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ORIGINAL PAPER

Prevalence and significance of relative apical sparing in aortic stenosis: insights from an echo and cardiovascular magnetic resonance study of patients referred for surgical aortic valve replacement

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Aims This study aims to assess the prevalence of relative apical sparing pattern (RASP) in patients with severe symptomatic aortic stenosis (AS), referred for surgical aortic valve replacement (AVR), to evaluate its significance, possible relation to amyloid deposition, and persistence after surgery.

Methods and results Prospective study of 150 consecutive patients [age 73 (interquartile range: 68–77), 51% women], with severe symptomatic AS referred to surgical AVR. All patients underwent cardiac magnetic resonance (CMR) before surgery. RASP was defined by [average apical longitudinal strain (LS)/(average basal LS + average mid LS)] > 1 by echocardiography. AVR was performed in 119 (79.3%) patients. Both Congo red and sodium sulphate-Alcian blue (SAB) stain were used to exclude amyloid on septal myocardial biopsy. LV remodelling and tissue characterization parameters were compared in patients with and without RASP. Deformation pattern was re-assessed at 3–6 months after AVR.

RASP was present in 23 patients (15.3%). There was no suspicion of amyloid at pre-operative CMR [native T1 value 1053 ms (1025–1076 ms); extracellular volume (ECV) 28% (25–30%)]. None of the patients had amyloid deposition at histopathology. Patients with RASP had significantly higher pre-operative LV mass and increased septal wall thickness. They also had higher *N*-terminal pro b-type natriuretic peptide (NT-proBNP) levels [1564 (766–3318) vs. 548 (221–1440) pg/mL, $P = 0.010$], lower LV ejection fraction (53.7 ± 10.5 vs. 60.5 ± 10.2%, $P = 0.005$), and higher absolute late gadolinium enhancement (LGE) mass [9.7 (5.4–14.1) vs. 4.8 (1.9–8.6) g, $P = 0.016$] at CMR. Follow-up evaluation after AVR revealed RASP disappearance in all except two of the patients.

Conclusion RASP is not specific of cardiac amyloidosis. It may also be found in severe symptomatic AS without amyloidosis, reflecting advanced LV disease, being mostly reversible after surgery.

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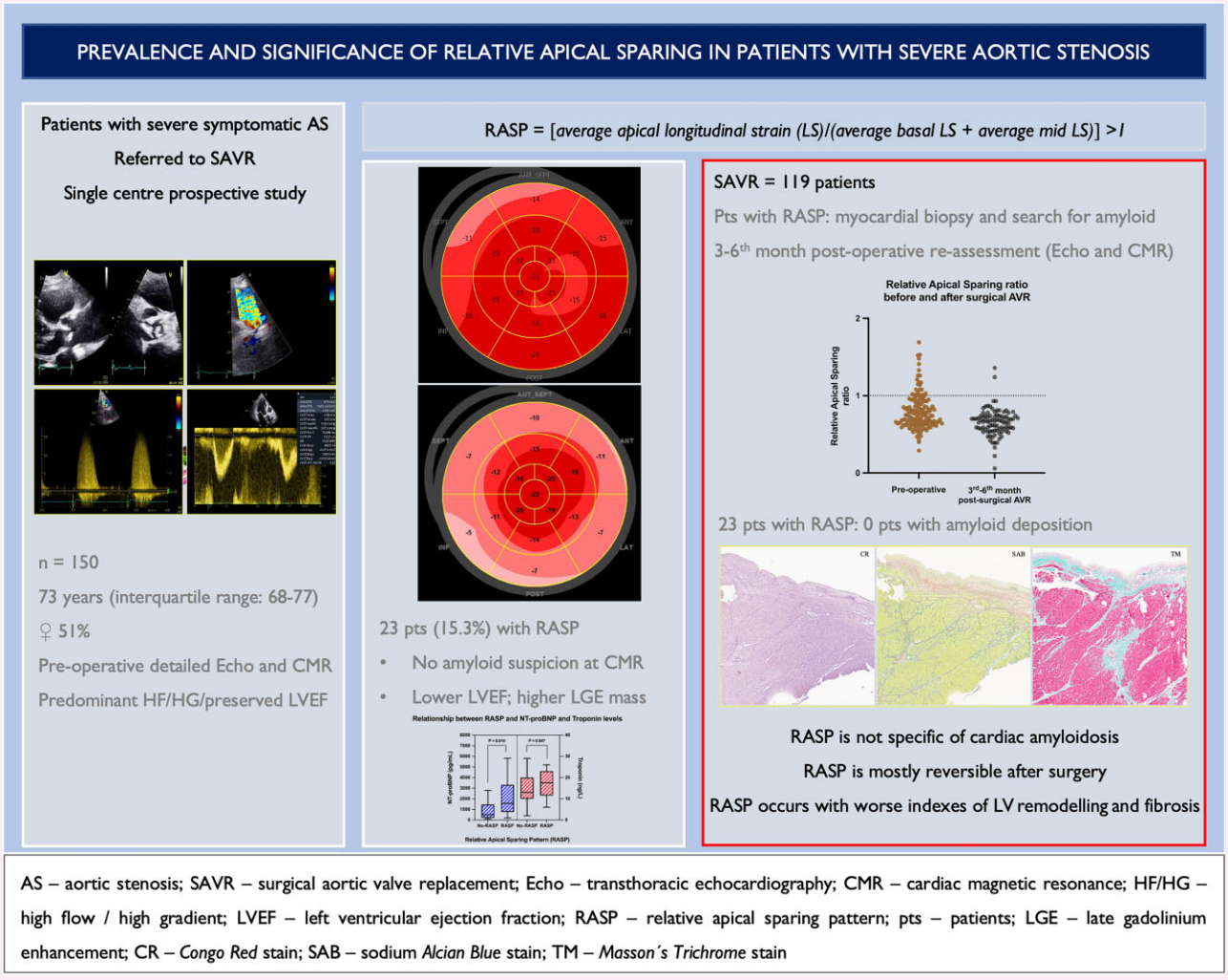
Graphical Abstract



Keywords severe aortic stenosis • relative apical sparing • surgical aortic valve replacement

Introduction

Aortic stenosis (AS) is currently the most common primary heart valve disease.[1] Compelling data supports the importance of left ventricular (LV) structural and functional remodelling to appropriately grade its severity, guide the clinical decision making, and stratify the risk of patients undergoing aortic valve replacement (AVR).[2,3] Even so, intervention is still recommended when patients with severe disease present with symptoms and in asymptomatic patients with reduced LV ejection fraction (EF).[1]

LV EF is largely dependent on loading conditions and may remain normal despite reduced myocardial contractility in hypertrophied LV due to changes in LV geometry.[4] Both factors limit its applicability in gauging LV systolic performance, particularly relevant in patients with severe AS. By contrast, myocardial deformation imaging is a less load-dependent measure of systolic function. Longitudinal deformation, as assessed by speckle tracking echocardiography, has been identified as an independent mortality and clinical events predictor in asymptomatic AS.[5] More recently, the combination of LV strain assessment throughout the cardiac cycle and noninvasively estimated LV pressure was proposed as a measure of instantaneous power, integrated over time to obtain myocardial work. In severe AS, LV systolic pressure does not equal non-invasive measurement of systolic blood pressure and it should be corrected with the addition of Doppler-derived mean aortic gradient.[6] This evaluation may be of value as it distinguishes if global longitudinal strain (GLS) reduction is due to reduced contractility (reflected as reduced myocardial work) or increased afterload (reflected as increased myocardial work).

Specific GLS patterns and regional deformation affection have been previously described for both diagnostic and prognostic purposes. Phelan *et al.*[7] established relative apical sparing pattern (RASP) as a red-flag marker for the suspicion of cardiac amyloidosis (CA) since it demonstrated high specifity (>90%) and sensibility (>80%) in distinguishing it from other causes of LV hypertrophy, including AS. However, there seems to be a predominant longitudinal strain impairment at basal LV segments, including with RASP, in some cohorts of patients with severe AS, and this could be related to more advanced disease stages and poorer prognosis after intervention.[8,9]

Yet, the coexistence of senile or wild-type transthyretin (TTR) CA and AS has been increasingly recognized in elderly patients, with

prevalence of CA ranging from 4 to 29% of patients with severe AS. Indeed, both disease entities are more frequently encountered in low-flow stages, in severely hypertrophied ventricles (paradoxical forms of AS), and in general, in older, higher surgical risk cohorts of patients, commonly referred for transcatheter valve implantation.[10] In this way, the pattern of myocardial deformation in patients with severe AS may be eventually explained by myocardial infiltration, LV remodelling in pressure overload conditions, or both.

CMR has recently provided valuable information regarding myocardial composition in older patients with severe AS and CA. Both native myocardial T1 and extracellular volume (ECV) have been validated in CA as surrogate markers of infiltration.[11] Nevertheless, the relation between specific myocardial deformation patterns, such as RASP, pre-operative CMR data, and occult amyloid deposition at histological analysis in patients with severe AS was not demonstrated.[12] Additionally, the evolution of RASP following AS treatment was not previously described, despite recent data showing its additive prognostic value and risk stratification potential.[9,13]

Hence, the aim of this study was to assess the prevalence of RASP in a group of patients with severe symptomatic AS, referred for surgical AVR, to evaluate its clinical significance, possible relation to amyloid deposition, and persistence after surgery.

Methods

Study population

One-hundred-fifty-seven patients undergoing elective AVR because of isolated severe symptomatic AS, defined according to European guideline on valvular heart disease,[1] were prospectively evaluated for study inclusion between April 2019 and January 2022 at our tertiary centre. We excluded patients with: (i) congenital AS or previous diagnosis of sub/supravalvular aortic stenosis; (ii) concomitant severe non-aortic valve dysfunction; (iii) moderate and severe aortic regurgitation; (iv) previous cardiac surgery; (v) active endocarditis; (vi) previous history of myocardial infarction, myocarditis, ischemic and non-ischemic cardiomyopathy including CA, and other infiltrative diseases; (vii) chronic kidney disease with glomerular filtration rate below 30 mL/min/1.73 m^2; (viii) non-cardiac inflammatory disease; and (ix) active infection, under immunosuppressive and chronic anti-inflammatory therapy, under chemotherapy, and with previous chest radiotherapy. Patients with poor acoustic window not allowing longitudinal strain assessment were also excluded ($n = 7$).

This prospective study is part of a correlation research protocol in patients with severe symptomatic AS, dedicated to LV adaptation and extracellular remodelling in this context, as assessed by multimodality imaging and histopathology from endomyocardial biopsies. This protocol was previously specified and approved by the ethical committee of Nova Medical School University (study number 61/2018/CEFCM), fulfilling the principles of the Helsinki declaration. All participants provided written informed consent.

Clinical data and study design (see supplementary data online, *Figure*)

Clinical parameters (demographics, major cardiovascular risk factors, and symptomatic status including the presence of angina, syncope, and New York Heart Association—NYHA class, current medication), 12-lead ECG, and transthoracic echocardiography (TTE) were collected at the study inclusion before AVR. CMR was carried out within 2 weeks after patient inclusion alongside blood sample for haematocrit (Htc), creatinine, high-sensitivity cardiac troponin I (hsTnI), and *N*-terminal pro b-type natriuretic peptide (NT-proBNP). Both TTE and CMR studies were performed within 6 months prior to AVR.

To assess LV morpho-functional changes after surgery and RASP evolution, all patients had a detailed echo and CMR study between the third and the sixth month after surgery, and these studies included the same parameters as that from pre-intervention, except for the estimation of post-operative ECV, that was not performed.

Study design and procedural schedule are depicted in Supplementary data online, *Figure*.

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.[14,15] 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).

2D speckle tracking strain analysis and RASP

According to consensus, speckle tracking longitudinal strain analysis was carried out in patients with adequate endomyocardial border definition in 4-, 2- and 3-chamber standard apical views: bidimensional grey-scale images with appropriate temporal resolution (40–80 frames per second temporal resolution) on three recorded consecutive cycles.[16] The longitudinal peak strain (LS) values for the six basal, six mid, and five apical segments of the LV were averaged to obtain regional basal, mid, and apical LS, respectively. As suggested[17] and for ease of interpretation, GLS values were registered as positive. Quantitative RASP was obtained using the formula proposed by Phelan *et al.*[7] (average apical LS)/(average basal LS + average mid LS), being defined as positive when above 1.0.

Additional deformation indexes such as instantaneous LV peak systolic twist and right ventricular free-wall strain were also registered.

TTE study at the third to sixth month after AVR included all the above-mentioned parameters in addition to specific prosthetic assessment, as recommended.[18]

Detailed echocardiographic measurements and derived indexes are described at Supplementary data online, *Material/Methods*.

Cardiac magnetic resonance

CMR study was performed at 1.5 T equipment (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany) using a clinical scan protocol, as previously published.[19] Technical details concerning post-contrast late gadolinium enhancement (LGE) imaging, native and post-contrast T1 mapping, and ECV quantification are specified in Supplementary data online, *Methods*.

Histological analysis for the presence of amyloid

Congo red (CR) staining histochemistry on 6 μm formalin-fixed and paraffin-embedded myocardial tissue sections was carried out in all patients with RASP. Myocardial samples were obtained either from intraoperative septal biopsy as per protocol design (harvested with a scalpel from the basal interventricular septum, preferably with included endocardium) or from complementary septal myectomy performed by the surgical team at the time of surgical AVR. Additionally, sodium sulphate-Alcian Blue (SAB) stain was also made as to confirm possible myocardial infiltration.[20] Interpretation was performed without any clinical information by RT and SR in bright-field (CR and SAB) and cross-polarized light (CR) using light microscope (Leica) with and without crossed polars, at 10× and 20× amplification.

Statistical analysis

Categorical values are presented as absolute number (and percentage) and continuous variables as mean ± standard deviation (normal distribution) or

as median and interquartile range (IQR; non-parametric). Kolmogorov–Smirnov test was used to test the normality of the variables. Pearson´s Chi-squared (χ^2) test, Mann–Whitney *U* test, and independent samples *t*-test were applied for comparison where appropriate. For statistical analysis involving pre- and post-operative data, pairwise comparisons were carried out.

The inter-observer variability of LS was assessed by calculating the intraclass correlation coefficient analysis on a random sample of 30 pre-operative echocardiograms, by comparing a repeated analysis performed one week later by a second blinded independent operator. It showed very good reproducibility inter-observer variability, with an intraclass correlation coefficient of 0.97 (95% CI, 0.96–0.99, $P < 0.001$).

A sensitivity analysis excluding the patients without high gradient AS and those with reduced LV EF was performed to assess to what degree the inclusion of patients with distinct haemodynamic characteristics of AS might have influenced our results.

For the specific account of possible confounding variables on the differences of imaging data in both groups of patients, with and without RASP, we made an adjustment analysis with both parametric and non-parametric ANCOVA (*Quade´s*).

Statistical significance was set at *P*-value < 0.05 (two-sided). All analyses were performed using SPSS v 26.0 (IBM Corporation, Armonk, NY, USA) and STATA v13.0 (StataCorp, College Station, TX, USA).

Results

Study population and global clinical data

A total of 150 patients with severe symptomatic AS and appropriate pre-operative echocardiographic study allowing LS analysis were included in the analysis, with median age of 73 [68–77] years, 76 (50.6%) of them being women. These were all ambulatory patients, mostly complaining of effort dyspnoea or functional impairment on daily activities (142 of them in NYHA ≥ II functional class). Baseline clinical-, laboratory-, and surgical-related data are summarized in *Table 1*. AVR was performed after the enrolment in 119 (79.3%) of the patients and 96 (80.7%) of them have complete post-operative evaluation at both eco and CMR studies between the third and the sixth month after hospital discharge (see Supplementary data online, *Figure* —study design). Intermediate to significant coronary artery disease, leading to the decision of concomitant surgical revascularization, was identified in 24 (20.2%) patients and this was the single most frequent additional surgical procedure beyond AVR. The great majority of patients (94.1%) had a bioprosthetic implantation and subaortic septal myectomy was added to the procedure, as reported by the surgical team, in 52.1% of the cases. Neither pseudoinfarct pattern nor low voltage ECG criteria were identified before surgery. Four patients needed a pacemaker implantation in the post-operative period given the occurrence of atrioventricular block. New-onset atrial fibrillation was detected in three patients at post-operative evaluation. Left bundle branch block was identified in 4 and 10 patients before and after AVR, respectively.

Table 1 Baseline clinical, laboratory, and surgical data of the study cohort

Total study population: *n* = 150	
Clinical characteristics	
Age, years	73 (68–77)
Male	74 (49.3%)
BSA m^2	1.80 ± 0.18
Hypertension	127 (84.7%)
Diabetes mellitus	43 (28.7%)
Dyslipidaemia	80 (53.3%)
Smoking history	21 (14.0%)
Previous stroke	8 (5,3%)
Atrial fibrillation	13 (8.7%)
Previous pacemaker implantation	3 (2.0%)
NYHA functional class	
I	8 (5.3%)
II	114 (76.0%)
III	28 (18.7%)
Anginal symptoms	45 (30.0%)
Syncope	32 (21.3%)
Laboratory results	
Htc, %	39.5 ± 4.2
Creatinine, mg/dL	0.90 (0.77–1.11)
Estimated glomerular filtration rate, mL/min	68.0 (53.5–87.5)
NT-proBNP, pg/mL	645 (244–1853)
Troponin, ng/L	13 (10–21)
Surgical data *n* = 119	
Isolated SAVR	88 (73.9%)
Mechanical prosthesis	7 (5.9%)
CABG	24 (20.2%)
Associated surgical procedure[a]	11 (9.2%)
Surgical myectomy[b]	62 (52.1%)
In-hospital mortality[c]	3 (2.5%)
Pacemaker implantation	4 (3.4%)

Values are median (interquartile range), mean ± standard deviation.
BSA, body surface area; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; and CABG, coronary artery bypass grafting.
[a]This included mitral valve prosthesis for prolapse with moderate mitral regurgitation (1), tricuspid ring implantation (1), interatrial septum defect/patent foramen ovale closure (2), aortic root enlargement (3), and supracoronary aortic graft for ascending aorta dilatation (4).
[b]Not included in associated surgical procedure.
[c]Causes of death included stroke (1), COVID-19 (1), and cardiogenic shock attributed to bypass graft failure.

Baseline and post-operative imaging data

Both echocardiographic and CMR data before and after surgical AVR are shown in Supplementary data online, *Table S1*. A mean period of 3.4 ± 2.0 months elapsed between imaging studies and valve surgery. This cohort was composed of 141 patients with high gradient severe AS (94%), 13 of them with reduced EF and 5 with a low-flow state. Nine patients had low gradient AS (two with reduced EF and seven of them with preserved EF). The mean maximum reported basal septum thickness before surgery was 16.0 ± 2.7 mm. At pre-operative imaging studies there was positive LV remodelling and hypertrophy, which have happened to significantly regress after AVR, as both assessed by echo and CMR. As expected, this was independent from the concomitant subaortic septal myectomy (see Supplementary data online, *Table S2*).

In what concerns LV systolic function and associated cardiac damage, there were significant improvements in LV EF, GLS, and parameters describing upstream repercussion of pressure overload (E/A and E/E´ ratio, left atrial volume, and pulmonary pressures), after surgery. There was a significant reduction of LV twist at post-operative echocardiographic evaluation. Significant reductions of right ventricular (RV) longitudinal function parameters were registered.

Table 2 Clinical and laboratory data in both groups of patients, with and without RASP

	No-RASP ($n = 127$)	RASP ($n = 23$)	*P*-value
Clinical characteristics			
Age, years	73 (68–77)	73 (69–80)	0.896
Male	60 (47.2)	14 (60.9)	0.305
BSA, m^2	1.81 ± 0.18	1.76 ± 0.20	0.239
Atrial fibrillation	5 (3.9)	8 (34.8)	**<0.001**
Hypertension	109 (85.8)	18 (78.3)	0.368
Diabetes mellitus	34 (26.8)	9 (39.1)	0.316
Creatinine, mg/dL	0.91 (0.77–1.11)	0.88 (0.76–1.08)	0.648
NYHA functional class			0.335
I	6 (4.7)	2 (8.7)	
II	96 (75.6)	18 (78.3)	
III	25 (19.7)	3 (13.0)	
Anginal symptoms	42 (33.1)	3 (13.0)	**0.043**
Syncope	28 (22.0)	4 (17.4)	0.671
NT-proBNP, pg/mL	508 (221–1440)	1564 (766–3318)	**0.010**
Cardiac troponin-T, ng/L	13 (10–19)	18 (12–23)	**0.047**

Values are median (interquartile range), mean ± standard deviation, or *n* (%).
Bold *P*-values are statistically significant.
BSA, body surface area; RASP, relative apical sparing pattern.

There was no severe prosthesis dysfunction at echocardiographic follow-up. Two patients with above labelled prosthetic gradients were identified with moderate patient–prosthesis mismatch. Four of the 96 patients (4.2%) had mild paravalvular regurgitation.

Non-ischemic LGE was identified in 98 patients (65.3%) before surgery, representing 4.3% [1.6–7.8%] of global LV mass. Among those with LGE, this was most frequently observed in the basal anteroseptum (38%) and basal and mid inferior (37 and 39%, respectively) interventricular septum. Small subendocardial ischaemic scars (representing no more than one LV segment) were identified in two patients with no previous history of myocardial infarction. There was a non-significant increase in LGE % of LV mass after AVR. Pre-operative native T1 values were considered slightly above normal for the institutional cut-off of 1021 ms [972–1070 ms]. Myocardial ECV was 28% [25–30%].

RASP: prevalence, post-AVR evolution, and characterization

RASP was identified in 23 patients (15.3%) of this cohort, and there were no significant clinical differences in this group of patients except for the less frequent anginal symptoms and higher prevalence of atrial fibrillation (*Table 2*). The prevalence of intermediate to significant coronary artery disease leading to concomitant surgical revascularization was not significantly different in patients with RASP vs. no-RASP [4 of 23 (17.4%) vs. 20 of 96 patients (20.8%), respectively; *P*-value for the difference: 0.713].

Patients with RASP had significantly higher transvalvular gradients despite no differences in flow, and higher pre-operative LV mass and positive remodelling as assessed by both echo and CMR study. This group had lower LV EF at CMR evaluation, with higher left atrial volumes and significantly more prevalent impairment of RV free-wall longitudinal strain. As would be expected, GLS was significantly lower, at the cost of significant reduction of LS at both basal and mid LV segments. At tissue characterization this strain pattern was associated with higher absolute LV LGE mass (*Table 3*). RASP was notable for significantly increased ambulatory levels of both NT-proBNP and cardiac troponin-T (*Figure 1*).

After surgical AVR only two of the 23 patients with pre-operative RASP kept this strain pattern (*Figure 2*) and there were no additional cases of RASP. Despite persistent significant differences in LS at basal and mid-ventricular levels in both groups of patients, with and without pre-operative RASP (*Figure 3*), these were no longer sufficient to maintain RASP. Except for increased LV mass as determined by post-operative CMR, the same patients with pre-operative RASP had non-significant differences in what concerns LV function, upstream cardiac repercussion, and LV tissue characterization after surgery (see Supplementary data online, *Table S3*). Three of the four patients with pacemaker implantation after AVR had pre-operative RASP and this precluded appropriate estimation of both native T1 values and LGE quantification. One of the two patients who remained with RASP had a pacemaker and the other two patients with pacemaker lost this strain pattern.

The results of the sensitivity analysis excluding patients without high gradient severe AS and those with reduced LV EF proved to be no different from the primary analysis (see Supplementary data online, *Tables S4–S7*).

Appropriate myocardial histopathology analysis, as defined by the study protocol, was performed in 112 patients (94.1% of patients submitted to AVR). Biopsy was not performed in 6 patients owing to the reported risk from the surgical team (thin interventricular septum); 1 patient had a very small biopsy sample with too scarce myocardium for analysis. All patients with RASP had appropriate myocardial biopsies and there was no reported infiltration at either CR or SAB staining techniques (*Figure 4*).

Discussion

The main findings of our study were that: (i) RASP is present in about 15% of patients from a cohort with predominant normal flow, high

Table 3 Pre-operative imaging data in patients with and without RASP

	No-RASP ($n = 127$)	RASP ($n = 23$)	*P*-value*
Echocardiography			
Aortic valve area, cm^2	0.73 ± 0.18	0.66 ± 0.17	0.333
Maximum aortic gradient, mmHg	96.1 ± 25.2	111.6 ± 32.7	**0.001**
Mean aortic gradient, mmHg	59.6 ± 16.7	69.4 ± 20.1	**0.002**
Relative wall thickness, mm	0.50 ± 0.12	0.59 ± 0.14	**0.003**
Maximum septal thickness, mm	15.7 ± 2.5	17.9 ± 3.2	**<0.001**
LV indexed mass, g/m^2	154.0 ± 50.7	190.5 ± 64.7	**0.003**
LVEDV, mL	86.8 ± 34.8	93.6 ± 31.4	0.264
LV ejection fraction, %	58.6 ± 9.4	54.9 ± 9.1	0.208
Stroke volume index, mL/m^2	47.4 ± 10.6	45.3 ± 12.5	0.750
Global longitudinal strain, %	15.3 ± 3.6	12.1 ± 2.3	**0.001**
Mean basal LS, %	12.1 ± 3.2	6.2 ± 3.3	**<0.001**
Mean mid LS, %	14.7 ± 3.5	10.2 ± 3.3	**<0.001**
Mean apical LS, %	19.3 ± 5.5	19.6 ± 5.6	0.931
Ratio mean apical LS/(mean basal LS + mean mid LS)	0.72 ± 0.14	1.32 ± 0.53	**<0.001**
LV twist, °	24.0 ± 9.6	23.2 ± 9.8	0.325
E/A ratio	0.73 (0.60–0.90)	0.69 (0.63–1.23)	0.796
E/E'' ratio	12.7 (9.7–17.6)	16.0 (12.8–24.5)	0.100
LAVI, mL/m^2	39.6 (34.0–51.9)	46.4 (37.0–65.0)	0.324
SPAP, mmHg	33.0 (27.0–40.8)	33.0 (28.5–43.5)	0.580
TAPSE, mm	22.3 ± 3.9	20.2 ± 3.8	0.468
STDI, cm/s	13.6 ± 3.0	12.7 ± 3.4	0.654
RV free-wall LS, %	26.6 ± 5.2	22.0 ± 7.7	**0.024**
Cardiac magnetic resonance			
LV indexed mass, g/m^2	77.9 ± 24.6	96.1 ± 28.8	**<0.001**
LVEDV, mL	152.9 ± 47.1	164.9 ± 47.3	0.103
Geometric remodelling, g/mL	0.94 (0.82–1.05)	1.02 (0.87–1.19)	**0.032**
LV ejection fraction, %	60.5 ± 10.2	53.7 ± 10.5	**0.032**
Delayed enhancement	80 (63.0)	18 (78.3)	0.294
Delayed enhancement, g	4.8 (1.9–8.6)	9.7 (5.4–14.1)	**0.019**
Delayed enhancement, % of mass	3.9 (1.6–7.1)	6.0 (3.4–10.5)	0.109
Global native T1, ms	1053 (1024–1076)	1049 (1036–1079)	0.832
Global ECV, %	28.0 (25.0–30.0)	28.0 (26.0–29.0)	0.522

Values are median (interquartile range), mean ± standard deviation, or *n* (%). Bold *P*-values are statistically significant.
A, peak late diastolic transmitral flow velocity; E, peak early diastolic transmitral flow velocity; E', peak early diastolic mitral annular tissue velocity; ECV, extracellular volume; LAVI, left atrial volume index; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LS, longitudinal strain; RV, right ventricle; SPAP, systolic pulmonary artery pressure; STDI, right ventricle tissue Doppler imaging systolic velocity; TAPSE, tricuspid annular plane systolic excursion; Other abbreviations as in *Tables 1* and *2*.
**P*-values after adjustment for atrial fibrillation, using parametric and non-parametric ANCOVA.

gradient, preserved EF, and severe AS; (ii) this LS pattern seems to be related to more advanced LV remodelling and cardiac damage in this setting; and (iii) RASP is mostly reversible after surgical AVR, which supports the absence of relation to concomitant amyloid infiltration, as proved by negative myocardial biopsy. This may eventually add value to GLS assessment in patients with severe AS, as this specific pattern may discriminate more severe LV disease. Moreover, and as suggested by an integrative approach, one should not strictly rely on RASP for raising CA suspicion in patients with severe AS proposed for surgical AVR.

As far as we are aware, this is one of the few studies simultaneously addressing the prevalence of RASP in a globally homogeneous cohort of patients with severe AS submitted to surgical AVR, and its evolution after pressure overload relief. Slight inferior prevalence of this LS pattern was found. Anyway, the association of RASP with indexes of more severe valvular disease, related LV dysfunction and global heart repercussion, is in line with previous published data.[9,13] We further demonstrated that RASP in these patients with severe AS occurs in the absence of CA, which is accordance with what was demonstrated by Robin *et al.*[21] Despite significant LV hypertrophy and increased septal thicknesses in these patients, neither ECG findings nor CMR tissue characterization indexes (above normal T1 native values; estimated ECV, much below the cut-off suggested for the diagnosis of CA[11])

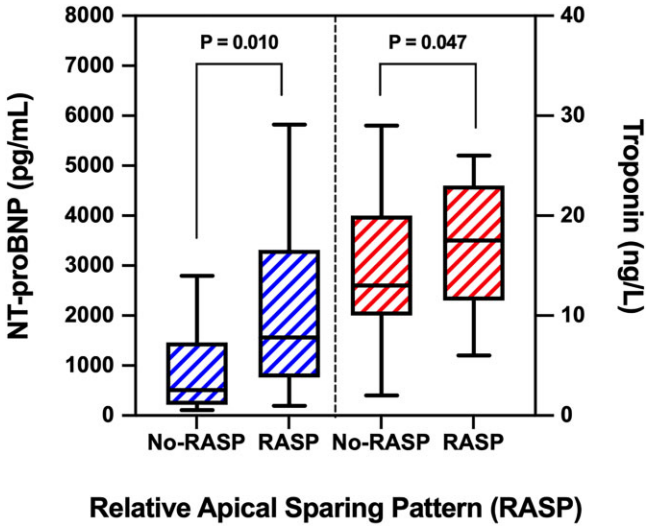


Figure 1 Relationship between RASP and NT-proBNP and troponin levels.

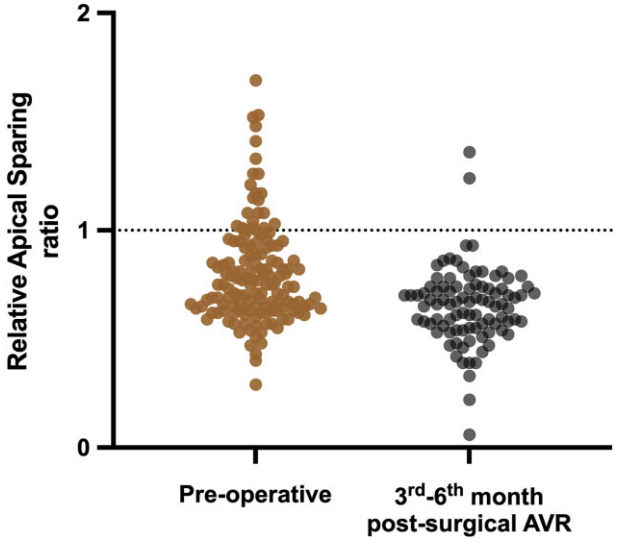


Figure 2 RASP before and after surgical AVR.

could have raised the suspicion of myocardial infiltration. As well, we found that all patients except two lost RASP at the third to sixth post-operative month, suggesting a reversible mechanism of regional functional impairment. Additionally, amyloid infiltration was excluded by myocardial biopsy histochemistry (negative CR staining). We merely performed this evaluation in patients with RASP, as the assessment of CA prevalence was beyond our aim in this protocol. Even so, we used SAB stain to support this finding. Indeed, SAB is assigned with features that may improve CA diagnosis, such as increased sensitivity and less equivocal reactions, and no need for special polarized light source.[20] We showed that RASP is not related to myocardial infiltration in this group of patients, as suggested by both pre- and post-operative non-invasive imaging, but definitively proved by negative myocardial biopsy.

We should recognize that global strain measurements could have been performed by CMR as good inter-technique agreement in strain measurements between speckle tracking echo and CMR and among distinct CMR techniques has already been demonstrated.[22] However, and from a methodological point of view and in terms of clinical application, we decided to use echo-derived RASP, as it is defined and routinely used as a red-flag marker of cardiac amyloidosis.[23] On the other hand, CMR-derived segmental strain is a less commonly used parameter due to inferior reproducibility and inter-technique agreement compared with global strain,[22] which could have been important for the analysis.

Previous studies have found distinct prevalence of concomitant amyloidosis, namely TTR CA, in patients with severe AS.[10] Dual pathology is more frequently recognized in older (aged >75) patients, with low-flow, low-gradient, mildly reduced EF AS phenotype, which mainly explains higher prevalence in patients referred for transcatheter valve intervention, with outcome benefit from the intervention anyhow.[24,25] However, it was also demonstrated that imaging modalities have different capacities to support and/or predict TTR CA in this scenario. In a

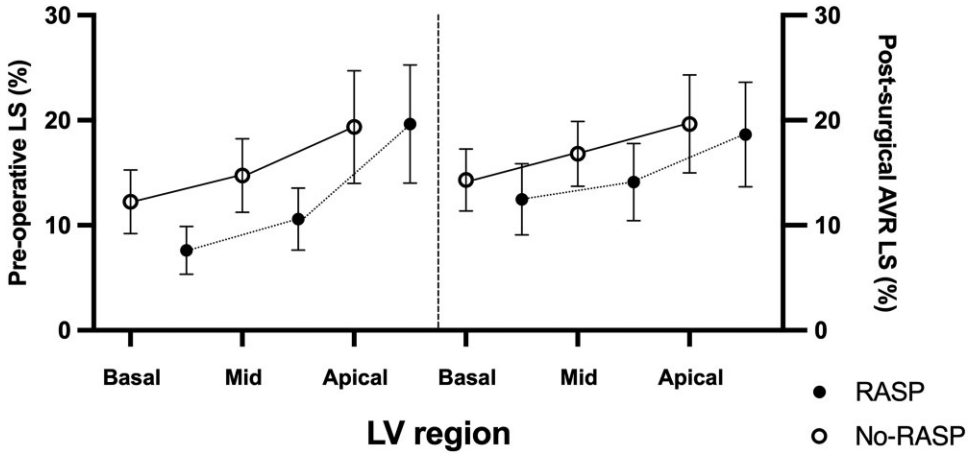


Figure 3 Comparison of LV regional LS pre- and post-AVR according to RASP.

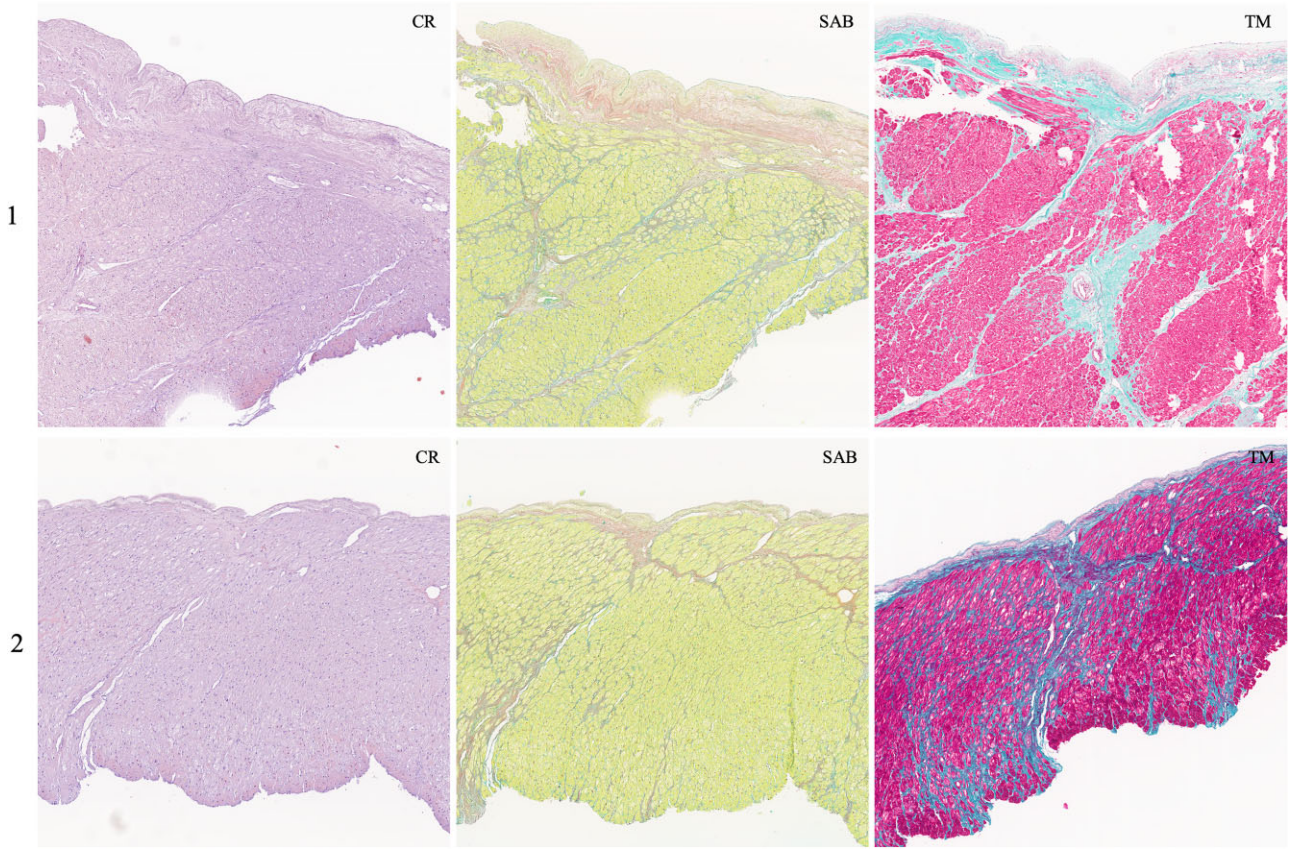


Figure 4 Myocardial histochemistry (×40) with both CR and SAB stain in two of the patients with RASP, both negative for amyloid infiltration despite distinct types and quantities of myocardial fibrosis, put in evidence at Masson´s trichrome (MT) stain at the same tissue area.

single-centre surgical AS cohort, echocardiography was non-contributory for the suspicion of dual pathology.[12] In what specifically concerns LS assessment, Castaño *et al.*[24] also found that RASP was no different among AS patients with and without CA, despite the identification of echocardiographic measurements, such as Doppler mitral annular S′, that should lead to subsequent screening for TTR CA.

Our cohort mainly included younger patients, with predominant classical high gradient, normal flow AS, referred for surgical AVR. These together were certain key factors explaining the absence of CA, and dual pathology prevalence would be expected to rise if additional patients with distinct haemodynamic categories had been included. Even so, our protocol stems with surgical myocardial biopsy,

precluded in transcatheter referred patients, and this prevalence assessment was not the aim of the study. Accordingly, we confirmed that RASP was both non-contributory to CA suspicion and unrelated to myocardial amyloid infiltration. This goes against the previous proposal from Phelan *et al.*[7] and may eventually result from distinct groups of patients included.

In what concerns global myocardial deformation assessment, our findings are in line with current evidence,[26,27] as pre-operative subnormal GLS, albeit overall preserved LV EF, is the consequence of increased afterload. In this cohort, subnormal GLS occurs at a stage beyond a relatively compensated myocardial contractile function, as all patients were symptomatic, with an indication for intervention. Notably, there was also a significant difference in LV rotational mechanics at basal and apical levels, i.e. increased twist before surgery. This supports the theoretical concept underlying EF preservation, owing to longer arm of movement of subepicardial helical fibre, less exposed to subendocardial stress in pressure overload conditions.[28]

Several mechanisms have been previously proposed to explain RASP in patients with severe AS: (i) increased cavity ratio at basal LV levels; (ii) distinct myocardial fibre orientation and resistance to subendocardial stress between the apex and LV base; (iii) unequal distribution of myocardial fibrosis with predominant involvement of the basal segments; and (iv) mitral ring calcifications,[8,9] more pronounced amyloid deposits at basal levels.[7,29] This last hypothesis is not definitely the case and, as said, one could already suspect it before myocardial biopsy results: RASP group was not characterized by significantly lower transvalvular gradients, flow, and LV ejection fraction at pre-operative echocardiography, more common features of dual pathology coexistence. Nevertheless, we still believe that RASP may identify a subgroup of patients with a more advanced stage of LV disease among those with classical severe symptomatic AS. Indeed, it was recently showed that RASP has incremental and independent prediction value for major adverse cardiac events and post-intervention complications in patients with severe AS, regardless the presence of amyloid infiltration.[8,9,13]

In accordance with our association results, we might speculate that RASP is a consequence of a distinct pattern of LV remodelling in patients with severe AS. Pronounced LV positive remodelling and hypertrophy, with predominant interventricular septal thickening at basal LV levels, and increased mass of replacement fibrosis, might jointly explain regional deformation impairment at basal LV segments. Curiously, our findings go further beyond the simple mechanism behind Laplace's law, where predominant LS impairment, with RASP, stems from the increased subendocardial wall stress at a level with increased ratio of the cavity.

Limitations

This prospective but observational study have some limitations. Because of its design we are not able to deduce the possible mechanisms or morpho-functional factors explaining RASP. Possibly, the distribution of patients across different groups of AS patients according to LV geometry/remodelling would result in very few representative numbers.

In the same line and since most of the patients had high gradient AS, we could not stratify the results according to distinct haemodynamic categories.

The length of time from the beginning of symptoms or clinical indication for AVR might have been useful in trying to find if RASP is a late-appearing marker of advanced LV impairment, even in patients with preserved LV EF. In the same way, clinical outcomes were not evaluated after surgery, what could have been of interest as to determine the prognostic value of this strain pattern.

The definition used for RASP is in accordance with position statements definitions of echocardiographic red flags for CA diagnostic algorithms. If we would expand endomyocardial biopsy screening with CR and/or SAB stain to the whole group of patients, we might eventually identify some very few cases of CA, despite the reduced probability, according to AS main phenotype and CMR data. If this was the case, additional echocardiographic strain criteria, such as the EF to GLS ratio, septal apical to basal strain ratio, or simple apical to basal strain ratio (not including mid-segments strain values) could be eventually useful in terms of differential diagnosis and LV remodelling characterization.

Finally, this was a moderate-sized study from a single, tertiary referral centre, and thus general extrapolation is limited and should be cautious.

Conclusions

The prevalence of RASP in patients with severe symptomatic AS undergoing surgical AVR was 15.3%. This deformation pattern is not related to amyloid infiltration, as suggested from pre-operative CMR, and excluded at septal myocardial biopsy, being mostly reversible after surgery. RASP occurs in patients with worse indexes of LV remodelling and fibrosis, reflecting an advanced stage of valvular disease.

Supplementary data

Supplementary data is available at *European Heart Journal - Cardiovascular Imaging* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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