Prognostic value of echocardiographic evaluation of cardiac mechanics in patients with aortic stenosis and preserved left ventricular ejection fraction

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Accepted: 31 October 2022

Abstract

Left ventricular ejection function (LVEF) is not reliable in identifying subtle systolic dysfunction. Speckle Tracking (ST) plays a promising role and hemodynamic forces (HDFs) are emerging as marker of LV function. The role of LV myocardial deformation and HDFs was investigated in a cohort of patients with aortic stenosis (AS) and normal LVEF. Two hundred fifty three patients (median age 79 years, IQR 73 – 83 years) with mild (n = 87), moderate (n =77) and severe AS (n =89) were retrospectively enrolled. 2D echocardiographic global longitudinal strain (GLS), circumferential strain (GCS) and HDFs were determined. The worsening of AS was associated with raising inappropriate LV mass ($p < 0.001$) and declined LVEF, despite being in the normal range ($p < 0.001$). ST and HDFs parameters declined as the AS became severe ($p<0.0001$, for all). When patients were grouped based on the median of LV endocardial GLS value (> -19,9%) and LV systolic longitudinal force (LVsysLF) value (< 12,49), patients with impaired ST and lower HDFs components had increased incidence of aortic valve replacement (AVR) and worse survival ($p <0.024$ and $p <0.037$, respectively). Among ST and HDFs parameters, only LVsysLF was independently associated with AVR and all causes mortality on multivariable Cox regression analysis (HR 0.94; 95% CI 0.89-0.99; $p= 0.012$). Reduced values of LVsysLF were associated with AVR and reduced survival in AS patients. LVsysLF could provide useful information in the stratification of patients with AS and possibly in the choice of timing for AVR.

Keywords Echocardiography · Aortic stenosis · Hemodynamic forces · Speckle Tracking

Introduction

Aortic stenosis (AS) is the most common primary valve disease leading to surgery or catheter intervention in western countries, with a growing prevalence due to the aging population [1]. Echocardiographic assessment of AS severity, the appearance of clinical symptoms, and evidence of reduced left ventricular (LV) function indicate the correct timing for aortic valve replacement (AVR), either surgical or percutaneous [1, 2]. However, pathophysiological changes such as the growth of LV mass (LVM) and the development of LV hypertrophy (LVH) begin earlier [3]. Over time, LVH induces impaired compliance and higher filling pressure until the increase in LVM exceeds individual needs to compensate LV hemodynamic load, leading to inappropriately high LVM (inLVM) [4]. The condition is characterized by reactive diffuse interstitial fibrosis, reversible after AVR, and by replacement fibrosis and cell death, which is irreversible and not affected by AVR [5]. The mechanism appears to be fundamental in the transition to symptoms, heart failure, and the consequent mortality risk even after AVR [6]. Hence, AS should be considered a disease of both valve and myocardium [7] in which the degree of cardiac remodelling and fibrosis are closely related to hemodynamic markers of myocardial performance such as LV ejection fraction (LVEF) [3]. LVEF is not sensitive to detect subtle myocardial dysfunction [8], and symptoms often occur before the LVEF declines [6]. Global longitudinal strain (GLS) and global circumferential strain (GCS) are emergent parameters of LV function that may detect LV impairment when EF is still normal [9] and may be helpful to assess AS even though evidence regarding their prognostic role remains uncertain [10]. We recently suggested a novel approach that considers both LV deformation values and hemodynamic forces (HDFs) parameters in the study of the LV systolic function [11]. Specifically, the longitudinal (base-apex oriented) HDFs are emerging as a new imaging marker of LV function [12]. We explored the modification and outcome of LV cardiac mechanic parameters according to AS severity among patients with preserved LVEF.

Methods

Study design and population

From an ongoing registry of patients with AS from our departmental echocardiographic database and a feasible analysis of LV GLS using two-dimensional (2D) speckle tracking (ST) at baseline (i.e. first available echocardiogram after AS diagnosis) between 2015 and 2019 were selected.

All echocardiographic data were clinically acquired and prospectively analysed. Patient demographic and clinical data were gathered from the departmental patient information system (Cardionet software) and follow up data were collected from hospital records and the regional health data warehouse and subsequently analysed retrospectively. We applied unavailable digital imaging, LVEF less than 54%, congenital heart disease, history of documented coronary artery disease, coexisting moderate/severe valvular heart diseases other than AS, active endocarditis, presence of pace-maker implanted or complete left bundle branch, resting heart rhythm abnormalities such as atrial fibrillation or flutter during echocardiogram performance and insufficient data, as exclusion criteria. The study complies with the Declaration of Helsinki and the Ethics Committee of the University of Trieste (protocol no. 0025052) approved the study. Informed consent was obtained from all individual participants included in the study.

Echocardiographic data

Standard echocardiography examinations were performed with Vivid E9 and E95 (GE Healthcare, Horten, Norway) machines equipped with a 2.5-MHz phased array transducer with a frame rate above 60 according to standardized procedures in our laboratory [11]. Three experienced operators, blinded to the clinical data, performed offline LV quantitative analysis according to the 2015 American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) recommendations [13]. Current guidelines define abnormal LVEF as $< 52\%$ in men and $< 54\%$ in women based on two standard deviations from the mean [13]. The LVM calculation was executed with linear measurements, using a formula validated by necropsy and normalized for body surface area [13–15]. LVH was defined as LVM > 95 g/m2 in women and > 115 g/m2 in men [12], and the excess of LVM was assessed as the ratio between the observed and predicted value [16]. The aortic valve (AV) assessment was performed from multiple windows to obtain the greatest peak AV velocity and mean AV gradient using the modified Bernoulli equation, and aortic valve area (AVA) was calculated using the continuity equation. AS definition was based on the ASE/EACVI recommendations [1, 2]. Patients were classified as mild AS (AVA > 1.5 cm2; mean gradient < 20 mmHg) moderate AS (AVA between 1.0 and 1.5 cm2; mean gradient between 20 and 40 mmHg) and severe AS (AVA < 1 cm2; mean gradient > 40 mmHg).

Cardiac mechanics image analysis

The LV 2D strain was quantified using commercially available software (2DCPA v.1.3; TomTec Imaging Systems Gmbh, Unterschleissheim, Germany). We performed the

analyses in all three apical views (LV four-chambers, two-chambers, and three-chambers). In the most suitable cardiac cycle, we manually traced the LV end-systolic borders, we adapted to include the entire myocardium the width of the region of interest (ROI), and we obtained the mean longitudinal subendocardial strain and the transmural variation (myocardial strain) in the whole myocardium [17]. The software, then, automatically traced the segments over the entire heartbeat and, finally, both the LV end-diastolic endocardial borders and the width of the ROI, were re-adjusted to include the entire myocardium [17]. We obtained the end-systolic volume (ESV), the end-diastolic volume (EDV). We evaluated the LV diameters from base to apex from the same borders, and their reduction from end-diastole to end-systole gave the GCS. The apical approach to GCS could have been less accurate because the entire circumference was not visible from the apical views; this criticality was minimized by using a triplane evaluation, thus applying the same approach and the same approximation commonly used in the evaluation of LV volumes. This approach to circumferential strain was more similar to the one used in Three-Dimensional (3D) echocardiography because the border followed the tissue during its longitudinal motion and but reducing artifacts in deformation such as those resulting from through-plane displacements of 3D geometry that sometimes affect the short axis transversal projections. The same ST data were then used to evaluate the HDFs associated with blood flow. We recently demonstrated how HDFs could be detected through the knowledge of the LV geometry, endocardial velocities obtained by ST, plus the area of the aortic and mitral orifices, carefully calculated by drawing the internal diameter of the valve's annulus from the parasternal long-axis-view [18]. The time profile of the longitudinal HDFs was used to extract a few parameters that characterized the various phases of the cardiac cycle [11]. We calculated: LV longitudinal force (LVLF) as the mean amplitude of the longitudinal force throughout the cardiac cycle; LV systolic longitudinal force (LVsysLF), calculated as the LVLF above but limited to the systolic phase only and LV impulse (LVim) as the mean longitudinal force during the systolic propulsive phase, when the force was positive (directed from the LV cavity toward aorta) [11]. The calculation of the HDF parameters was performed with a prototype software (2DCPA v.1.4; TomTec Imaging Systems Gmbh, Unterschleissheim, Germany) that was identical to the version used for strain and volumes with the only difference of the additional capability of HDF quantification.

Clinical data

Baseline clinical and laboratory data, along with events of interest (including all-cause death, surgical AVR, and transcatheter AVR), were collected from patients' e-charts after the baseline echocardiogram was performed and before the end of 2020. The primary outcome was a composite of all-cause mortality and AVR. Medical therapy (no need for AVR) was considered as a positive outcome.

Statistical analysis

Descriptive statistics were calculated between study groups. Continuous variables were expressed as median with interquartile range (IQR) [25°; 75°] since the data were not normally distributed according to the results of the Kolmogorov-Smirnov test; categorical variables were expressed as absolute numbers and percentages. Differences between groups were evaluated employing the Mann-Whitney test and Kruskal-Wallis test (when comparing more than 2 groups simultaneously) for continuous variables, while Chi-square ($\chi 2$) or Fisher's exact test were used for dichotomous variables.

Cox regression analysis was performed to assess the association between variables and the prespecified outcome, applying a backward stepwise approach for the multivariable analysis.

The functional form of the association between the risk of events (death and AVR) and the echocardiographic parameters values was explored by means of a non-parametric smoothed regression (function "plsmo" of the R package "Hmisc").

We defined a two-sided P-value < 0.05 as statistically significant. All statistical analyses were conducted using IBM SPSS Statistics 24.0 package (New York, NY) statistical software version 20 and the R software version 4.0.5, package "Hmisc".

Results

Clinical and echocardiographic data of the study population

Out of a population of 300 subjects, originally evaluated for ST analysis, 47 were excluded for inadequate imaging or did not meet the inclusion criteria. The remaining 253 patients (median age 79 years, IQR 73–83 years, 50,2% male) represented our study population and they were divided into three groups according to AS severity: 87 (34%) had mild AS, 77 (30%) moderate AS, and 89 (35%) severe AS. The female sex was more represented among the severe AS cohort. Cardiovascular risk factors were evenly distributed among the three groups, as was medical therapy. Conversely, heart failure at baseline was more frequently reported in severe AS (p 0.013) and NYHA functional class worsened with the increasing severity of AS (p 0.028). Baseline clinical data are reported in Table 1. At the echocardiographic evaluation,

Table 1 Baseline demographic data of the total population according to AS severity. Data are expressed as median value with interquartile range or numbers (percentages)

Variables	Mild AS 87 pts	Moderate AS 77 pts	Severe AS 89 pts	P^*
Age (years)	77 (72–81)	79 (75–84)	80 (75–84)	0.055
Gender (male, %)	51 (59%)	41 (53%)	35 (39%)	0.031
BMI (Kg/m^2)	26.4 (23.7–28.7)	27.4 (24–29.7)	25.9 (23.7–28.1)	0.178
SBP (mmHg)	143 (130–160)	140 (130–156)	143 (130–155)	0.351
DBP (mmHg)	80 (70–85)	80 (70–80)	80 (70–80)	0.459
Hypertension (%)	73 (84%)	69 (90%)	71 (80%)	0.222
Diabetes (%)	23 (26%)	23 (30%)	17 (19%)	0.256
Hyperlipidaemia (%)	52 (60%)	50 (65%)	53 (60%)	0.730
Heart failure (%)	20 (23%)	25 (33%)	39 (44%)	0.013
NYHA III/IV (%)	5 (6%)	7 (9%)	16 (18%)	0.028
eGFR < 60 ml/min/m^2 (%)	31 (36%)	34 (44%)	38 (43%)	0,483
Betablockers (%)	42 (4%)	41 (53%)	42 (47%)	0.714
ACEi/ARB (%)	61 (70%)	60 (78%)	64 (72%)	0.504
Aspirin (%)	29 (33%)	36 (47%)	45 (51%)	0.055
OAT (%)	26 (30%)	23 (30%)	16 (18%)	0.118
Statin (%)	43 (50%)	47 (61%)	46 (52%)	0.293
Calcium blocker (%)	29 (33%)	23 (30%)	24 (27%)	0.654
Diuretic (%)	35 (40%)	33 (43%)	42 (47%)	0.642

*P-value represents comparison between the three groups

AS Aortic stenosis; *BMI* Body mass index; *SBP* Systolic blood pressure; *DBP* Diastolic blood pressure; *NYHA* New York Heart Association; *eGFR* Estimated glomerular filtration rate; *ACEI* Angiotensin-converting enzyme inhibitors; *ARBs* Angiotensin receptor blockers; *OAT* Oral anticoagulation

Table 2 Echocardiographic Baseline echocardiographic parameters of the total population according to aortic stenosis severity. Data are expressed as median value with interquartile range

Variables	Mild AS 87 pts	Moderate AS 77 pts	Severe AS 89 pts	P^*
LVEDD (mm)	49 (44–54)	50 (45–53)	47 (44–54)	0.472
LVESD (mm)	28 (24–34)	28 (25–32)	28 (24–33)	0.968
LVEDV (ml)	80 (60–101)	76 (65–94)	77 (60–94)	0.738
LVESV (ml)	27 (20–39)	28 (23–34)	33 (23–40)	0.120
IVS (mm)	11 (9–13)	12 (10–13)	13 (12–14)	< 0.001
LVM index (gr/m^2)	100 (85–129)	113 (92–133)	128 (111–154)	< 0.001
inLVM (%)	28 (32%)	31 (40%)	63 (70%)	< 0.001
AV peak PG (mmHg)	25 (20–30)	47 (40–59)	76 (67–91)	< 0.001
AV mean PG (mmHg)	14 (11–17)	28 (25–34)	50 (43–61)	< 0.001
AVA (cm^2)	1.7 (1.5 – 1.8)	1.1 (1.0–1.2)	0.7 (0.6 – 0.8)	< 0.001
LVEF (%)	65 (60–69)	64 (60–67)	58 (54–63)	< 0.001
Myocardial GLS (%)	− 18.1 (− 20.6; − 16.2)	− 17.6 (− 19.6; − 15.2)	− 16.6 (− 17.8; − 13.9)	< 0.001
Endocardial GLS (%)	− 22.2 (− 24; − 19.6)	− 20.8 (− 23.6; − 18.4)	− 19.2 (− 21.1; − 17.2)	< 0.001
Myocardial GCS (%)	− 24.6 (− 26.6; − 21.4)	− 24.0 (− 26.7; − 20.1)	− 21.7 (− 25.2; − 19.3)	0.001
Endocardial GCS (%)	− 33.5 (− 36.9; − 30.5)	− 33.1 (− 36.5; − 29.8)	− 29.3 (− 34.0; − 26.2)	< 0.001
LVLF (%)	10.38 (8.72;12.93)	10.24 (7.98;11.99)	9.04 (7.30;11.25)	0.002
LVsysLF (%)	14.41 (11.92;17.70)	14.50 (10.42;17.95)	11.80 (8.51;14.95)	< 0.001
LVIm (%)	13.14 (10.74;16.10)	13.29 (9.27;16.52)	10.83 (7.87;13.53)	< 0.001

*P-value represents comparison between the three groups

AS Aortic stenosis; *LV* Left ventricular; *LVEDD* LV End Diastolic Diameter; *LVESD* LV end systolic diameter; *LVEDV* LV end diastolic volume; *LVESV* LV end systolic volume; *LVM* LV mass; *inLVM* Inappropriate LV mass; *AV* Aortic valve; *PG* Pressure gradient; *AVA* Calculated aortic valve area (continuity equation); *LVEF* LV ejection fraction; *GCS* Global circumferential strain; *GLS* Global longitudinal strain; *LVLF* LV longitudinal force; *LVsysLF* LV systolic longitudinal force; *LVIm* LV impulse

patients with severe AS showed significantly higher LVM, mainly inLVM ($p < 0.001$), while LVEF was comparatively reduced ($p < 0.001$). On the other hand, there were no statistically significant differences in LV diameters and volumes. Baseline standard echocardiographic features are summarized in Table 2.

LV speckle tracking and hemodynamic forces parameters

ST parameters and HDFs components proved to be uniformly preserved trough mild to moderate AS, while AS progression to severe grading entailed decreased values of both ST parameters and HDFs components ($p < 0.001$) (Fig. 1). Among patients with severe AS, median endocardial GLS and GCS were − 19,2% (IQR − 21,1%;− 17,2%) and − 29,3% (IQR − 34,0%; − 26,2%), respectively, whereas the components of HDFs such as median LV longitudinal forces (LVLF), LV systolic longitudinal forces (LVsysLF) and LV impulse (LVim) were 9,04% (IQR 7,30%; 11,25%), 11,80% (IQR 8,51%; 14,95%) and 10,83% (IQR 7,87%; 13,53%), respectively (Table 2).

Outcomes and survival data

During a median follow-up of 24 months (IQR 15–41 months), 116 events were observed, including 74 AVR (37 surgical and 37 transcatheter) and 42 deaths. Predictably, events mainly occurred among patients with moderate to severe AS (106 events). Thus, the survival analyses were focused on the subgroup of 166 patients with moderate or severe AS. Table 3 summarizes this cohort's baseline clinical and echocardiographic parameters according to medical treatment vs. the composite end-point of AVR/all-cause of mortality. Overall, there were no statistical differences in clinical parameters between the two groups, apart from a higher prevalence of advanced NYHA classes (p 0.002) among patients who experienced AVR or death, as expected. Moreover, at echocardiographic evaluation, those patients presented significantly reduced ST parameters and HDFs components, mainly LVsysLF and LVimp ($p < 0.001$).

At Cox regression analysis, only AV mean gradient (HR 1.03; 95% CI 1.18–1.43; $p < 0.001$), LVsysLF (HR 0.94; 95% CI 0.89–0.99; p 0.012), and NYHA III/IV classes (HR 1.71; CI 1.01–2.90; p 0.045) emerged as variables independently associated with AVR and all-cause mortality in patients with moderate and severe AS. Conversely, neither LVEF nor endocardial GLS maintained statistical significance when pooled together with other covariates at multivariable analysis (Table 4).

When median values of endocardial GLS (− 19.9%) and LVsysLF (12.49) (Supplemental Table 1) were used to explore the impact of these parameters on survival among the cohort of patients with moderate to severe AS, Kaplan Meier curves showed significantly increased incidence of AVR and all-cause mortality among patients with the higher ST parameter and the lower HDFs component (p 0.024 and p 0.037, respectively; Fig. 2). However,

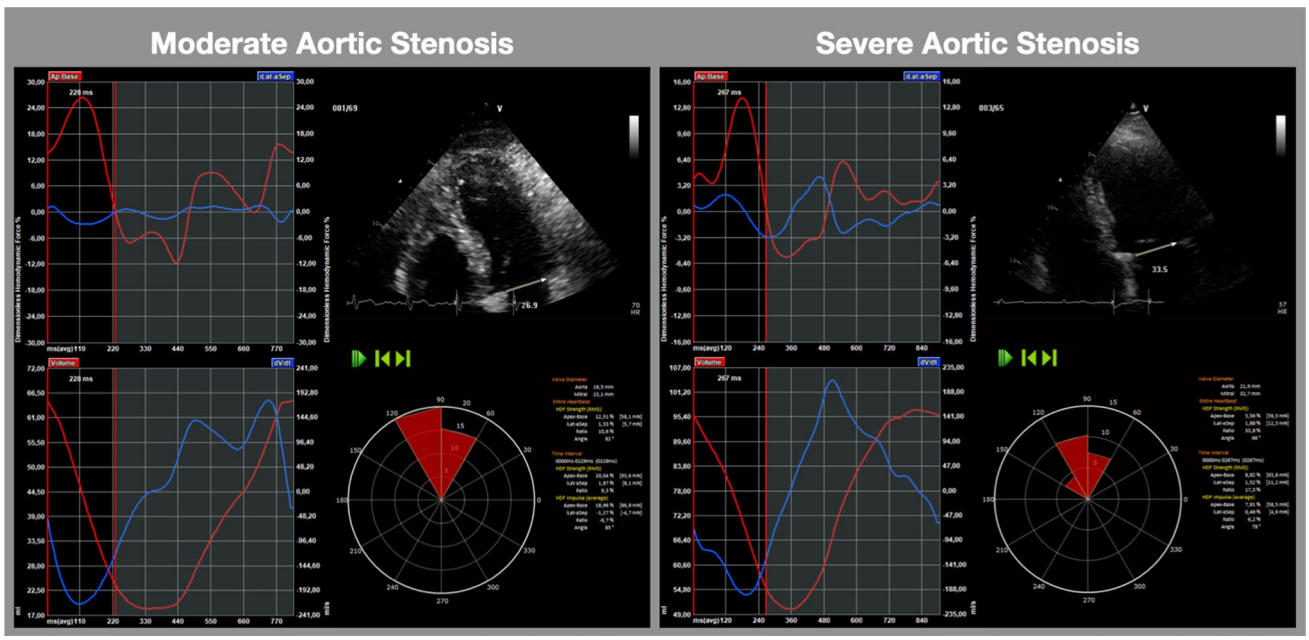

Fig. 1 Examples of software analyzes in a male patient with moderate aortic stenosis (left panel) and in a patient with severe aortic stenosis (right panel). Hemodynamic forces are calculated and displayed

Table 3 Baseline clinical and echocardiographic parameters of moderate and severe AS patients divided according to medical treatment vs. surgical/transcatheter AVR or death for all-cause. Data are expressed as median value with interquartile range or numbers (percentages)

Variables	Medical treatment 70 pts	AVR/death 96 pts	P^*
Age (years)	80 (76–83)	79 (75–85)	0.846
Gender (male. %)	30 (43%)	46 (48%)	0.518
Hypertension (%)	62 (89%)	78 (81%)	0.200
Diabetes (%)	22 (31%)	18 (19%)	0.059
Hyperlipidaemia (%)	46 (66%)	57 (59%)	0.406
Heart failure	23 (33%)	41 (43%)	0.198
NYHA III/IV (%)	3 (4%)	20 (21%)	0.002
eGFR < 60 ml/min/m2	30 (42.9%)	42 (44%)	0.909
Betablockers (%)	33 (47%)	50 (52%)	0.530
ACEi/ARB (%)	57 (81%)	67 (70%)	0.089
Aspirin (%)	30 (43%)	51 (53%)	0.191
OAT (%)	18 (26%)	21 (22%)	0.564
Statin (%)	43 (61%)	50 (52%)	0.231
Calcium blocker (%)	21 (30%)	26 (27%)	0.680
Diuretic (%)	31 (44%)	44 (46%)	0.843
LVEF (%)	64 (59–67)	59 (54–64)	< 0.001
LVM index (gr/m^2)	112 (93–132)	127 (110–154)	< 0.001
inLVM (%)	29 (41%)	65 (68%)	0.003
AV mean PG (mmHg)	30 (25–39)	44 (40–58)	< 0.001
Myocardial GLS (%)	− 17.5 (− 19.6; − 15.2)	− 16.6 (− 18.2; − 13.9)	0.005
Endocardial GLS (%)	− 20.5 (− 23.2; − 18.6)	− 19.2 (− 21.5; − 17.2)	0.011
Myocardial GCS (%)	− 24.5 (− 26.9; − 20.2)	− 21.9 (− 25.0; − 19.3)	0.006
Endocardial GCS (%)	− 33.0 (− 36.2; − 28.0)	− 30.1 (− 34.8; − 26.6)	0.023
LVLF (%)	10.07 (8.14;12.51)	8.98 (7.27;11.05)	0.007
LVsysLF (%)	14.05 (10.50;17.85)	11.38 (8.49;14.93)	< 0.001
LVIm (%)	12.48 (9.85;16.42)	10.52 (7.86;13.94)	< 0.001

*P− value represents comparison between the two groups

NYHA. New York Heart Association; eGFR. Estimated Glomerular Filtration Rate; ACEi. Angiotensin-Converting Enzyme Inhibitors; ARBs. Angiotensin Receptor Blockers; OAT. Oral Anticoagulation; LV. Left Ventricular; LVEF. LV Ejection Fraction; LVM. LV Mass; inLVM: Inappropriate LV Mass; AV. Aortic Valve; PG. Pressure Gradient; GLS. Global Longitudinal Strain; GCS. Global Circumferential Strain; LVLF. LV Longitudinal Force; LVsysLF. LV Systolic Longitudinal Force; LVIm. LV Impulse

when these parameters were separately examined according to the degree of AS, only LVsysLF < 12.49 proved to be of value in predicting prognosis among moderate AS (p 0.018). Conversely, events were equally distributed between patients with endocardial GLS higher and lower than − 19.9%, both in the moderate and severe AS subgroup (Fig. 3). The functional form of the association between events (AVR or death) and the echocardiographic parameters is illustrated in Supplemental Fig. 1, which indicates a linear relationship for LVsysLF, LVLF, and endocardial GLS.

Reproducibility

Reproducibility analyses performed on the same set of images in 10 subjects are summarized in Table 5. Intra-observer and inter-observer analysis revealed excellent reproducibility (p < 0.001). On the three intra-observer assessments, the intra-class correlation varies between 0.91 and 0.944 (p < 0.0001) and between 0.818 and 0.972 (p < 0.0001) for the ST and HDFs components, respectively. In the inter-observer analysis, the inter-observer analysis ranges from 0.922 to 0.927 (p < 0.0001) and between 0.884 and 0.939 (p < 0.0001), for the ST and HDF components, respectively.

Table 4 Univariable and multivariable Cox regression analysis for surgical/transcatheter AVR or death for all-cause for moderate and severe AS patients

Variables	Univariable[a]		Multivariable[b]	
	HR (95% CI)	P-value	HR (95% CI)	P-value
NYHA III/IV	2.52 (1.52–4.18)	< 0.001	1.71 (1.01–2.90)	0.045
LVM index	1.01 (1.00–1.01)	< 0.001		
AV mean PG	1.03 (1.02–1.04)	< 0.001	1.03 (1.18–1.43)	< 0.001
LVEF	0.95 (0.92–0.98)	0.002		
Endocardial GLS	1.07 (1.01–1.14)	0.019		
LVsysLF	0.91 (0.86–0.96)	< 0.001	0.94 (0.89–0.99)	0.012

h. Hazard ratio; *CI* Confidence interval; *NYHA* New York heart association; *LV* Left ventricle; *AV* Aortic valve; *PG* Pressure gradient; *LVM* LV mass; *LVEF* LV ejection fraction; *GLS* Global longitudinal strain; *LVsysLF* LV systolic longitudinal force

Discussion

In this cohort of patients with a wide range of AS and normal LVEF, through an integrated approach to cardiac mechanics, we demonstrated that HDFs such as LVsysLF was able to detect subtle myocardial dysfunction better than traditional and newer echocardiographic techniques such as pressure AV mean gradient, LVEF or LV GLS and LV GCS. LVsysLF can have an incremental prognostic value in patients with moderate AS.

LV dysfunction and AS

The finding of LVEF < 50% can play a crucial role in AVR timing; however, LVEF has already proved not to be a reliable parameter lacking accuracy in identifying subtle changes in myocardial contractility [8]. There is growing evidence for the importance of detecting even a mild degree of LV systolic dysfunction; in addition, the risk is higher above the standard LVEF cut-point, and a safer threshold would be LVEF < 60%, mainly when the LV cavity is small [6]. Capoulade et al. demonstrated that in a large sample of consecutive AS patients, the best LVEF cut-off was 56% [19] while Stassen et al. showed that those moderate AS patients with LVEF ≥ 50% and LV GLS < 16% had an increased risk for all-cause mortality [20]. In our study, all patients had LVEF in the normal range, albeit a relatively lower LVEF was reported in patients undergoing AVR/death. AS was associated with a raising LVM, and inLVM was present in most patients with severe AS. As demonstrated in literature, inLVM is characterized by decreased myocardial perfusion and increased systolic wall stress [21, 22]. These phenomena involve predominantly endocardial layers, leading first to interstitial and later to replacement fibrosis [23]. Several cardiac magnetic resonance imaging (CMR) studies showed that LV structural and functional abnormalities may be frequent despite an LVEF > 50% [24]. The late gadolinium enhancement (LGE) can detect focal fibrosis in the myocardium of patients with AS [25], and a graded relationship between AS severity and longer myocardial longitudinal magnetization relaxation time (T1 time) was found to be independent of CMR-derived LVEF [26]. Interestingly, myocardial fibrosis persisted even after AVR in patients with symptomatic severe AS [23]. Diffuse myocardial fibrosis

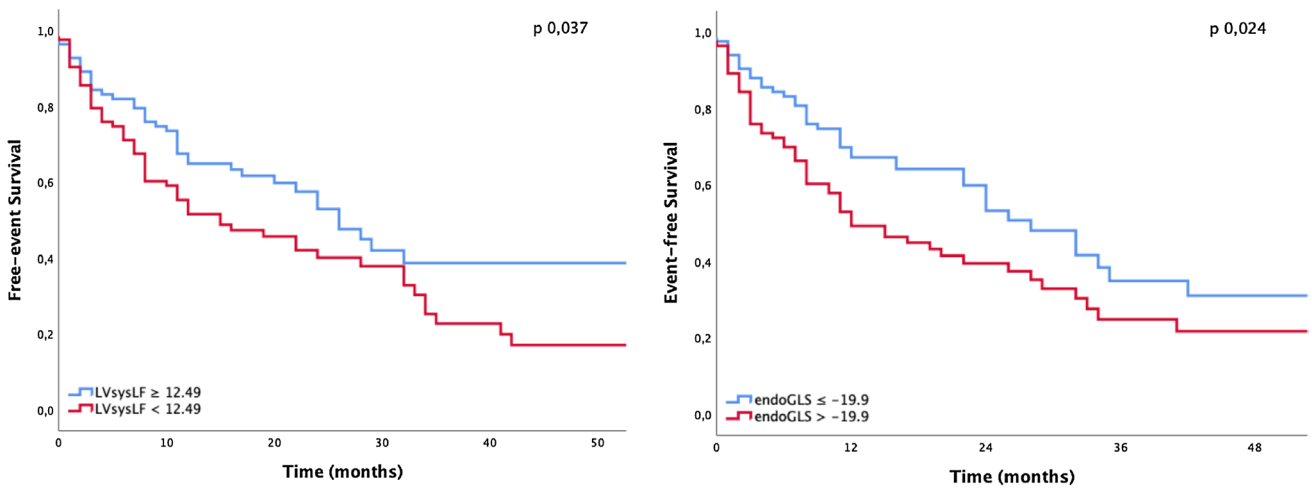

Fig. 2 Event-free survival curves in patients with moderate and severe aortic stenosis according to median values of Left Ventricular Systolic Longitudinal Force (12.49-left panel) and endocardial Global Longitudinal Strain (− 19.9%-right panel). Event = surgical/transcatheter AVR or death for all causes

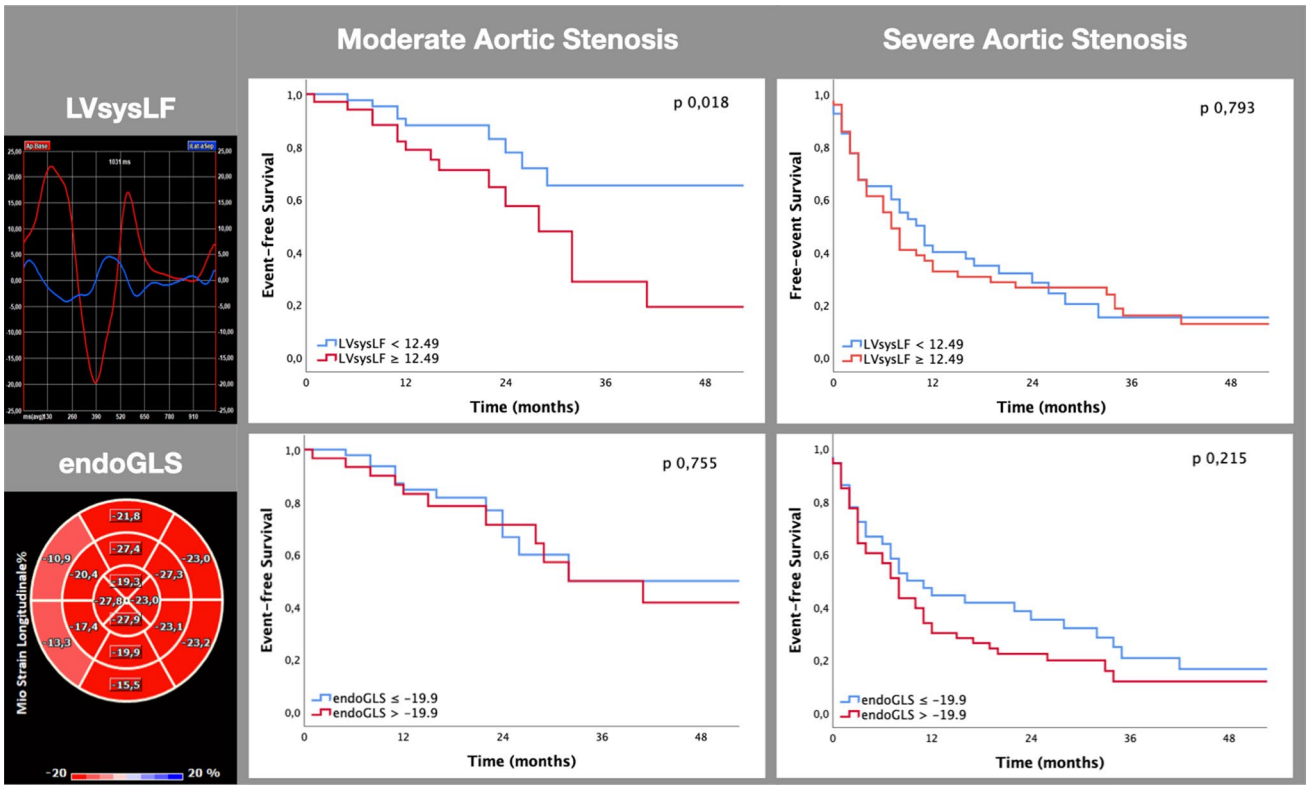

Fig. 3 Separate event-free survival curves for moderate and severe aortic stenosis according to Left Ventricular Systolic Longitudinal Force (12.49-upper panels) and endocardial Global Longitudinal Strain (− 19.9%-lower panels) median values. Event = surgical/transcatheter AVR or death for all-cause. The images of the bull's eye and LV hemodynamic forces refer to the case of a patient with severe AS."

caused impaired cardiac deformation parameters on echocardiography. Reduced LV GLS was associated with AVR and death for any causes in patients with severe AS patients [27], and it was often detectable even in asymptomatic patients with severe AS and normal LVEF [28]. In our study, for the calculation of both LV GLS and GCS, we used software to analyse the images from the three apical views overcoming the known limits due to the deformation artefacts deriving from through-plane displacements in the short axis views [29, 30]. We proved that ST parameters were uniformly preserved from mild to moderate AS, comparable to reference values previously reported in healthy people[11]; nevertheless, the natural course of the ST parameter was characterized by deterioration over time in the AS disease. Recently, Zhu et al. reported that impaired GLS in moderate AS patients added higher mortality risk even among those undergoing AVR [31]. In that study, the GLS cut-off value for survival with or without AVR was lower than our study, and this data can be explained by the fact that they included several diabetic patients, and up to 50% of the study population had CAD. It has already been demonstrated that the association with CAD and diabetes contributed to impairing the GLS[32].

HDFs and AS

The longitudinal (base-apex oriented) HDFs are emerging as a new imaging marker of LV function [12, 33]. This study is the first to apply an extension of the strain software package for echocardiography to explore the role of HDFs parameters in AS patient. Along with the severity of AS, HDFs behave like LVEF and GLS. In particular, their mean values remain unchanged between mild to moderate AS, despite lower than healthy people's values [11], and they fall in severe AS patients. We found that LV endoGLS and LVsysLF may detect those at high risk for AVR and death for all causes. Conversely, in patients with moderate AS and normal LVEF, LVsysLF seems to identify the same high-risk population better than LV endoGLS.

Study limitations

The present was a single-centre prospective study with a small sample of patients. Subjects with poor echocardiographic images for LV GLS were excluded, and this could result in a selection bias. The new ST software package used is vendor-independent, but its clinical utility remains

Table 5 Intra-observer and inter-observer variability between the three operators

Variables	Intra-class correlation (rho)	95% Confidence Intervals	P*
Intra-observer variability 1			
Endocardial GLS	0.941	0.915–0.957	< 0.0001
Endocardial GCS	0.910	0.862–0.992	< 0.0001
LVLF	0.944	0.924–0.980	< 0.0001
LVimp	0.880	0.833–0.892	< 0.0001
Intra-observer variability 2			
Endocardial GLS	0.920	0.990 – 0.971	< 0.0001
Endocardial GCS	0.944	0.877–0.983	< 0.0001
LVLF	0.915	0.877–0.941	< 0.0001
LVimp	0.818	0.664–0.822	< 0.0001
Intra-observer variability 3			
Endocardial GLS	0.933	0.790–0.990	< 0.0001
Endocardial GCS	0.928	0.820–0.977	< 0.0001
LVLF	0.972	0.857–0.988	< 0.0001
LVimp	0.893	0.858–0.975	< 0.0001
Inter-observer variability			
Endocardial GLS	0.927	0.789–0.980	< 0.0001
Endocardial GCS	0.922	0.739–0.980	< 0.0001
LVLF	0.939	0.824–0.983	< 0.0001
LVimp	0.884	0.655–0.969	< 0.0001

GCS Global circumferential strain; *GLS* Global longitudinal strain; *LVLF* Left ventricular longitudinal force; *LVimp* Left ventricular impulse

unproven, and its cut-off of standard versus abnormal values may vary with different analysis software.

Conclusion

The assessment of the HDFs could provide an additional level of knowledge of the LV function in AS patients. The evaluation of LVsysLF needs to be integrated with other objective signs of AS-related cardiac damage [34] and ST parameters in these patients, and it may help defining the optimal timing for AVR (before symptoms and irreversible cardiac damage occur). This integrated approach could stratify moderate AS patients into higher mortality risk classes; however, it needs extensive validation in further clinical studies before being accepted into clinical practice.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10554-022-02756-z.

Author contributions GF and LP conception and design of the study; AP, EC and GB analysis and interpretation of data; MDF and DC drafting of the manuscript; GP, ADL and GFS final approval of the manuscript submitted.

Funding DC and GP received partial support for this study from the Italian Ministry of Education and Research, project PRIN no. 2017A889FP.

Declarations

Conflict of interest GP is s senior scientific consultant for Medis Medical Imaging Systems BV (Leiden, The Netherlands). GF, DC, ADL, GFS, LP, AP, MDF, GB and ADL declare that no funds, grants, or other support were received during the preparation of this manuscript.

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