071
44. Kamimura D, Suzuki T, Furniss AL, et al. Elevated serum osteoprotegerin is associated with increased left ventricular mass index and myocardial stiffness. *J Cardiovasc Med*. 2017;18(12):954–961. doi:10.2459/JCM.0000000000000549