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Impact of aortic stenosis on layer-specific longitudinal strain: relationship with symptoms and outcome

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Aims The present study sought to assess the impact of aortic stenosis (AS) on myocardial function as assessed by layer-specific longitudinal strain (LS) and its relationship with symptoms and outcome.

Methods and results We compared 211 patients (56% males, mean age 73 ± 12 years) with severe AS and left ventricular ejection fraction (LVEF) ≥50% (114 symptomatic, 97 asymptomatic) with 50 controls matched for age and sex. LS was assessed from endocardium, mid-myocardium, and epicardium by 2D speckle-tracking echocardiography. Despite similar LVEF, multilayer strain values were significantly lower in symptomatic patients, compared to asymptomatic and controls [global LS: 17.9 ± 3.4 vs. 19.1 ± 3.1 vs. 20.7 ± 2.1%; endocardial LS: 20.1 ± 4.9 vs. 21.7 ± 4.2 vs. 23.4 ± 2.5%; epicardial LS: 15.8 ± 3.1 vs. 16.8 ± 2.8 vs. 18.3 ± 1.8%; $P < 0.001$ for all]. On multivariable logistic regression analysis, endocardial LS was independently associated to symptoms ($P = 0.012$), together with indexed left atrial volume ($P = 0.006$) and LV concentric remodelling ($P = 0.044$). During a mean follow-up of 22 months, 33 patients died of a cardiovascular event. On multivariable Cox-regression analysis, age ($P = 0.029$), brain natriuretic peptide values ($P = 0.003$), LV mass index ($P = 0.0065$), LV end-systolic volume ($P = 0.012$), and endocardial LS ($P = 0.0057$) emerged as independently associated with cardiovascular death. The best endocardial LS values associated with outcome was 20.6% (sensitivity 70%, specificity 52%, area under the curve = 0.626, $P = 0.022$). Endocardial LS (19.1 ± 3.3 vs. 20.7 ± 3.3, $P = 0.02$) but not epicardial LS (15.2 ± 2.8 vs. 15.9 ± 2.5, $P = 0.104$) also predicted the outcome in patients who were initially asymptomatic.

Conclusion In patients with severe AS, LS impairment involves all myocardial layers and is more prominent in the advanced phases of the disease, when the symptoms occur. In this setting, the endocardial LS is independently associated with symptoms and patient outcome.

Keywords aortic stenosis • multilayer strain • endocardial longitudinal strain • speckle-tracking echocardiography

Introduction

Aortic stenosis (AS) is currently the most common valvular heart disease, and its prevalence is increasing as the population ages.[1] Symptomatic patients with severe AS have a high mortality rate and require prompt aortic valve replacement (AVR).[2,3] Although asymptomatic patients are at increased risk for untoward events, their management remains controversial. Current guidelines consider AVR as reasonable in asymptomatic patients with reduced (<50%) left ventricular ejection fraction (LVEF) and in patients who exhibit

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symptoms during an exercise test.[4,5] However, symptoms are subjective and LVEF can remain normal for long despite markedly impaired myocardial function. We previously demonstrated that 2D LV global longitudinal strain (GLS) could detect early subtle myocardial dysfunction in AS patients.[6–9] The impairment of global LV longitudinal function is associated with myocardial fibrosis, which is, in turn, a potential prognostic marker in patients with AS.[10] However, longitudinal function is actually largely governed by the subendocardial myocardial fibres, which are affected first by the pathological changes (hypertrophy, increased wall stress, and reduced arterial compliance) associated with AS.[11,12] Recent 2D strain software allows separate evaluation of endocardial, mid-myocardial, and epicardial myocardial deformation. To date, little is known about the impact of AS on the different myocardium layers. The present study sought to investigate the relationship between changes in layer-specific strain and the clinical outcome of patients with severe AS and preserved LVEF.

Methods

Patient population

A total of 249 patients with severe AS who were prospectively examined in our heart valve clinic between January 2007 and February 2018 were evaluated. Inclusion criteria were severe AS defined by an aortic valve area ≤0.6 cm^2/m^2 by echocardiography, normal LVEF (≥50%) as calculated by 2D echocardiography, no more than mild associated cardiac valve lesion, sinus rhythm, and good images quality. Thirty-nine patients were excluded for suboptimal quality of speckle-tracking image analysis. The final study population consisted of 211 patients, which were divided into two groups, according to the symptomatic status. The control group included 50 patients matched for age and sex. All patients gave written informed consent and the hospital ethics committee approved the study.

Echocardiographic measurements

Transthoracic echocardiograms were performed using a Vivid ultrasound (7, E9 or E95) System (GE Healthcare, Horten, Norway) and stored on a dedicate workstation for off-line analysis (EchoPAC, version 201, GE Healthcare). For each echocardiographic measurement, at least two cardiac cycles were averaged. Conventional echocardiographic measurements were performed in accordance with the guidelines.[13–15] Valvulo-arterial impedance (Zva) was calculated as the sum of systolic blood pressure and mean transaortic gradient, divided by indexed LV stroke volume. Strain analysis was based on speckle-tracking approach, measured by an experienced cardiologist and expressed as an absolute value. The acquisitions were performed in apical long-axis, four-, and two-chamber views (frame rate 70–90 frames/s).[16,17] LV was divided into six myocardial segments in each view, and GLS calculated as the average LS at end-systole. For measuring layer-specific strain, attention was taken to cover the entire myocardial wall thickness by the region of interest (ROI) of each segment. Calculation of transmural variation of LS across the entire myocardium was based on the assumption of a linear distribution. Endocardial and epicardial LS were measured on the endocardial and epicardial ROI border, respectively, whereas the mid (centre line) of the ROI represented the average values of the transmural wall thickness (GLS). LS gradient was calculated as the difference between endocardial and epicardial LS.[18] Right ventricle (RV) LS was calculated as the average of regional strain from RV free wall segments and interventricular septum.

Clinical follow-up

Patients were routinely followed-up and managed according to available guidelines, and clinical information was obtained from direct patient interview, telephone calls with physicians, patients, or next of kin, or review of autopsy records and death certificates. Cardiovascular-related mortality was the endpoint.

Statistical analysis

Data are reported as mean ± standard deviation for continuous variables or percentages of individuals for categorical variables. The χ^2 test or Fisher's exact test was used to compare qualitative variables. One-way analysis of variance test was used to compare the three groups. When a significant difference was found, *post hoc* testing with Bonferroni comparisons for identified specific group differences was used. Variables with a *P*-value <0.05 on univariable analysis were incorporated into the multivariable logistic regression model for the prediction of symptoms and cardiovascular mortality. Receiver operator characteristics (ROC) curves were generated to determine the cut-off value that best predicted the occurrence of symptoms and cardiovascular mortality. The Kaplan–Meier method was used for cumulative survival analysis with the log-rank test for assessing statistical differences between the curves. Statistical analyses were performed using IBM-SPSS, version 23 (SPSS Inc., Chicago, IL, USA). Reproducibility analyses were previously published by our group.[17,19]

Results

Baseline patients' characteristics

Of the 211 patients, 114 (54%) were classified as symptomatic baseline (syncope = 4, dyspnoea = 98, angina = 7, and acute pulmonary oedema = 5) (*Table 1*). Compared with the 97 (56%) asymptomatic patients, they did not differ in age, gender, LV ejection fraction, and presence of risk factors but had higher body mass index, systolic blood pressure, aortic pressure gradients, brain natriuretic peptide (BNP) levels, and smaller aortic valve area. Symptomatic patients also had more pronounced cardiac chambers remodelling, diastolic dysfunction, and impaired RV function. Despite similar LV ejection fraction between groups, multilayer strain values (GLS, endocardial, epicardial, and gradient LS) were significantly lower in symptomatic patients (*Figure 1*). Asymptomatic patients also had lower strain values when compared with controls. In all groups, endocardial systolic strain was higher than epicardial strain.

Symptomatic vs. asymptomatic AS

The impact of specific layer strains on symptoms was evaluated in two multivariable models, where GLS was taken as the reference (GLS vs. endocardial LS or epicardial LS). In the first model, concentric remodelling [$P = 0.044$, odds ratio (OR) = 2.294], indexed left atrial volume ($P = 0.006$, OR = 1.035), and endocardial LS ($P = 0.012$, OR = 1.150) emerged as independent cofactors associated with symptoms after adjustment for body mass index, BNP level, types of remodelling, and severity of AS (*Table 2*). In the second model, concentric remodelling ($P = 0.04$, OR = 2.429), indexed left atrial volume ($P = 0.006$, OR = 1.036), and GLS ($P = 0.015$, OR = 1.17) emerged as independent cofactors associated with symptoms after adjustment for body mass index, BNP level, LV mass, types of remodelling, and severity of AS (*Table 3*). At ROC curve analysis (*Figure 2*), a

Table 1 Baseline clinical and echocardiographic characteristics

Variables	Controls ($n = 50$)	Asymptomatic AS group ($n = 97$)	Symptomatic AS group ($n = 114$)	*P*-value
Clinical variables				
Age (years)	71.1 ± 4.7	71.9 ± 12.2	74.9 ± 11.0	0.071
Male gender, *n* (%)	25 (50)	55 (57)	64 (56)	0.713
Body mass index (kg/m^2)	25.5 ± 3.4	26.1 ± 4.0	27.8 ± 5.8[a,b]	0.007
Body surface area (m^2)	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	0.472
Systolic arterial pressure (mmHg)	128 ± 11	137 ± 18[a]	135 ± 20	0.028
Diastolic arterial pressure (mmHg)	77 ± 8	73 ± 10	73 ± 11	0.052
BNP (log)		4.4 ± 1.1	4.9 ± 1.1[b]	0.007
Diabetes mellitus, *n* (%)		20 (21)	30 (26)	0.353
Hypertension, *n* (%)		69 (73)	89 (78)	0.362
Hypercholesterolaemia, *n* (%)		64 (67)	74 (65)	0.790
Current smoking, *n* (%)		15 (16)	16 (14)	0.746
Coronary artery disease, *n* (%)		10 (10)	21 (19)	0.092
LV dimensions and geometry				
Interventricular septum (mm)	9.6 ± 1.2	12.2 ± 2.0[a]	13.7 ± 2.4[a,b]	<0.001
LV posterior wall (mm)	9.8 ± 1.9	10.6 ± 1.6[a]	11.5 ± 1.7[a,b]	<0.001
LV end-diastolic diameter (mm)	42.7 ± 5.3	44.9 ± 5.9	45.5 ± 6.2[a]	0.023
LV end-systolic diameter (mm)	29.3 ± 5.1	30.1 ± 6.0	29.8 ± 5.7	0.732
LV mass index (g/m^2)	76.8 ± 20.2	103.7 ± 27.2[a]	120.0 ± 27.5[a,b]	<0.001
Relative wall thickness	0.46 ± 0.1	0.48 ± 0.10	0.51 ± 0.11[a]	0.019
Normal geometry, *n* (%)	19 (38)	19 (23)[a]	10 (10)[a,b]	<0.001
Concentric remodelling, *n* (%)	25 (50)	30 (36)[a]	19 (18)[a,b]	<0.001
Concentric hypertrophy, *n* (%)	5 (10)	26 (31)[a]	62 (60)[a,b]	<0.001
Eccentric hypertrophy, *n* (%)	1 (2)	9 (11)	13 (12)	0.109
Aortic valve severity				
Mean pressure gradient (mmHg)		43.8 ± 12.9	47.7 ± 14.4[b]	0.044
Peak aortic velocity (m/s)		4.2 ± 0.6	4.3 ± 0.6	0.143
Aortic valve area (cm^2)		0.81 ± 0.15	0.78 ± 0.20	0.153
Indexed aortic valve area (cm^2/m^2)		0.45 ±0.08	0.42 ± 0.09[b]	0.017
Indexed stroke volume (mL/m^2)		45.5 ± 10.0	44.7 ± 9.2	0.554
Zva (mmHg/mL/m^2)		4.2 ± 1.0	4.3 ± 1.0	0.530
Low flow–low gradient, *n* (%)		11 (11)	7 (6)	0.184
low flow–high gradient, *n* (%)		4 (4)	8 (7)	0.358
Normal flow–low gradient, *n* (%)		22 (23)	17 (15)	0.156
Normal flow–high gradient, *n* (%)		60 (62)	79 (70)	0.219
LV-RV dimension function				
LV end-diastolic volume (mL)	83.0 ± 24.3	89.8 ± 31.8	94.7 ± 34.8	0.138
LV end-systolic volume (mL)	30.2 ± 10.4	33.9 ± 14.9	35.9 ± 15.0	0.095
LVEF (%)	64 ± 5	63 ± 7	62 ± 16	0.325
Indexed left atrial volume (mL/m^2)	26.5 ± 8.6	35.3± 12.5[a]	44.9 ± 19.6[a,b]	<0.001
Mitral *E/A* ratio	0.9 ± 0.3	0.9 ± 0.3	1.0 ± 0.9	0.363
Average *E*/e'	7.4 ± 1.8	12.9 ± 5.6[a]	13.5 ± 5.2[a]	<0.001
TTPG (mmHg)	17 ± 8	29 ± 11[a]	31 ± 12[a]	<0.001
TAPSE (mm)	22 ± 3	23 ± 4	23 ± 3	0.747
RV s' (cm/s)	13 ± 3	13 ± 3	12 ± 3[a]	0.014
Right atrial volume (mL)	32.7 ± 10.8	40.3 ± 20.0	44.3 ± 28.7[a]	0.015
LV-RV longitudinal strain				
RV GLS (%)	20.3 ± 4.5	19.7 ± 3.6	20.2 ± 4.0	0.285
LV GLS (%)	20.7 ± 2.1	18.5 ± 2.8[a]	17.4 ± 2.8[a,b]	<0.001

Continued

Table 1 *Continued*

Variables	Controls ($n = 50$)	Asymptomatic AS group ($n = 97$)	Symptomatic AS group ($n = 114$)	*P*-value
Endocardial LS (%)	23.4 ± 2.5	21.1 ± 3.2[a]	19.6 ± 3.4[a,b]	<0.001
Epicardial LS (%)	18.3 ± 1.8	16.2 ± 2.5[a]	15.4 ± 2.6[a,b]	<0.001
Gradient endocardial-epicardial LS	5.1 ± 1.1	4.8 ± 1.1	4.3 ± 1.6[a,b]	0.001

Values are expressed as *n* (%) or mean ± SD.
AS, aortic stenosis; BMI, body mass index; BNP, brain natriuretic peptide; BSA, body surface area; EF, ejection fraction; GLS, global longitudinal strain; LV, left ventricle; RV, right ventricle; TTPG, trans-tricuspid pressure gradient; Zva, valvulo-arterial impedance.
[a]$P < 0.05$ vs. controls.
[b]$P < 0.05$ vs. asymptomatic group.

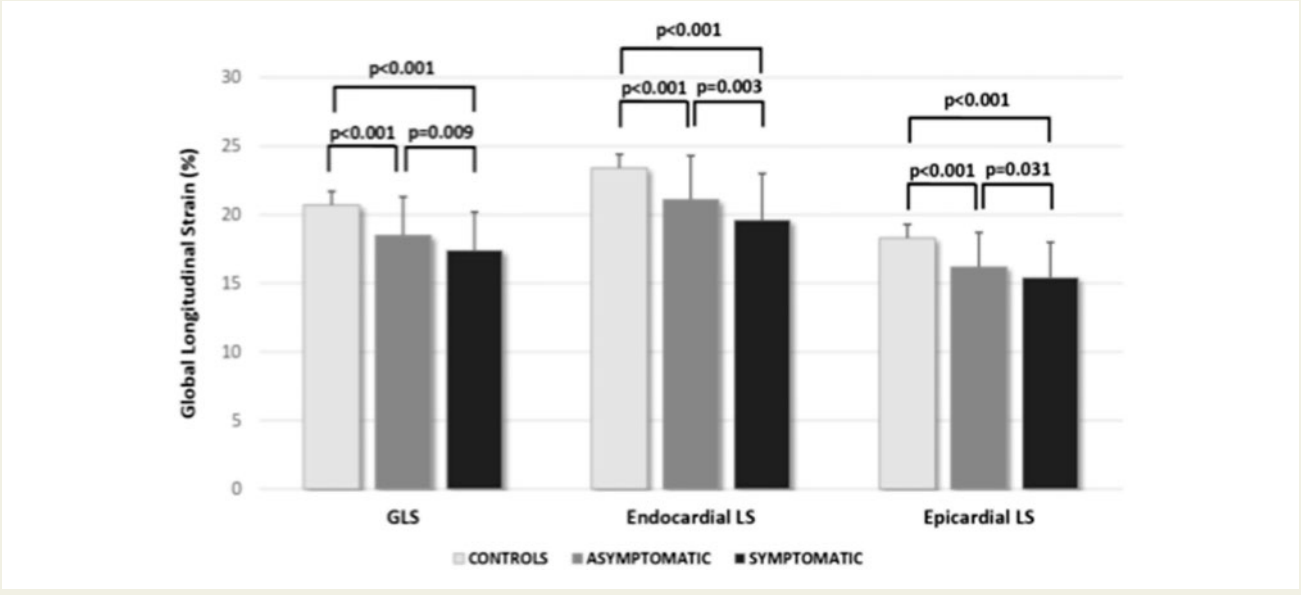

Figure 1 GLS (mid-myocardial), endocardial, and epicardial longitudinal strain in controls, asymptomatic and symptomatic severe AS patients.

Table 2 Univariable and multivariable logistic regression analyses of clinical and echocardiographic parameters associated with symptoms (Model 1)

Parameters	Univariate			Multivariate		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Body mass index	1.070	1.011–1.132	0.020			
BNP	1.425	1.097–1.851	0.008			
LV mass index	1.023	1.011–1.036	<0.001			
Normal geometry	2.748	1.200–6.291	0.017			
Concentric remodelling	2.485	1.274–4.849	0.008	2.294	1.021–5.150	0.044
Concentric hypertrophy	3.293	1.796–6.037	<0.001			
Mean pressure gradient	1.021	1.000–1.046	0.047			
Indexed aortic valve area	0.024	0.001–0.538	0.019			
Indexed left atrial volume	1.044	1.021–1.067	<0.001	1.035	1.010–1.061	0.006
GLS	1.124	1.032–1.223	0.007			
Endocardial LS	1.118	0.039–1.204	0.003	1.150	1.032–1.282	0.012

BNP, brain natriuretic peptide; CI, confidence interval; GLS, global longitudinal strain; LS, longitudinal strain; LV, left ventricle; OR, odds ratio.

Table 3 Univariable and multivariable logistic regression analysis of clinical and echocardiographic parameters associated with symptoms (Model 2)

Parameters	Univariate			Multivariate		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Body mass index	1.070	1.011–1.132	0.020			
BNP	1.425	1.097–1.851	0.008			
LV mass index	1.023	1.011–1.036	<0.001			
Normal geometry	2.748	1.200–6.291	0.017			
Concentric remodelling	2.485	1.274–4.849	0.008	2.429	1.084–5.445	0.040
Concentric hypertrophy	3.293	1.796–6.037	<0.001			
Mean pressure gradient	1.021	1.000–1.046	0.047			
Indexed aortic valve area	0.024	0.001–0.538	0.019			
Indexed left atrial volume	1.044	1.021–1.067	<0.001	1.172	1.032–1.332	0.015
GLS	1.124	1.032–1.223	0.007	1.036	1.010–1.032	0.006
Epicardial LS	1.118	0.039–1.204	0.003			

BNP, brain natriuretic peptide; CI, confidence interval; GLS, global longitudinal strain; LS, longitudinal strain; LV, left ventricle; OR, odds ratio.

subendocardial LS of 21% in patients with severe AS was associated with symptoms with a sensitivity of 70% and a specificity of 65% [area under the curve (AUC) = 0.692, $P < 0.001$].

Predictors of clinical outcome

After a median follow-up period of 22 months (interquartile range: 7–51 months), 145 patients with severe aortic stenosis underwent AVR (transcatheter AVR = 38, surgical replacement = 107), and 33 patients died of a cardiovascular event (after AVR = 20, heart failure = 4, sudden death = 7, cardiac tamponade = 1, stroke = 1). In the univariable Cox-regression analysis, patients who died were older ($P = 0.002$), had higher values of BNP and LV mass ($P < 0.001$), greater LV end-diastolic diameter ($P = 0.004$), and LV volumes ($P = 0.044$ for end-diastolic, $P = 0.015$ for end-systolic), right and left atrial volumes ($P < 0.001$), diastolic dysfunction and pulmonary hypertension ($P < 0.001$). In addition, significant correlations between GLS ($P = 0.006$), endocardial LS ($P = 0.003$), epicardial LS ($P = 0.045$) and mortality were observed. For the other parameters, including severity of AS, no significant correlations with the outcome were found ($P > 0.1$ for all) (*Table 4*). On multivariable Cox-regression analysis, age ($P = 0.029$), BNP values ($P = 0.003$), LV mass index ($P = 0.0065$), LV end-systolic volume ($P = 0.012$), and endocardial LS ($P = 0.0057$) emerged as independently associated with cardiovascular death. The best endocardial LS values associated with outcome was 20.6% (sensitivity 70%, specificity 52%, AUC = 0.626, $P = 0.022$) (*Figure 3A*). The cumulative event rate for cardiovascular death was significant higher in AS patients with more impaired endocardial LS (<20.6%) compared to those with preserved endocardial LS (≥20.6%) (21.6% vs. 11.3% at 5-year follow-up, respectively; log-rank $P = 0.035$) (*Figure 3B*).

During a median period of 30 months (interquartile range: 14–36 months), 9 (9%) out of the 97 asymptomatic patients died from cardiovascular deaths (most of them after symptoms development). These patients had higher values of BNP, more pronounced cardiac chambers remodelling, diastolic dysfunction, and pulmonary hypertension. Both GLS (16.9 ± 2.9 vs. 18.2 ± 2.8, $P = 0.031$) and endocardial LS (19.1 ± 3.3 vs. 20.7 ± 3.3, $P = 0.02$) but not epicardial LS (15.2 ± 2.8 vs. 15.9 ± 2.5, $P = 0.10$) were reduced in patients who died.

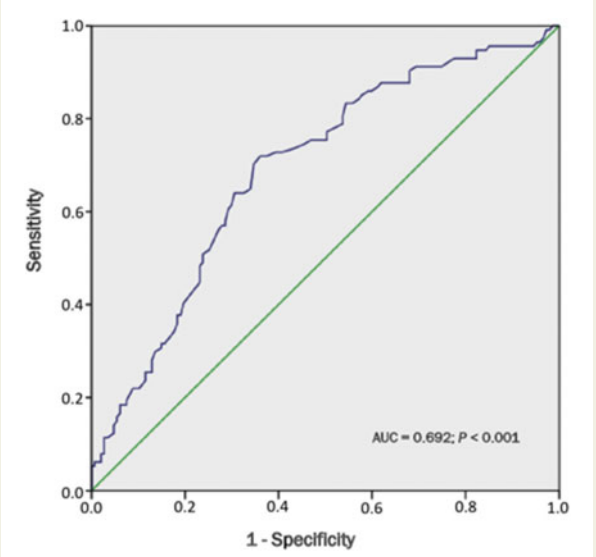

Figure 2 ROC curve of endocardial longitudinal strain associated with symptoms in patients with severe AS.

Discussion

In patients with severe AS and preserved LVEF, the present study demonstrates that: (i) GLS (mid-myocardial), as well as endocardial and epicardial LS values are lower in patients with severe AS as

Table 4 Univariable and multivariable predictors of cardiovascular mortality

Parameters	Univariable			Multivariable		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	1.067	1.025–1.110	0.002	1.12	1.017–1.32	0.029
Body mass index	1.012	0.939–1.090	0.762			
Body surface area	1.972	0.357–10.905	0.436			
Systolic arterial pressure	0.986	0.967–1.005	0.142			
Diastolic arterial pressure	0.968	0.934–1.004	0.084			
LogBNP	2.160	1.457–3.201	<0.001	2.12	1.03–4.45	0.003
Diabetes mellitus	0.606	0.294–1.250	0.175			
Hypertension	0.719	0.296–1.747	0.466			
Hypercholesterolaemia	1.336	0.655–2.726	0.426			
Current smoking	1.172	0.452–3.042	0.744			
Coronary artery disease	0.334	0.155–0.722	0.005			
LV mass index	1.022	1.009–1.035	0.001	1.06	1.017–1.12	0.0065
Interventricular septum	1.092	0.917–1.300	0.325			
LV posterior wall	1.173	0.949–1.451	0.141			
LV end-diastolic diameter	1.087	1.027–1.151	0.004			
LV end-systolic diameter	1.060	0.998–1.125	0.059			
Relative wall thickness	0.343	0.009–13.159	0.565			
Normal geometry	2.534	0.602–10.660	0.205			
Concentric remodelling	1.187	0.507–2.782	0.693			
Concentric hypertrophy	0.735	0.354–1.523	0.407			
Eccentric hypertrophy	0.701	0.267–1.839	0.471			
Mean pressure gradient	0.989	0.963–1.016	0.425			
Peak aortic velocity	0.691	0.404–1.182	0.177			
Aortic valve area	4.607	0.567–37.437	0.153			
Indexed aortic valve area	22.554	0.325–1565	0.150			
Indexed stroke volume	1.009	0.973–1.046	0.646			
Zva	0.864	0.578–1.292	0.476			
LV end-diastolic volume	1.009	1.000–1.018	0.044			
LV end-systolic volume	1.025	1.005–1.045	0.015	1.107	1.02–1.20	0.012
LV EF	0.951	0.900–1.005	0.073			
Indexed left atrial volume	1.034	1.020–1.049	<0.001			
Average *E*/e'	1.096	1.045–1.149	<0.001			
TTPG (mmHg)	1.052	1.026–1.079	<0.001			
TAPSE (mm)	0.934	0.848–1.028	0.163			
RV s'	0.857	0.716–1.025	0.092			
Right atrial volume	1.019	1.009–1.029	<0.001			
RV GLS	1.008	0.963–1.054	0.744			
LV GLS	1.212	1.057.1.390	0.006			
Endocardial LS	1.190	10.061–1.334	0.003	2.75	1.33–5.69	0.0057
Epicardial LS	1.164	1.003–1.351	0.045			
Gradient endocardial-epicardial LS	1.308	1.101–1.552	0.002			

AS, aortic stenosis; BNP, brain natriuretic peptide; CI, confidence interval; EF, ejection fraction; GLS, global longitudinal strain; HR, hazard ratio; LS, longitudinal strain; LV, left ventricle; TTPG, trans-tricuspid pressure gradient; Zva, valvulo-arterial impedance.

compared to controls; (ii) symptomatic patients with severe AS have decreased values of all layers of LV strain compared to asymptomatic patients with similar LVEF; (iii) endocardial LS is more sensitive than GLS and epicardial LS to characterize the symptomatic status of AS patients; (iv) endocardial LS is an independent predictor of cardiovascular outcome.

Multilayer strains and symptoms

Symptom development and a LVEF <50% are the main triggers for AVR in patients with severe AS. However, symptoms are subjective, patients may be unable to perform an exercise test to characterize them, and a LVEF <50% already demonstrates advanced myocardial involvement (i.e. extensive myocardial fibrosis) with limited

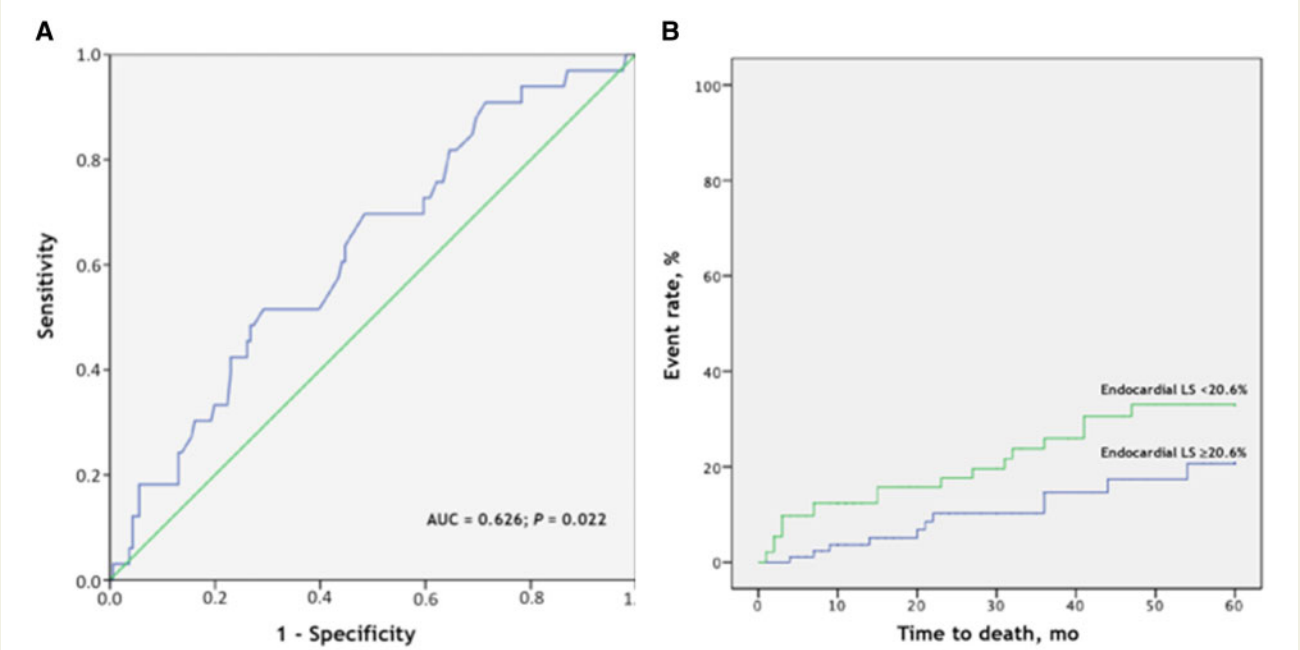

Figure 3 ROC curve of endocardial longitudinal strain associated with cardiovascular death in patients with severe AS (*A*). Kaplan–Meier estimates for cardiovascular death during follow-up in patients with severe AS divided into two groups according to baseline endocardial longitudinal strain: more impaired (<20.6%, green line) vs. more preserved (≥20.6%, blue line) (*B*).

reversibility after AVR.[20,21] In the HAVEC registry, patients with LVEF between 50% and 59% had less favourable outcomes and experienced more heart failure-related deaths than those with LVEF >60%, even after AVR.[4] Reduced LV GLS is an early marker of impaired contractile function when LVEF is still preserved and is also associated with the presence of myocardial fibrosis.[22] Recent series in patients with AS have also linked GLS with subsequent cardiac events and worsening of strain abnormalities as AS progresses despite the lack of a simultaneous fall in LVEF.[23–29] Spatial configurations of ventricular myocardial fibres in the subendocardial and subepicardial layers provide sequential contractile activity of the ventricle and contribute to LV GLS. The endocardium undergoes greater dimensional changes (both thickening and shortening) during systole than does the epicardium in healthy myocardium. In AS, as the subendocardial fibres are more sensitive to microvascular ischaemia (subendocardial blood flow maldistribution related to LV hypertrophy and increased wall stress) and fibrosis, the longitudinal function is likely the first to be altered.[30–32] However, as the AS progresses, all myocardial layers are gradually affected but to a different extent. Cho *et al.*[33] reported lower epicardial, mid-wall, and endocardial LS in 45 patients with severe AS compared to 18 healthy controls, and correlated LS with LV mass index, LVEF, left atrial volume, and N-terminal pro-B-type natriuretic peptide.[33] In 36 AS patients, Ozawa *et al.*[12] correlated the impairment of multilayer LS, particularly of endocardial LS, with the severity of AS. The present study confirms and extends these findings in a larger population and provides new insights into the relationship between regional strain impairment and symptoms in AS. As observed, all layer-specific strains were decreased in patients with AS as compared to controls. However, the reduction in regional strains, particularly of endocardial LS, was more pronounced in symptomatic patients. Hence, the assessment of multilayer strains appears to be promising and may complement conventional echocardiographic parameters (e.g. LV remodelling, left atrial volume) to discriminate the symptomatic status in AS.

Multilayer strains and outcomes

Comorbidities are frequent in patients with AS (e.g. age, coronary artery disease) and increase the overall cardiovascular risk profile of patients. Biomarkers have consistently shown to be associated with patient outcome. Higher BNP values are associated with increased mortality risk. Echocardiography also plays a major predictive role in AS.[32,34] As reported, the severity of AS, the degree of LV hypertrophy and remodelling, the diastolic burden (e.g. increased in LV filling pressure, left atrial enlargement), the augmented pulmonary pressures and dilated right atrium, and the extent of regional LV systolic dysfunction as estimate by GLS are all potential predictors of poor outcome. These data are also confirmed in our study in which we also show a prognostic value of layer-specific strains. Alteration of endocardial LS was strongly and independently associated with higher cardiovascular mortality rate in patients with AS and preserved LVEF. Reduced endocardial strain was observed in patients who died regardless of the symptomatic status at the entry point. Consequently, LVEF, which only takes into account the LV chamber or wall thickness as a whole, is insufficient to estimate the degree of dysfunction within the different layers of the myocardial wall, which represents a more sensitive marker of myocardial involvement and outcome. An endocardial LS below 20.6% yielded the strongest predictive

accuracy for cardiovascular death, even if with moderate accuracy, likely due to low hard event rates. Further prospective studies with larger number of patients could confirm the data and determine the exact role of endocardial LS in predicting cardiovascular events.

Limitations

This study has some limitations. We included in the study only patients with severe AS based on aortic valve area and preserved LV ejection fraction. The sub-categorization of AS according to flow-gradient pattern was not performed. The presence of patients with coronary artery disease could affect our data. However, coronary artery disease incidence was similar in both groups with and without symptoms, and patients with wall motion abnormalities were preventively excluded from the analysis. The gradient of strain across the myocardium is a nonlinear phenomenon, and the definition of the layers is arbitrary and is based on simple division into three parts. Because the spatial resolution of ultrasound is limited, there will always be a certain degree of overlap. Despite interobserver and intraobserver reproducibility of LV GLS have demonstrated to be comparable with conventional echocardiography parameters, the variability of LS measurement related to ultrasound system and the software for the off-line analysis could represent a limitation. The decision to perform surgery was made by individual cardiologists in charge of the patients. Serial echocardiographic assessment over time was not performed.

Conclusions

In severe AS, LS impairment involves all myocardial layers and is more prominent in the endocardial layer. This impairment becomes even more evident in the advanced phases of the disease when the symptoms occur. Regardless of the symptomatic status, reduced LS conveys a worse outcome. Further studies are needed to better determine the role of endocardial LS in predicting the progression of aortic valve disease and the occurrence of cardiovascular events.

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