Original Article

Two-Dimensional Strain for the Assessment of Left Ventricular Function in Low Flow–Low Gradient Aortic Stenosis, Relationship to Hemodynamics, and Outcome

A Substudy of the Multicenter TOPAS Study

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Background—Decision making in patients with low flow–low gradient aortic stenosis mainly depends on the actual stenosis severity and left ventricular function, which is of prognostic importance. We used 2-dimensional strain parameters measured by speckle tracking at rest and during dobutamine stress echocardiography to document the extent of myocardial impairment, its relationship with hemodynamic variables, and its prognostic value.

Methods and Results—In 47 patients with low flow–low gradient aortic stenosis, global peak systolic longitudinal strain (PLS) and peak systolic longitudinal strain rate (PLSR) were analyzed. PLS and PLSR at rest and peak stress were −7.56±2.34% and −7.41±2.89% (P=NS) and −0.38±0.12 s^{-1} and −0.53±0.18 s^{-1} (P<0.001), respectively. PLS and PLSR inversely correlated with left ventricular ejection fraction at rest (r_s=−0.52; P<0.0001 and −0.38; P=0.008) and peak stress (r_s=−0.39; P=0.007 and −0.45; P=0.002). The overall 2-year survival rate was 60%. Univariate predictors of survival were peak stress left ventricular ejection fraction (P=0.0026), peak stress PLS (P=0.0002), peak stress PLSR (P<0.0001), and N-terminal pro–B-type natriuretic peptide (P<0.0001). Three hierarchically nested multivariable Cox regression models were constructed—model 1: The Society of Thoracic Surgeons score as an indicator of clinical risk (area under the receiver operating characteristic=0.59); model 2: model 1+N-terminal pro–B-type natriuretic peptide and peak stress left ventricular ejection fraction (area under the receiver operating characteristic=0.83; incremental P<0.0001); model 3: model 2+peak stress PLSR (area under the receiver operating characteristic=0.89; incremental P=0.035).

Conclusions—In patients with low flow–low gradient aortic stenosis, 2-dimensional strain parameters are strong predictors of outcome. Peak stress PLSR may add incremental prognostic value beyond what is obtained from N-terminal pro–B-type natriuretic peptide and peak stress left ventricular ejection fraction. A larger study is needed to confirm these findings. **(*Circ Cardiovasc Imaging.* 2013;6:268-276.)**

Key Words: aortic stenosis ■ Doppler echocardiography ■ heart failure ■ low flow ■ myocardial strain ■ stress echocardiography

Low flow–low gradient aortic stenosis (LFAS) is a rare condition affecting ≈5% to 10% of patients with aortic stenosis (AS).[1,2] Patients with LFAS represent the most challenging subset of patients with AS. Decision making depends on the degree of stenosis severity and of myocardial functional impairment. Dobutamine stress echocardiography (DSE) helps to discriminate true-severe (TS) from pseudosevere AS and to assess myocardial contractile reserve, which is of prognostic importance.[3–5]

Clinical Perspective on p 276

In current practice, the evaluation of myocardial function is still based on conventional echocardiographic parameters, such as visual assessment of systolic ventricular function and calculation of Doppler-derived stroke volume or left ventricular ejection fraction (LVEF) using Simpson's rule. Those methods have several limitations, including angle, operator, and image quality dependency. Speckle-tracking echocardiography is a new, angle-independent imaging modality that has been shown to detect even subtle changes sensitively in myocardial function in a variety of cardiac diseases.[6–12] By frame-to-frame analysis of natural markers (speckles) within

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the myocardium, one can obtain with adequate reproducibility the peak longitudinal strain (PLS) as the ratio of change in length to the initial length and peak longitudinal strain rate (PLSR) as the rate at which deformation occurs, which is expressed in s^{-1}.[13–15] In patients with severe AS, LV strain and strain rate may be impaired, despite preserved LVEF.[16] In addition, asymptomatic patients with severe AS and impaired 2-dimensional strain parameters have an increased risk of cardiac events.[17]

The aim of the present study was to evaluate LV function by using PLS and PLSR at rest and during dobutamine stress echocardiography and to examine their association with hemodynamic variables and outcome in patients with LFAS.

Methods

Study Population

Sixty-two consecutive patients with LFAS (effective orifice area [EOA] ≤1.2 cm^2, indexed EOA ≤0.6 cm^2/m^2, LVEF ≤40%, and a mean pressure gradient ≤40 mm Hg) recruited in the context of the True or Pseudo Severe Aortic Stenosis (TOPAS) study[1,2,18–20] were included in this substudy. Exclusion criteria were more than mild aortic or mitral regurgitation, mitral stenosis, atrial fibrillation, left bundle branch block, paced rhythm, unstable angina, acute pulmonary edema, serum creatinine level >2 mg/dL, pregnant or lactating women, and unwillingness to provide informed consent. Clinical examination and standard echocardiography as a part of routine evaluation were performed in all patients. Patients were followed for a median of 35 months (25th—75th percentiles, 28–37 months). The Society of Thoracic Surgeons score was calculated to assess the baseline risk profile (http://riskcalc.sts.org/STSWebRiskCalc273/).[21,22] The present study was approved by the local ethics committee. All participants gave informed consent.

Echocardiography

Echocardiographic examination was performed using commercially available equipment (Vivid-7; General Electric Vingmed, Milwaukee, WI) with a 3.5-MHz transducer. All patients underwent DSE as previously described.[1,19] Briefly, after the acquisition of data at rest, the protocol started with intravenous administration of 2.5 µg/kg per minute dobutamine, which was increased up to 20 µg/kg per minute by increments of 2.5 or 5 µg/kg per minute at 8-minute intervals to obtain a steady state. A minimum of 3 consecutive beats of parasternal and apical standard views were recorded at rest and at each stage of the DSE protocol. Continuous-wave Doppler of the aortic valve velocity spectrum, as well as pulsed-wave Doppler of the LV outflow tract velocity spectrum, was recorded at rest and at each step of the dobutamine protocol. Raw data were stored digitally for postprocessing analysis. LV volumes were assessed by standard 4-chamber and 2-chamber views. LVEF was calculated by the biplane Simpson method. EOA was calculated by continuity equation using the time-velocity integral of the continuous-wave Doppler spectrum of the aortic valve and the time-velocity integral of the pulsed-wave Doppler spectrum of the LV outflow tract and its diameter.

The differentiation between TS-AS versus pseudosevere-AS was achieved with the use of the projected EOA at standardized normal flow rate.[1,2,18,19] A projected EOA <1 cm^2 was considered as being consistent with the presence of TS-AS. Presence of myocardial contractile reserve was defined as >20% increase in stroke volume from rest to peak dobutamine stress.[23,24] To obtain optimal temporal resolution for speckle-tracking analysis even in peak stress measurements, only examinations with frame rates >60 frames/s were included. Offline PLS and PLSR analysis was performed using GE EchoPac software (version 7.0.0; GE Vingmed, Horten, Norway) from apical 4-, 2-, and 3-chamber views.[13,14,16] Treating physicians were blinded to the projected EOA, and measurements were obtained by speckle-tracking analysis.

N-Terminal Pro–B-Type Natriuretic Peptide

Blood samples for N-terminal pro–B-type natriuretic peptide (NT-proBNP) measurements were drawn after 30 minutes of rest just before DSE. Lithium heparin Vacuette (Greiner Bio-one, Kremsmünster, Austria) tubes were used for blood collection. NT-proBNP was quantified immediately after blood collection using commercially available immunoassays (Cobas proBNP II; Roche diagnostics GmbH, Mannheim, Germany).

Statistical Analysis

Continuous variables are described as mean and SD and compared between groups by Student *t* tests. Paired differences between rest and peak stress conditions were evaluated for statistical significance by paired Student *t* tests. Categorical variables are described by frequencies and percentages and compared, if appropriate, by χ^2 tests, otherwise by Fisher exact tests. Correlation of variables was assessed by the Spearman correlation coefficient. Before any statistical testing, all continuous variables were evaluated for normality using Shapiro–Wilk tests. Skewed variables (eg, NT-proBNP) were then log-base-2 transformed before further statistical evaluation. Overall survival was defined as time from study entry to time of all-cause death. Survival times of patients alive at their last follow-up visit were censored. Survival times were described by the product-limit method, dichotomizing continuous parameters at their sample median. Univariate Cox regression analyses were used to assess the association of baseline variables with overall survival.[25] Three hierarchically nested multivariable Cox regression models were built: the first one contained only the Society of Thoracic Surgeons score as an indicator of clinical risk, the second also included NT-proBNP and peak stress LVEF, and the third also included peak stress strain rate. For these models, we used bias-corrected multivariable Cox regression to account for the limited number of events per variable.[26,27] The incremental value of these models was evaluated using likelihood ratio tests.

Results are presented as hazard ratios and 95% confidence intervals (95% CI). Time-dependent receiver operating characteristic (ROC) analysis, using leave-one-out cross-validated linear predictors, was used to assess the predictive accuracy of the parameters to predict 2-year survival.[28] $P \leq 0.05$ were considered as indicating statistical significance. IBM SPSS Statistics (IBM, Vienna, Austria), versions 19 and 20, and R, version 2.13, were used for statistical analysis.

Results

Of the 62 patients with LFAS fulfilling the inclusion criteria of the TOPAS study, 47 patients qualified for speckle-tracking analysis. In the remaining 15 patients, PLS and PLSR analysis was not feasible as a result of low temporal resolution (frame rates <60 frames/s). Forty-three of the 47 patients in whom speckle tracking was feasible underwent coronary angiography. Baseline characteristics, including the presence or absence of coronary artery disease (CAD) and NT-proBNP levels, are shown in Table 1. Rest and peak stress echocardiographic and hemodynamic parameters are shown in Table 2. There was no significant difference between PLS at rest (−7.56±2.34%) and PLS at peak stress (−7.41±2.89%; *P*=NS). However, PLSR at rest (−0.38±0.12 s^{-1}) was significantly higher than PLSR at peak stress (−0.53±0.18 s^{-1}; $P<0.001$). Mean improvement in PLSR from rest to peak stress was 48%. On the basis of an improvement ≥48% in PLSR, 23 (49%) displayed an improvement in PLSR, whereas 24 (51%) did not.

Relationship Between 2-Dimensional Strain Parameters and Hemodynamic Variables

Table 3 depicts correlation coefficients of PLS and PLSR with echocardiographic parameters, clinical characteristics, and NT-proBNP. On the basis of projected EOA ≤1 cm^2,

Table 1. Baseline Characteristics of All Patients and Patients Grouped According to the Occurrence of Events During Follow-up

	All Patients (n=47)	Patients With Events (n=18)	Patients Without Events (n=29)
Age, y	73±10	75±9	71±11
Sex			
Male, n (%)	39 (83)	15 (83)	24 (83)
Female, n (%)	8 (17)	3 (17)	5 (17)
Body surface area, m^2	1.9±0.2	1.9±0.2	1.9±0.2
Systolic blood pressure, mm Hg	119±19	117±13	121±21
Diastolic blood pressure, mm Hg	74±10	73±9	74±10
NYHA functional class, n (%)			
I	7 (15)	1 (6)	6 (21)
II	23 (49)	10 (56)	13 (45)
III	16 (34)	7 (39)	9 (31)
IV	1 (2)	0 (0)	1 (3)
Coronary artery disease, n (%)			
No CAD	14 (34)	3 (19)	11 (41)
1–vessel disease	7 (16)	2 (13)	5 (19)
2–vessel disease	6 (14)	2 (13)	4 (15)
3–vessel disease	16 (37)	9 (56)	7 (26)
Previous cardiovascular surgery, n (%)			
No	36 (77)	13 (72)	23 (79)
CABG	9 (19)	5 (28)	4 (14)
Peripheral vascular surgery	1 (2)	0 (0)	1 (3)
Both	1 (2)	0 (0)	1 (3)
Arterial hypertension, n (%)	37 (79)	9 (50)	8 (28)
Diabetes mellitus, n (%)	17 (36)	9 (50)	8 (28)
EOA projected, cm^2	0.93±0.14	0.92±0.16	0.94±0.13
NT-proBNP, pg/mL median (Q1–Q3)	3966 (2396–9010)	12 377 (4042–18 291)	4123 (1727–4269)
LV function			
LVEF, %			
At rest	28.43 (6.38)	27.44 (7.69)	29.03 (5.47)
At peak stress	36.23 (7.96)	32.28 (6.94)	38.69 (7.65)
PLS, %			
At rest	–7.56 (2.34)	–6.67 (2.56)	–8.10 (2.05)
At peak stress	–7.41 (2.89)	–5.63 (2.37)	–8.5 (2.6)
PLSR, s^{-1}			
At rest	–0.38 (0.12)	–0.34 (0.14)	–0.40 (0.10)
At peak stress	–0.53 (0.18)	–0.4 (0.16)	–0.62 (0.14)

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; EOA, effective orifice area; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PLS, peak longitudinal strain; and PLSR, peak longitudinal strain rate.

30 (64%) patients had TS-AS and 17 (36%) patients had pseudosevere-AS.

There were no significant differences in PLS and PLSR between patients with TS-AS and pseudosevere-AS at rest or with peak dobutamine stress. Two-dimensional strain parameters at rest and peak stress showed no significant differences, whether CAD was present or absent.

Predictors of Outcome

During follow-up, 16 patients underwent valvular intervention (14 had surgical aortic valve replacement, 1 patient underwent valve implantation by the apical approach, and 1 patient had transfemoral valve implantation). In those 16 patients, median time to valvular intervention was 72 days (7–203 days). There were no significant differences in age, valve EOA at rest and peak stress, projected EOA, LVEF at rest and peak stress, or mean transvalvular flow at rest and peak stress between medically managed patients and those with intervention. Patients who subsequently underwent valvular intervention had significantly higher peak stress mean pressure gradients (44±11 versus 37±11 mm Hg; P=0.04). On the basis of a relative increase in stroke volume (SV) >20% during DSE, 20 (43%) patients had contractile reserve, whereas 27 (57%) had no contractile reserve. Overall, 18 (39%) patients died during

Table 2. Echocardiographic and Hemodynamic Parameters at Rest and Peak Stress

Variable	Rest	Peak Stress	*P* Value
LV geometry and function			
End-diastolic volume, mL	171±57	151±52	<0.001
LVEF, %	28±6	36±8	<0.001
Stroke volume, mL	59±18	72±23	<0.001
Mean transvalvular flow, mL/s	200±52	315±88	<0.001
PLS, %	–7.56±2.34	–7.41±2.89	0.687
PLSR, s^{-1}	–0.38±0.12	–0.53±0.18	<0.001
Aortic valve hemodynamics			
Peak jet velocity, m/s	3.2±0.4	3.8±0.5	<0.001
Mean pressure gradient, mm Hg	25±6	39±11	<0.001
EOA, cm^2	0.8±0.2	1.1±0.3	<0.001
Hemodynamics			
Systolic blood pressure, mm Hg	119±19	119±20	0.772
Diastolic blood pressure, mm Hg	74±10	71±10	0.102
Heart rate, bpm	76±14	106±22	<0.001

Data are given as mean±SD. EOA indicates effective orifice area; LVEF, left ventricular ejection fraction; PLS, peak longitudinal strain; and PLSR, peak longitudinal strain rate.

follow-up, and the overall 2-year survival rate was 60% (95% CI, 47%–77%). In the valvular intervention group, there was 1 perioperative death and 3 postoperative deaths. All deaths were of cardiac cause. Age and body surface area were not associated with mortality (Table 4).

Relationship Between Conventional Echocardiographic Parameters and Outcome

Conventional echocardiographic parameters at rest were not significantly associated with survival (Table 4). Peak stress LVEF, peak stress transvalvular flow, and peak stress stroke volume index (SVi) correlated with survival, whereas peak stress EOA did not (Figure 1 and Table 4). Contractile reserve, presence of CAD, or type of treatment was not significantly related to outcome (Table 4).

Relationship Between 2-Dimensional Strain Parameters, NT-proBNP, and Outcome

Peak stress PLS (hazard ratio, 1.35; 95% CI, 1.15–1.58; *P*=0.0002) and peak stress PLSR (hazard ratio per 0.1%, 1.56; 95% CI, 1.27–1.93; *P*<0.0001) were significantly related to survival (Table 4). Figures 2 and 3 depict survival probabilities for patients grouped with respect to their median peak stress PLSR (–0.5 s^{-1}) and median peak stress PLS (–7.41%). The 2-year survival rate in patients with peak stress PLSR < –0.5 s^{-1} was 91% (95% CI, 81%–100%), but only 40% (95% CI, 24%–66%) in patients with peak stress PLSR ≥ –0.5 s^{-1}. NT-proBNP was associated with survival in univariate analysis (*P*=0.0001; Table 4). Figure 4 depicts the survival curves for patients grouped with respect to the median NT-proBNP (3965 pg/mL).

Hierarchical Multivariable Analysis

Nested multivariable Cox regression models revealed a cross-validated area under the ROC of 0.59 for the Society of Thoracic Surgeons score (model 1). The second model (model 2) also included NT-proBNP, as well as peak stress LVEF, and revealed an area under the ROC of 0.83 with an incremental *P*<0.0001. The third model also included peak stress PLSR and revealed an area under the ROC of 0.89, with an incremental *P* value of 0.035. Figure 5B shows the cross-validated ROC curves to predict 2-year survival by the 3 models. Table 5 depicts the 3 hierarchical multivariable Cox regression analyses. Figure 5A shows the cross-validated ROC curves to predict 2-year survival for single parameters at rest and peak stress.

Discussion

Our data demonstrate that 2-dimensional strain parameters reflect the severity of myocardial disease in patients with LFAS. Both longitudinal strain and strain rate are severely impaired in patients with LFAS, and the extent of impairment of myocardial strain in these patients seems to be more pronounced than what has been previously reported in patients with other cardiac diseases.[6–9,11,12,16,29–32] Assessment of 2-dimensional strain parameters during stress provided significant incremental prognostic information.

Two-Dimensional Strain Parameters in LFAS

The present study evaluated the value of PLS and PLSR in patients with LFAS at rest and stress conditions. In LFAS, the impairment of LV systolic function may be because of afterload mismatch, concomitant cardiomyopathy, and CAD. Accurate assessment of stenosis severity and degree of myocardial impairment are essential for risk stratification and therapeutic decision making in patients with LFAS. Resting echocardiography is usually unable to determine the

Table 3. Correlation Coefficients of PLS and PLSR With Echocardiographic Parameters, Clinical Characteristics, and NT-proBNP

	PLS at Rest	PLSR at Rest		Peak Stress PLS	Peak Stress PLSR
Mean gradient at rest	–0.19	–0.07	Peak stress mean gradient	–0.19	–0.14
LVEF at rest	**–0.52****	**–0.38****	Peak stress LVEF	**–0.39****	**–0.45****
Stroke volume at rest	**–0.41****	–0.08	Peak stress stroke volume	**–0.30***	0.02
Mean transvalvular flow rate at rest	**–0.39****	–0.14	Peak stress mean transvalvular flow rate	–0.28	–0.18
NT-proBNP	**0.34***	0.27	NT-proBNP	**0.42****	**0.46****
Age	–0.01	0.01	Age	–0.09	0.044

LVEF indicates left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PLS, peak longitudinal strain; and PLSR, peak longitudinal strain rate. Bold type indicates significant correlations (**at the 0.01 level and *at the 0.05 level).

Table 4. Univariate Cox Regression Analyses of Mortality

Variable	Univariate HR (95% CI)	*P* Value
Age (per decade)	1.40 (0.87–2.24)	0.1620
Body surface area (per m^2)	1.77 (0.22–14.3)	0.5903
Society of Thoracic Surgeons score	1.04 (1.00–1.07)	0.045
CAD (present vs absent)	2.40 (0.68–8.43)	0.1722
Type of treatment (valvular intervention vs medical)	0.53 (0.18–1.62)	0.2680
NT-proBNP (per doubling)	2.21 (1.48–3.29)	0.0001
LVEF at rest (per 10%)	0.70 (0.31–1.56)	0.3770
EOA at rest (per 0.1 cm^2)	0.89 (0.70–1.14)	0.3526
SV at rest (per 10 mL/s)	0.86 (0.65–1.13)	0.2804
SVi at rest (per 10 mL/m^2)	0.67 (0.38–1.17)	0.1540
Mean transvalvular flow at rest (per 50 mL/s)	0.63 (0.37–1.07)	0.0875
Peak stress LVEF	0.89 (0.83–0.96)	0.0026
Peak stress EOA	0.30 (0.05–1.87)	0.1960
Peak stress SVi	0.96 (0.91–1.00)	0.0496
Peak stress mean transvalvular flow (per 100 mL/s)	0.43 (0.22–0.84)	0.0135
Peak stress PLS	1.35 (1.15–1.58)	0.0002
Peak stress PLSR (per 0.1%)	1.56 (1.27–1.93)	<0.0001
EOA projected (per 0.2 cm^2)	0.74 (0.35–1.55)	0.417
Contractile reserve (yes vs no)	0.64 (0.24–1.70)	0.3669

CAD indicates coronary heart disease; CI, confidence interval; EOA, effective orifice area; HR, hazard ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PLS, peak longitudinal strain; PLSR, peak longitudinal strain rate; SV, stroke volume; and SVi, stroke volume index.

underlying severity of the valve stenosis, and dobutamine stress is recommended for this purpose. Contractile reserve has been reported as a marker of risk in these patients. However, myocardial function and its ability to increase during stress are determined by several factors. Ischemic events and other causes of myocardial remodeling lead to replacement of contractile fibers by fibrotic tissue. The analysis of LV longitudinal kinetics has been shown to be a useful tool for monitoring LV function during the reverse remodeling process after aortic valve replacement in patients with AS.[33] Weidemann et al[9] showed that the extent of LV longitudinal shortening is a sensitive marker of the degree of myocardial fibrosis and a strong marker of clinical outcomes in patients with AS and preserved LVEF. Fibrosis develops predominantly in the subendocardial layer in AS, leading to reduced longitudinal function. Carasso et al[32] observed that PLS and PLSR are associated with the degree of myocardial impairment and improve after aortic valve replacement. PLS and PLSR were more severely impaired in present series of patients with LFAS compared with data reported in the literature for various grades of AS severity (PLS: −17.1±3% for mild AS to −14.5±3.9% for severe AS).[16,29–31,34,35]

Increase of 2-Dimensional Strain Parameters During Dobutamine Stress and Relationship to Hemodynamics

There was no significant difference in PLS between rest and dobutamine stress, whereas peak stress PLSR was significantly lower than resting PLSR. This phenomenon was previously reported by Donal et al[29] in patients with asymptomatic moderate-to-severe AS undergoing treadmill exercise testing. They concluded that reduced coronary flow reserve and subendocardial fibrosis may have prevented a change in PLS, despite the improvement in LVEF and increase in pressure gradients during exercise. As PLS is load dependent, the absence of an increase in PLS may also be explained by afterload mismatch in AS.[36] Mechanical interaction of fibers is modified by changes in LV geometry during dobutamine infusion. We observed a significant reduction in LV end-diastolic volume, which positively influenced the velocity of contraction (PLSR), but not the absolute amount of contraction (PLS) to the same extent. Increase in heart rate during stress could explain the lack of change in PLS. Jamal et al[36]

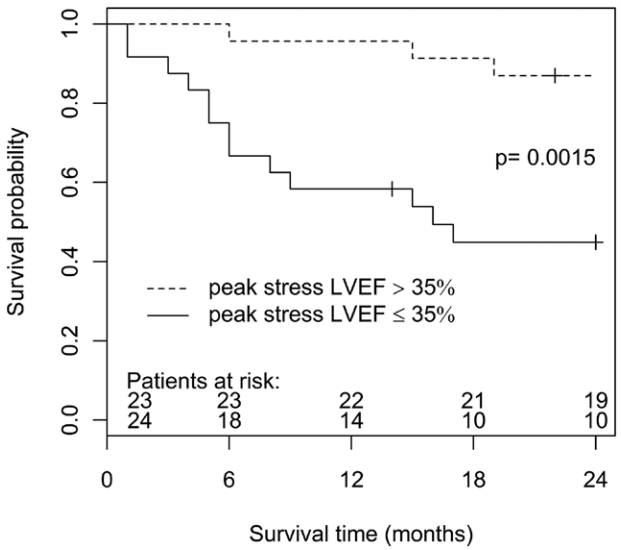

Figure 1. Kaplan–Meier survival curve according to peak stress left ventricular ejection fraction (LVEF) ≤35% and >35%.

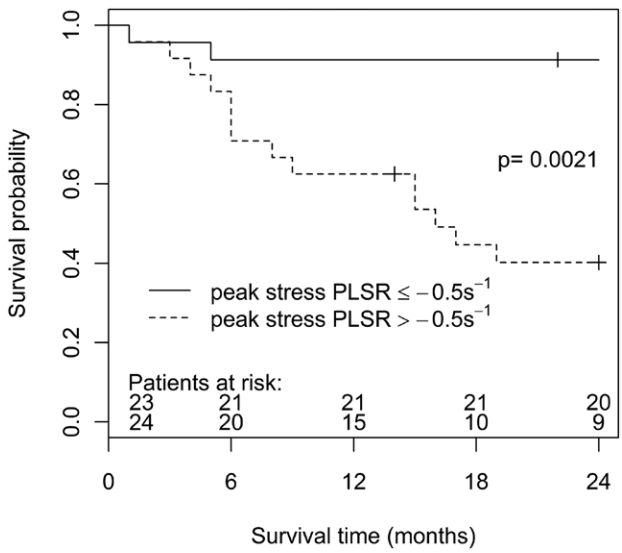

Figure 2. Kaplan–Meier survival curve according to peak stress peak longitudinal strain rate (PLSR) ≥ −0.5 s^{-1} and < −0.5s^{-1}.

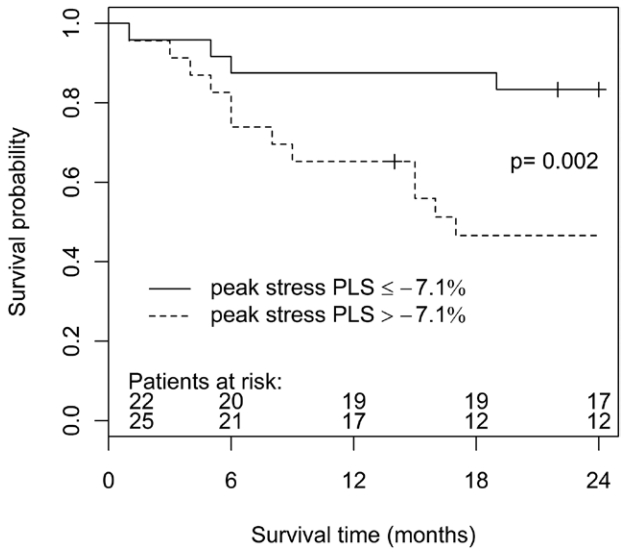

Figure 3. Kaplan–Meier survival curve according to peak stress peak longitudinal strain (PLS) ≤ −7.1% and > −7.1%.

demonstrated that PLS at high heart rates was diminished because of shortening of diastole and the ejection period and decreased preload in animals. PLSR showed a linear increase with incremental increase of dobutamine infusion. In contrast, PLS had a nonlinear relationship with a decrease between 2.5 and 5µg/kg per minute and an increase at higher doses.[36]

There was also no significant difference in PLS and PLSR at rest and during stress between our patients with or without CAD. An inability to increase coronary flow and hence longitudinal shortening may have influenced the results of this study. Reant et al[37] examined the validity of strain measurements in an animal model under various conditions of flow-limiting and nonflow-limiting coronary artery stenosis at rest and during dobutamine infusion. Longitudinal strain was abnormal at rest in flow-limiting coronary artery stenosis and

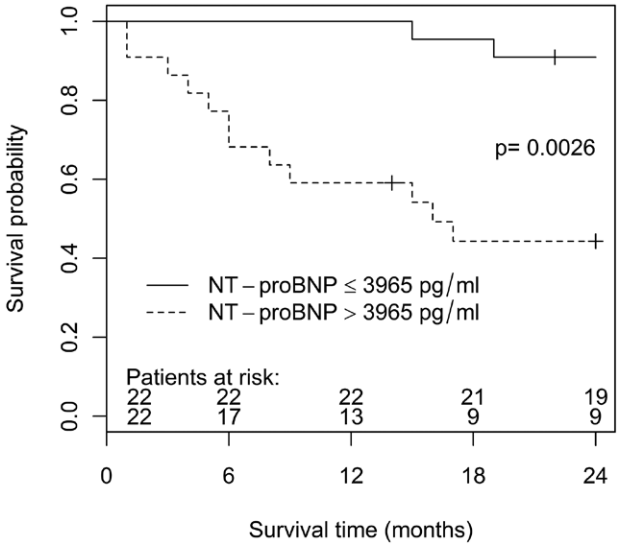

Figure 4. Kaplan–Meier survival curve according to N-terminal pro–B-type natriuretic peptide (NT-proBNP) ≥3965 pg/mL and <3965 pg/mL.

in nonflow-limiting stenosis during stress. Longitudinally oriented subendocardial fibers are more susceptible to ischemia, and therefore longitudinal function may be altered earlier and to a larger extent compared with radial function.

Two-Dimensional Strain Parameters and the Severity of AS

Several studies, including predominantly patients with preserved LVEF, reported that the LV longitudinal function is closely related to AS severity.[30,32,38,39] In the present study of patients with LFAS, no correlation was found between parameters of longitudinal strain and parameters of AS severity. This lack of association may be explained by the following reasons: (1) the accuracy of the resting parameters of stenosis severity is low in the presence of a low-flow state and that of stress parameters is limited in the subset of patients with no contractile reserve and no or minimal increase in flow with dobutamine stress. There were a high proportion of such patients in this series. (2) Patients with LFAS often have comorbidities and concomitant myocardial disease that may influence strain parameters independently of AS severity.

Two-Dimensional Strain Parameters and Outcome

The treatment of patients with AS has undergone a paradigm shift in recent years. Even elderly patients with comorbidities previously precluding consideration for surgical treatment may nowadays be eligible for a transcatheter aortic valve implantation procedure. Clavel et al[40] showed that transcatheter aortic valve implantation is associated with better recovery of LV function compared with conventional valve replacement in patients with severe AS and depressed LV ejection fraction, and these results were also observed in the subset of patients with low gradient. Previous studies reported that lack of contractile reserve, more severe stenosis as measured by the projected EOA, and increased plasma BNP are associated with worse outcome in LFAS.[1–5,18,40,41]

In our series, contractile reserve as defined by stroke volume increase of >20% had no significant impact on outcome. This could be explained by differences in the dobutamine protocols, as well as differences in the baseline characteristics of the study populations. Monin et al[3] used a dobutamine protocol where the infusion was stopped when heart rate increased by ≥10 bpm.[4–5,41] In contrast, we stopped the DSE when a heart rate of >220/min minus age was reached. In addition, patients included in our study had more comorbidities.[2,19] Accordingly, the 3-year survival in our series was as low as 60%. Clavel et al[2] also observed that contractile reserve was not a predictor of outcome in the whole TOPAS cohort.[18,19] As reported in previous studies of the TOPAS cohort, we also found that increased resting plasma levels of natriuretic peptides and lower peak stress LVEF are strong predictors of mortality in LFAS. However, myocardial strain parameters were not analyzed in these previous studies. An important finding of the present study is that longitudinal strain parameters are strongly associated with outcome in patients with LFAS. Among echocardiographic parameters, peak stress PLSR was the strongest predictor of overall survival. Furthermore, peak stress PLSR may add incremental prognostic value beyond what is obtained from NT-pro BNP and peak stress LVEF.

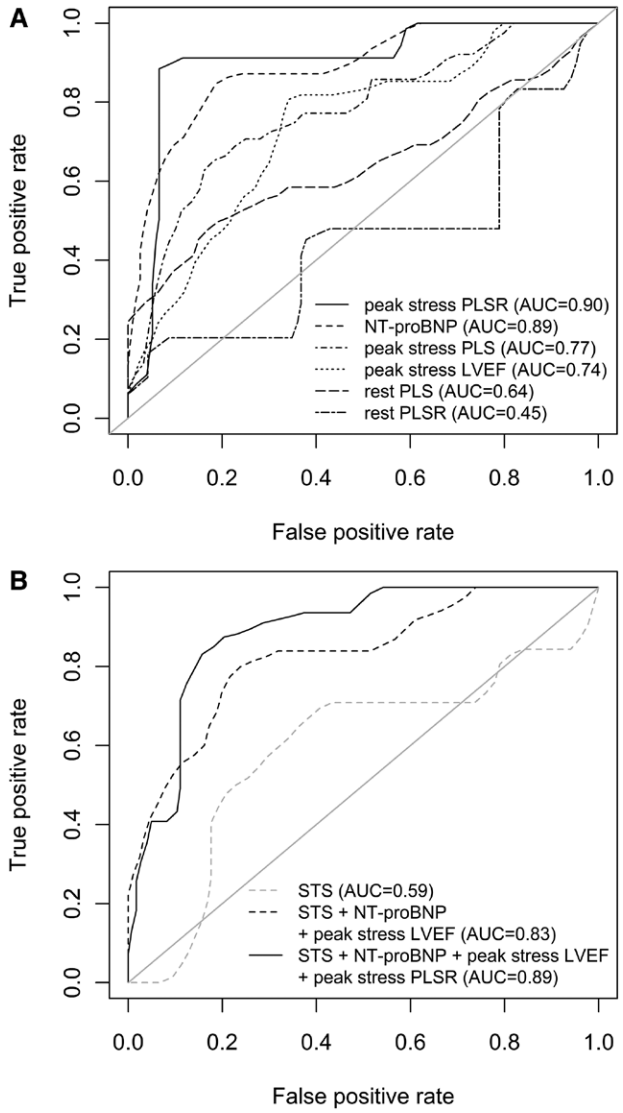

Figure 5. Cross-validated receiver operating characteristic (ROC) curves to predict 2-year survival by (**A**) peak stress peak longitudinal strain rate (PLSR), N-terminal pro–B-type natriuretic peptide (NT-proBNP), peak stress peak longitudinal strain (PLS), peak stress left ventricular ejection fraction (LVEF), rest PLSR, and rest PLS. **B**, (1) Society of Thoracic Surgeons (STS) score; (2) STS score, NT-proBNP, and peak stress LVEF; and (3) STS score, NT-proBNP, peak stress LVEF, and peak stress PLSR. AUC indicates area under the curve.

These associations persisted after adjustment for baseline risk factors. However, this study includes a relatively small number of patients. Before clinical utilization of longitudinal strain parameters for risk assessment, larger trials are needed to confirm our findings. Peak stress longitudinal strain and strain rate are powerful predictors of survival and may thus provide a valuable tool to enhance risk stratification in this high-risk population.

Study Limitations

Subanalysis of the impact of strain parameters on outcome of patients who underwent valvular intervention versus those who were treated medically was not possible as a result of the small group size. Furthermore, valve intervention was not performed immediately after the baseline stress echocardiography, and the time to intervention varied extensively from one patient to the other.

The number of events was small, thus limiting the statistical power for the multivariable analysis of predictors of mortality. This limitation may, at least in part, explain the lack of independent association between NT-proBNP, peak stress LVEF, or projected EOA and outcomes in this study. Furthermore, the incremental prognostic value of peak stress longitudinal strain and strain rate will have to be confirmed in future studies with larger number of patients.

Because circumferential and radial function assessment by speckle tracking is often limited by image quality and variability, which is impaired during stress echocardiography, we concentrated on longitudinal function that is documented to play an important role in AS.[17,29] The optimal frame rate for speckle-tracking analysis seems to be 50 to 70 fps. Although only loops with frame rates >60 frames/s were used for analysis, we cannot rule out undersampling, especially at peak stress where heart rates were significantly increased.[42]

Table 5. Hierarchical Multivariable Cox Regression Analyses

Model	Variables	AUROC*	Incremental *P* Value
1	STS score	0.59	…
2	Model 1+NT-proBNP+peak stress LVEF	0.83	<0.0001
3	Model 2+peak stress PLSR	0.89	0.0346

AUROC indicates area under the receiver operating characteristic; NT-proBNP, N-terminal pro–B-type natriuretic peptide; LVEF, left ventricular ejection fraction; PLSR, peak longitudinal strain rate; and STS, Society of Thoracic Surgeons.

*Based on leave-one-out cross-validation

Conclusions

Our findings demonstrate that longitudinal strain parameters are severely impaired in patients with LFAS at rest but may improve with dobutamine stress in a substantial proportion of patients. Peak stress longitudinal strain and strain rate are powerful predictors of survival and may thus provide a valuable tool to enhance risk stratification in this high-risk population. A larger study is needed to confirm the incremental prognostic value of the peak stress longitudinal strain parameters.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Low flow–low gradient aortic stenosis represents a difficult challenge in terms of diagnosis and treatment. Dobutamine stress echocardiography is recommended to confirm stenosis severity as well as to assess myocardial contractile reserve that is an important prognostic marker. Yet, estimation of myocardial functional reserve is based on stroke volume increase and peak stress left ventricular ejection fraction during dobutamine stress echocardiography. We examined global 2-dimensional strain parameters at rest and during stress for evaluation of myocardial impairment and its value for risk stratification in patients with low flow–low gradient aortic stenosis. Longitudinal strain rate and strain are severely reduced in low flow–low gradient aortic stenosis patients at rest but may improve with dobutamine stress echocardiography in a substantial proportion of patients. Peak stress longitudinal strain rate was the most powerful predictor of mortality in this series, and this parameter seemed to provide incremental prognostic value beyond other factors. The superiority of peak strain rate may be explained by the fact that it better reflects the maximum systolic performance of the subendocardial layer at peak stress. Hence, the assessment of longitudinal strain parameters during dobutamine stress echocardiography could serve as an adjunctive diagnostic tool to enhance risk stratification and clinical decision making in low flow–low gradient aortic stenosis.

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Two-Dimensional Strain for the Assessment of Left Ventricular Function in Low Flow–Low Gradient Aortic Stenosis, Relationship to Hemodynamics, and Outcome: A Substudy of the Multicenter TOPAS Study

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