Global Strain in Severe Aortic Valve Stenosis
Relation to Clinical Outcome After Aortic Valve Replacement

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Background—Global longitudinal systolic strain (GLS) is often reduced in aortic stenosis despite normal ejection fraction. The importance of reduced preoperative GLS on long-term outcome after aortic valve replacement is unknown.

Methods and Results—A total of 125 patients with severe aortic stenosis and ejection fraction >40% scheduled for aortic valve replacement were evaluated preoperatively and divided into 4 groups according to GLS quartiles. Patients were followed up for 4 years. The primary end points were major adverse cardiac events (MACEs) defined as cardiovascular mortality and cardiac hospitalization because of worsening of heart failure; the secondary end point was cardiovascular mortality. MACE and cardiac mortality were significantly increased in patients with lower GLS. Estimated 5-year MACE was increased: first quartile 19% (n=6) / second quartile 20% (n=6) / third quartile 35% (n=11) / fourth quartile 49% (n=15); *P*=0.04. Patients with increased age, left ventricular hypertrophy, and left atrial dilatation were at increased risk. In Cox regression analysis, after correcting for standard risk factors and ejection fraction, GLS was found to be significantly associated with cardiac morbidity and mortality. In a stepwise Cox model with forward selection, GLS was the sole independent predictor: hazard ratio=1.13 (95% confidence interval, 1.02–1.25), *P*=0.04. Comparing the overall log likelihood χ^2 of the predictive power of the multivariable model containing GLS was statistically superior to models based on EuroScore, history with ischemic heart disease, and ejection fraction.

Conclusions—In patients with symptomatic severe aortic stenosis undergoing aortic valve replacement, reduced GLS provides important prognostic information beyond standard risk factors.

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Key Words: aortic valve stenosis ■ survival ■ global strain

Aortic valve stenosis (AS) is characterized by left ventricular (LV) pressure overload, which may lead to LV hypertrophy and compromised coronary flow reserve.[1] These alterations may cause subendocardial ischemia even in the absence of epicardial coronary artery disease and may gradually affect systolic and diastolic function.[2] LV ejection fraction (LVEF) is the most routinely used parameter when assessing LV systolic function; in AS, it is, however, well known that LVEF may remain normal during chronic pressure overload despite reduced myocardial contractility by use of preload reserve[3] or changes in LV geometry.[4]

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Newer echocardiographic techniques based on automatic tracking of movement of speckles on 2-dimensional images allow assessment of systolic strain, which reflects longitudinal and radial myocardial function. Global longitudinal systolic strain (GLS) and strain rate have been shown to correlate strongly with invasively assessed myocardial contractility parameters such as dP/dT[5] and end-systolic pressure–volume relation.[6] As subendocardial ischemia is primarily known to affect longitudinal myocardial fibers,[7] the use of longitudinal strain analysis may be useful in AS to identify patients with reduced contractility despite normal EF. Identification of this population is important, as reduced contractility may lead to increased long-term mortality despite aortic valve replacement (AVR).

The purposes of this study were, thus, to characterize the relationship of GLS and LV remodeling in patients with severe AS and to demonstrate the importance of preoperative GLS and strain rate on long-term outcome including cardiovascular mortality and cardiac hospitalization after AVR in patients with AS.

Methods

The present study is a prespecified substudy of a prospective single-center randomized study to evaluate the effect of candesartan compared with conventional treatment on reverse remodeling in

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consecutive patients undergoing AVR for symptomatic AS.[8] The study was registered with the National Board of Health and the Danish Data Protection Agency and was approved by the local ethical committee, and all patients gave written informed consent. ClinicalTrials.gov Identifier: NCT00294775

Screening and Inclusion

Patients eligible for the study were aged >18 years with symptomatic severe AS (estimated aortic valve area<1 cm^2) scheduled for AVR at Odense University Hospital during the period February 2006 and May 2008. Patients with LV systolic dysfunction (LVEF<40%), renal failure (s-creatinine >220 μmol/L), previous aortic valve surgery, planned additional valve repair/replacement, acute infective endocarditis, predominantly aortic valve regurgitation, or treatment with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker at the time of enrolment were excluded. The need for AVR was decided by consensus among senior cardiologists, cardiac surgeons, and anesthetists not involved in the present study. Of the 238 patients screened for participation, 49 refused participation in the study, 59 met at least 1 exclusion criteria, and 5 did not undergo surgery, leaving 125 patients in the study. Patients were divided into 4 groups according to global strain quartiles.

The severity of preoperative symptoms was evaluated using the New York Heart Association (NYHA) functional class for dyspnea and the Canadian Cardiovascular Society (CCS) functional class for angina.

Ischemic heart disease was defined as a history with prior myocardial infarction, previous revascularization with percutaneous coronary intervention (PCI), or coronary artery bypass grafting or if preoperative coronary angiography demonstrated significant stenosis requiring coronary artery bypass grafting in addition to AVR.

Echocardiography

All echocardiograms were performed and analyzed by the same operator on a GE Vivid 5 ultrasound machine (GE Medical System, Horten, Norway), the day before surgery. All echocardiograms were digitally stored and later analyzed completely blinded for all clinical and survival data.

Aortic valve area was estimated with quantitative Doppler using the continuity equation. The diameter of the LV outflow tract was measured 5 mm below the annulus from a zoomed image of the LV outflow tract obtained in the parasternal long-axis view. Peak flow velocity across the valve was determined in the apical window or the echocardiographic window, where the highest peak velocity could be obtained by placing the continuous wave Doppler cursor as parallel as possible with the flow across the valve. Peak transvalvular gradient was estimated using the Bernoulli equation. Finally, the peak systolic flow velocity in the outflow tract was estimated with pulsed-wave Doppler. LVEF was estimated using Simpson's biplane method.[9]

LV mass was estimated according to the joint recommendations of the American (ASE) and European (EAE) associations of echocardiography using Devereux's.[10] LV wall thickness and dimensions were estimated from the average of 3 consecutive 2-dimensional images obtained in the parasternal long-axis view according to guidelines. In males, left ventricular mass index (LVMi)> 116 g/m^2 and in women >100 g/m^2 was considered indicative of LV hypertrophy. Relative wall thickness was calculated for assessment of LV geometry using the formula 2×PWT/LV diastolic diameter.[10]

Left atrial volume index (LAVi) was measured in LV end systole in the frame preceding mitral valve opening. The volume was measured using the biplane area length method and corrected for body surface area.

Mitral inflow was assessed in the apical 4-chamber view using pulsed-wave Doppler with the sample volume paced at the tips of mitral leaflets during diastole. From the mitral inflow profile, the E- and A-wave peak velocities and DT were measured. Doppler tissue imaging of the mitral annulus was obtained from the apical 4-chamber, apical 2-chamber, and apical long-axis views, using a sample volume placed in the septal, lateral, anterior, inferior, and posterior mitral valve annulus. The e' velocity from each site and the mean value were determined, and the respective E/e' ratios were derived. For all Doppler recordings, a horizontal sweep of 100 mm/s was used; for patients in sinus rhythm, an average of 5 consecutive beats were measured, 10 for patients with atrial fibrillation.

GLS was analyzed using EchoPAC PC 08 (GE Medical system, Horten, Norway) speckle tracking software 2-D. GLS was determined as the magnitude of strain at the aortic valve closure, and systolic strain rate (SR_S) was determined as the maximal negative SR value during the ejection phase. Both parameters were assessed in all 3 apical planes, and the mean values (GLS_{mean}, SR_{smean}) were calculated. Frame rate was kept as high as possible with a minimum frame rate of 70/s.

Systemic arterial pressure was measured with the use of an arm cuff sphygmomanometer in the right arm with the patient in the supine position, at the same time as the Doppler measurement of stroke volume (SV) was measured in the LV outflow tract. The ratio of stroke volume index (SVi) to brachial pulse pressure (PP) was used as an indirect measure of total systemic arterial compliance: SAC=SVi/PP.[11] The systemic vascular resistance was estimated by the formula SVR=(80×MAP)/CO, where MAP is the mean arterial pressure defined as diastolic pressure plus one third of PP and CO is the cardiac output.

As a measure of global LV load, we calculated the valvuloarterial impedance Z_{va}=(SAP+MG)/SVi, where SAP is the systolic arterial pressure, MG is the mean transvalvular pressure gradient, and SVi is the stroke volume index.[11]

Plasma N-Terminal Probrain Natriuretic Peptide

Blood samples were collected immediately after the echocardiogram, after the subject had been resting recumbent for at least 30 minutes. Samples were collected in ethylenediamine tetra-acetic acid tubes. These were then centrifuged, and plasma samples were stored at −80°C for later analysis. NT-proBNP was determined using an ELECSYS proBNP immunoassay (Roche Diagnostics GmbH, Mannheim, Germany).

Clinical Follow-Up

By July 2011, data on outcomes were collected from the Danish Personnel Register (survival status) and from discharge notes available in the Danish admission registry. In case of ambiguous information, local hospitals were contacted, and detailed patient charts were reviewed.

The main end point for this study was a major adverse cardiac event (MACE), defined as cardiovascular mortality and cardiac hospitalization due to worsening of heart failure; the secondary end point was cardiovascular mortality. End points were ascertained by one of the investigators who was blinded to all echocardiographic measurements.

Statistics

Data are presented as mean±SD or number and percentages. The differences between the groups were tested using ANOVA; categorical variables were tested by Fisher exact test. In case of significant differences between the groups, paired comparisons were performed using Tukey range test.

Because of non-Gaussian distribution, NT-pro BNP was logarithm transformed. Reproducibility of measurements of GLS was assessed by intraclass correlation coefficients. Mortality and event rates were calculated using the product limit method and were plotted according to the Kaplan–Meier method, and death rates were compared using the log-rank test. Further estimation of risk was performed using Cox proportional hazard models. The overall differences between the models were tested by calculating the overall difference in log likelihood χ^2 between models. The assumptions (proportional hazard assumption, linearity of continuous variables, and lack of interaction) were tested and found valid. A P value <0.05 was considered significant. STATA/SE 9.0 (StataCorp LP, TX) software was used for statistical analysis.

Results

A total of 125 patients were included in this study; thirty-eight patients met the combined end point MACE. Table 1 provides baseline clinical and echocardiographic data according to MACEs during follow-up. AVR was performed in all patients. Coronary artery bypass grafting was performed in 37 (30%) patients with no difference between the groups; complete revascularization was achieved in all patients. No difference in the size or type of aortic valve prosthesis was seen between groups; additionally, the use of β-blockers, calcium channel blockers, ACE inhibitors, and diuretics was equal between groups preoperatively. There was a trend toward increased age in patients experiencing MACEs (75±7 vs. 71±10 years; *P*=0.06). Patients with MACEs had increased occurrence of atrial fibrillation (26% vs. 10%; *P*=0.03), increased levels of NT-proBNP, increased LVMi (146±43 vs. 124±38 g/m^2), reduced e'$_{sep}$ velocity (5.3±1.7 vs. 5.9±1.6 cm/s; *P*=0.04) and increased LA volume index (57±18 vs. 45±18 mL/m^2; *P*=0.0009). Longitudinal systolic function was reduced in patients with MACEs; global longitudinal strain (−13.7±3.8 vs. 16.3±3.4; *P*=0.0002), s'$_{sep}$ (5.3±1.5 vs. 5.9±1.4 cm/s; *P*=0.03), and systolic strain rate (−0.76±0.22 vs. −0.87±0.18 s^{-1}; *P*=0.002).

GLS in the complete cohort was −15.5±3.7. GLS was −20.0±1.6 in the first quartile, −16.9±0.7 and −14.3±0.9 in the 2 middle quartiles, respectively, and −10.3±1.4 in the fourth quartile. Table 2 shows echocardiographic data distributed among GLS quartiles. Aortic valve area and peak aortic valve velocity were similar among groups, Z_{va} was significantly lower in group 1. LV end-diastolic volume, LV end-systolic volume and log-NT-proBNP increased across groups 1 through 4. In group 4, LVEF was significantly lower, and LVMi was significantly higher than the other groups. The duration of heart failure symptoms prior to surgery was similar among GLS quartiles (1.9±0.8 vs. 2.2±0.8 vs. 1.9±0.7 vs. 2.1±0.7 months; *P*=0.35, data not shown).

Table 1. Patient Characteristics

	Patients with MACE (n=38)	Patients without MACE (n=87)	
Age, y	75±7	71±10	0.06
Sex (male)	24 (63)	55 (63)	0.58
NYHA I/II/III/IV	11/16/10/1	12/49/26/0	0.07
CCS I/II/III/IV	19/15/4/0	44/39/5/0	0.60
Atrial fibrillation	10 (26)	9 (10)	0.03
Diabetes mellitus	2 (6)	9 (28)	0.28
CABG	9 (24)	28 (32)	0.40
Ischemic heart disease	12 (32)	26 (30)	0.55
EuroScore	6.1±1.5	5.6±2.1	0.22
Ejection fraction, %	54±8	54±8	0.64
LV end-diastolic volume, mL	110±36	109±33	0.96
LV end-systolic volume, mL	52±20	51±18	0.80
LVMi, g/m^2	146±43	124±38	0.004
LA volume index, mL/m^2	57±18	45±18	0.0009
E-velocity, m/s	0.8±0.2	0.8±0.2	0.90
A-velocity, cm/s	1.0±0.3	0.9±0.3	0.09
Deceleration time, ms	202±66	197±56	0.66
E'$_{sep}$, cm/s	5.3±1.7	5.9±1.6	0.04
S'$_{sep}$, cm/s	5.3±1.5	5.9±1.4	0.03
Global longitudinal strain	−13.7±3.8	−16.3±3.4	0.0002
Systolic strain rate	−0.76±0.22	−0.87±0.18	0.002
Log NT-proBNP	6.7±1.2	6.0±1.3	0.006

NYHA indicates New York Heart Association; CCS, Canadian Cardiovascular Society; CABG, coronary aortic bypass graft; LV, left ventricular; LVMi, left ventricular mass index; and LA, left atrial.

Factors Associated With GLS

Reproducibility of measurements of GLS was tested in a subset of 50 patients. The reproducibility was excellent with an intraclass correlation coefficient for intraobserver variability of 0.93 (CI 0.90–0.96; *P*<0.001).

Reduced GLS was associated with increased LVMi, relative wall thickness, LV end-diastolic volume, and Z_{va} (Table 3). In addition, GLS was significantly correlated with SVi (β=−0.08; *P*=0.007), LAVi (β=0.068; *P*<0.001), LVEF (β=−0.16; *P*<0.001), and log-NT-proBNP (β=1.25; *P*<0.001). In a multivariate regression analysis including the aforementioned variables, except LAVi and NT-proBNP (because of significant colinearity with LVMi), parameters independently associated with GLS were LVMi, LVEF, RWT, LV end-diastolic volume, and $Z_{va.}$

Clinical Outcome

The mean follow-up duration in the total cohort was 3.8±1.5 years (median 4.0 years). Survival status was available for all patients. Overall, there were 29 deaths, 4 in group 1, 6 in group 2, 6 in group 3, and 13 in group 4. The causes of 4 deaths were not because of any cardiac condition (n=2 cancer, n=1 infectious disease, n=1 subarachnoid hemorrhage), and 25 patients had a cardiac cause of death (n=15 sudden cardiac death, n=7 postoperative death, n=2 congestive heart failure, n=1 aortic aneurism). Thirty-eight patients met the combined end point MACE (n=20 cardiac death, n=18 congestive heart failure).

Overall mortality, cardiac mortality, and MACEs were significantly increased in patients with lower global strain (estimated 5-year MACEs: first quartile 19% [n=6] / second quartile 20% [n=6] / third quartile 35% [n=11] / fourth quartile 49% [n=15]; *P*=0.04; Figure 1).

Twenty-two patients were still symptomatic at discharge (19=NYHA functional class II; n=2 NYHA functional class III; n=1 NYHA functional class IV), of which 27% (n=6) met the combined end point MACE.

In a univariable Cox regression analysis global strain, LAVi, LVMi, LV posterior wall thickness, E/e', s'$_{sep}$, log-NT-proBNP, and age were predictors of MACEs (Table 4). In a stepwise Cox model with forward selection of the aforementioned variables, except s'$_{sep}$ (because of significant colinearity with GLS), GLS was the sole factor significantly associated with MACEs hazard ratio=1.13 (95% confidence interval 1.01–1.25), *P*=0.018. We tested several multivariate models in all GLS was significantly associated with MACEs and cardiac death (online-only data supplement Figures I and II), including a predefined model containing EuroScore, known ischemic heart disease, and ejection fraction (Table 4). Although ejection fraction was

Table 2. Echocardiographic Data

	GLS first quartile (n=31)	GLS second quartile (n=31)	GLS third quartile (n=31)	GLS fourth quartile (n=32)	
Aortic valve area, cm^2	0.9±0.2	0.9±0.3	0.8±0.3	0.8±0.3	0.29
AV_{max}, m/s	3.8±0.6	3.8±0.8	4.0±0.8	4.1±0.8	0.49
Z_{va}	4.0±1.1*	5.1±1.7	5.1±1.6	5.2±1.4	0.01
Ejection fraction, %	58±8	55±6	55±7	50±7†	0.0001
LVEDV, mL	96±24	103±35	112±30	125±39‡	0.004
LVESV, mL	41±13	47±16	51±16	63±23†	<0.0001
LVMi, g/m^2	121±26	121±36	127±34	153±53§	0.003
IVST, mm	13±2	13±2	13±2	13±3	0.53
LVPWT, mm	12±2	13±2	13±2	14±2‡	0.001
Relative wall thickness	0.57±0.14	0.58±0.12	0.60±0.11	0.64±0.18	0.14
E wave, m/s	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.3	0.68
A wave, m/s	1.0±0.3	1.0±0.2	0.9±0.2	0.9±0.4	0.51
Deceleration time, ms	210±52	205±57	191±50	188±73	0.39
E'_{sep}, cm/s	6.2±1.9	5.9±1.4	5.8±1.4	5.0±1.8§	0.04
Diastolic function 0/1/2/3	3/18/7/2	1/14/11/4	0/16/5/8	1/14/6/9	0.16
LAVi, mL/m^2	42±17	45±16	49±17*	59±20‡	0.001
E/e'_{sep}	13.2±4.0	14.6±4.9	14.1±4.6	17.7±6.5†	0.005
S'_{sep}, cm/s	6.5±1.2	6.1±1.4	5.7±1.1*	4.5±1.5†	<0.0001
Stroke volume index, mL	47±11	41±14	39±14	38±12	0.04
Global strain	−20.0±1.6	−16.9±0.7	−14.3±0.9	−10.3±1.4	
GLS 4-chamber, %	−20.2±3.1	−17.3±2.1	−14.8±2.3	−10.7±2.3	
GLS 2-chamber, %	−19.6±2.7	−16.6±3.2	−14.0±2.6	−10.5±2.0	
GLS long axis, %	−20.1±3.6	−16.5±2.3	−14.1±2.4	−9.9±2.3	
Strain rate S, s^{-1}	−0.99±0.13	−0.92±0.10	−0.82±0.16	−0.59±0.13	
Log proNT-proBNP	5.5±1.1	5.9±1.0	6.5±1.2‡	7.0±1.5‡	<0.0001

LVEDV indicates left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVMi, left ventricular mass index; IVST, interventricular septum thickness, LVPWT, LV posterior wall thickness; LAVi, left atrial volume index; and GLS, global longitudinal systolic strain.

*P<0.05 compared with the second, third, and fourth quartiles, †P<0.05 compared with the first, second, third quartiles, ‡P<0.05 compared with the first and second quartiles, §P<0.05 compared with the first quartile.

not an independent predictor, it was included in multivariate models (Table 4). Nevertheless, GLS was still a significant predictor.

Comparing the overall log likelihood χ^2 of the predictive power of the multivariable model, two models containing GLS were statistically superior to models based on age, LVMi, and LAVi or EuroScore, ischemic heart disease, and ejection fraction, Figure 2.

Discussion

The main finding in our study is that preoperative longitudinal LV systolic function assessed with speckle tracking analyses is significantly associated with long-term postoperative MACEs and cardiac mortality in symptomatic patients with severe AS and LVEF>40% after aortic valve surgery. Second, we demonstrated that preoperative global strain is dependent on LV afterload, LV preload, and the extent of LV remodeling.

It is well known that patients with AS have reduced LV longitudinal systolic function despite normal LVEF.[12–16] In hypertension, it has been demonstrated that afterload per se affects longitudinal systolic function[17] with a compensatory increased contribution to ventricular emptying from radial LV fibers, thereby maintaining LVEF. In the present study, this understanding was extended to patients with AS where we found GLS was associated with global LV afterload (Z_{va}) after adjustment for confounders. This finding agrees with the findings of Miyazaki et al who demonstrated that GLS gradually decreased as AS severity increased.[16] A previous study in patients with AS demonstrated that coronary flow is severely impaired in AS and that increased afterload is the main reason;[1] this correlates well with our findings as we have demonstrated that patients with reduced global longitudinal strain have decreased systemic arterial compliance, a factor that may affect coronary flow.[18] Subendocardial ischemia related to increased afterload may thus play an important factor. However, in addition to increased afterload, AS leads to LV remodeling including LV hypertrophy, myocardial fibrosis, and altered LV geometry; all factors were potentially capable of affecting longitudinal systolic function. As postoperative LV reverse remodeling is a slow and not fully reversible process,[19] structural changes in the myocardium may be of greater clinical importance as they may affect postoperative prognosis.[20]

Table 3. Regression Analysis: Factors Associated With Global Strain

		Univariable		Multivariable R^2=0.36	
	R	β (95% CI)	*P*	β (95% CI)	*P*
Age	0.09	0.036 (–0.04 to 0.11)	0.34		
Gender		0.75 (–0.6 to 2.1)	0.29		
Diabetes mellitus		0.014 (–0.003 to 0.03)	0.10		
Aortic valve area	–0.16	–2.2 (–4.7 to 0.3)	0.09		
Mean gradient	0.16	0.04 (–0.00 to 0.7)	0.06		
Z_{va}	0.28	0.7 (0.2 to 1.1)	0.004	0.6 (0.2 to 1.1)	0.005
Ejection fraction	–0.33	–0.2(–0.3 to –0.1)	<0.001	–0.1 (–0.2 to 0.1)	0.002
LVMi	0.32	0.03 (0.01 to 0.05)	<0.001	0.02 (0.01 to 0.04)	0.007
RWT	0.23	6.1 (1.5 to 10.7)	0.01	6.9 (2.3 to 11.3)	0.003
LVEDV	0.35	0.04 (0.02 to 0.06)	<0.001	0.02 (0.01 to 0.04)	0.045
LAVi	0.34	0.068 (0.033 to 0.10)	<0.001		
SAC	–0.20	–3.2 (–6.4 to –0.1)	0.048		
SVi	–0.26	–0.08 (–0.12 to –0.02)	0.007		
Log NT-proBNP	0.43	1.25 (0.78 to 1.72)	<0.001		
Candesartan		–0.13 (–1.5 to 1.2)	0.85		

Z_{va} indicates valvuloarterial impedance; LVMi, left ventricular mass index; RWT, relative wall thickness; LVEDV, left ventricular end-diastolic volume; LAVi, left atrial volume index; SAC, systemic arterial compliance; and SVi, stroke volume index; .

We demonstrated that GLS was dependent on LV hypertrophy and LV geometry, a finding that correlates well with previous studies, which have demonstrated that postoperative improvement in longitudinal systolic function is dependent on regression of LV hypertrophy.[12] The mechanism is probably increased oxygen consumption of the hypertrophied LV.

To the best of our knowledge, this is the first study to demonstrate that GLS is significantly associated with cardiac morbidity and mortality incremental to conventional risk factors in patients undergoing AVR. The link between poor outcome and longitudinal LV function could be multiple. Myocardial fibrosis has recently gained significant attention, where it has been demonstrated to affect postoperative remodeling and postoperative outcome.[13,21] Weidemann et al demonstrated that longitudinal strain was significantly decreased in patients with severe myocardial fibrosis, and thus it has been proposed that GLS may be used as a noninvasive marker reflecting myocardial fibrosis.[13] Based on this, it could be speculated that reduced GLS may reflect the impact of myocardial fibrosis on LV longitudinal systolic function in AS and provide the link to poor outcome.

Myocardial fibrosis, however, would also be anticipated to be associated with decreased LV compliance and cause diastolic dysfunction. We were unable to detect differences in deceleration time or diastolic function, although there was a trend toward increased presence of restrictive filling. Whether this is because of inherent insensitivity to detect subtle differences in LV chamber compliance or whether LV compliance was unaffected is not clear.

GLS correlated significantly with other well-known risk factors for poor outcome after aorta valve replacement including LAVi,[20] LVMi,[20] E/e',[22] and increased NT-proBNP.[23] GLS was, however, the strongest predictor for postoperative outcome in our population providing information additional to the

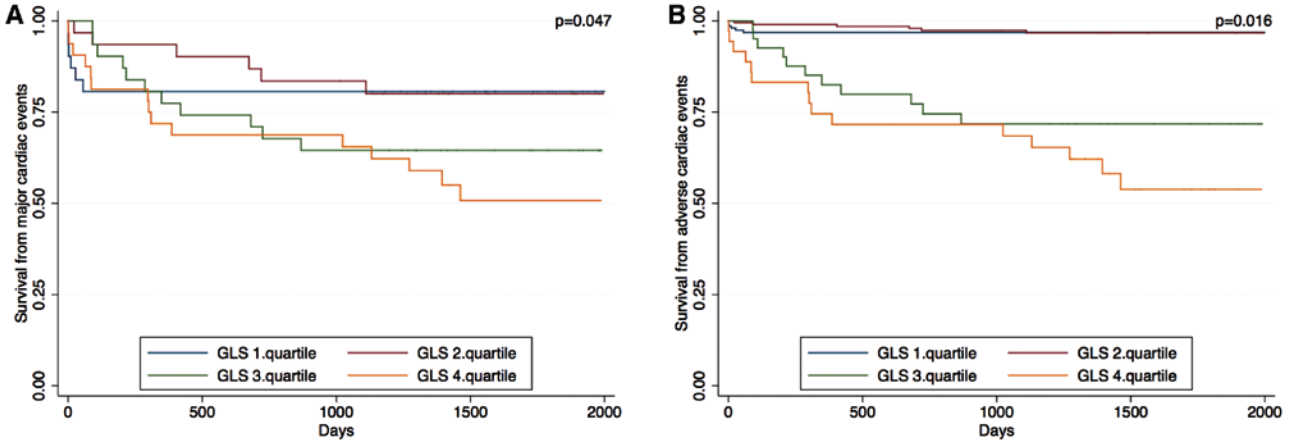

Figure 1. Survival from adverse cardiac event as a function of the level of global strain unadjusted (**A**), adjusted for EuroScore, ejection fraction, known history of ischemic heart disease (**B**). GLS indicates global longitudinal systolic strain.

Table 4. Univariable and Multivariable Predictors of MACEs

	Univariable		Multivariable		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
GLS	1.18 (1.1–1.3)	0.001	1.12 (1.01–1.25)	0.028	1.15 (1.02–1.28)	0.018
LVEF, %	0.98 (0.94–1.03)	0.49			1.03 (0.98–1.08)	0.31
LVEF<50%	1.27 (0.6–2.6)	0.50				
Age	1.04 (1.00–1.08)	0.04	1.02 (0.98–1.07)	0.31	1.02 (0.98–1.07)	0.30
EuroScore	1.12 (0.96–1.31)	0.14				
Diabetes	1.7 (0.8–3.7)	0.19				
IHD	0.76 (0.4–1.5)	0.44				
CABG	0.63 (0.3–1.4)	0.24				
Mean gradient	1.01 (1.00–1.03)	0.15				
NYHA III/IV	1.05 (0.52–2.11)	0.90				
LAVi	1.03 (1.01–1.04)	<0.001	1.01 (0.99–1.04)	0.18	1.02 (0.99–1.04)	0.15
LVMi	1.01(1.00–1.02)	0.003	1.00 (0.99–1.01)	0.94	1.00 (0.99–1.01)	0.97
RWT	7.7 (0.8–77)	0.08				
E/e'_{avg}	1.08 (1.02–1.15)	0.01				
Log NT-proBNP	1.46 (1.14–1.86)	0.003				
LVEDV	1.00 (0.99–1.01)	0.73				
LVESV	1.00 (0.98–1.02)	0.98				
LVPWT	7.7 (1.8–33)	0.005				
S'_{sep}	0.74 (0.58–0.93)	0.01				
Z_{va}	0.87 (0.69–1.09)	0.22				
SR_s	10.0 (2–50)	0.005				
Candesartan	0.67 (0.35–1.28)	0.23				

HR indicates hazard ratio; GLS, global longitudinal systolic strain; LVEF, left ventricular ejection fraction; IHD ischemic heart disease; CABG, coronary artery bypass grafting; NYHA, New York Heart Association; LAVi, left atrial volume index; LVMi, left ventricular mass index; RWT, relative wall thickness; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVPWT, LV posterior wall thickness; Z_{va} valvuloarterial impedance; and SR_s, systolic strain rate.

aforementioned parameters as well as to traditional risk factors such as age, gender, diabetes mellitus,[24] and EuroScore.[23]

This may reflect that GLS is affected by both physiology and anatomy.

The increased levels of NT-proBNP, higher E/e', and increased LAVi in patients with decreased GLS suggest that patients would have had a longer duration of heart failure symptoms before surgery; this was, however, not the case and this further questions the unambiguity of symptom estimation. This is further challenged by the increased mortality/morbidity seen in patients with reduced global strain, as this suggests that surgery should be considered before the onset of symptoms has occurred. Although not demonstrated in a randomized setting, the benefit of early surgery has been

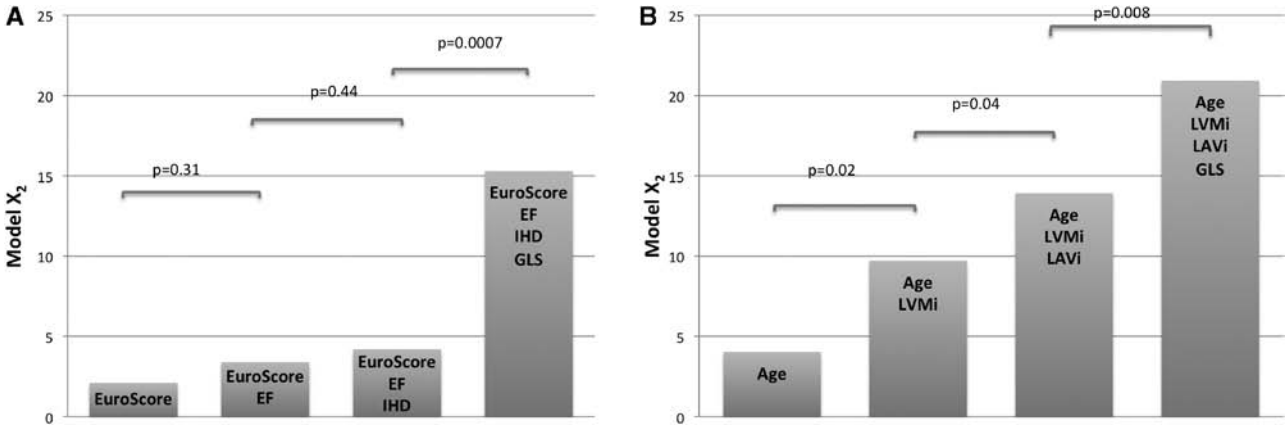

Figure 2. Incremental prognostic information of EuroScore, ejection fraction, ischemic heart disease and global strain in predicting cardiac mortality. Global strain also provided incremental information to age, left ventricular mass index, and left atrial volume index. EF indicates ejection fraction; GLS, global longitudinal systolic strain; IHD ischemic heart disease; LAVi, left atrial volume index; and LVMi, left ventricular mass index.

suggested in a study of 622 asymptomatic patients with AS, in whom survival was improved in those having AVR, even in patients who remained asymptomatic.[25] The benefit of early surgery has further been suggested in a recent, small randomized study.[26] Larger studies are, however, warranted.

Study Limitations

The sample size was small with relatively fewer events, which make our models unstable with a potential risk of overfitting the models. The present study should be considered as hypothesis generating, and clearly, larger studies including patients with more subnormal LVEF are warranted. We were not able to demonstrate that LVEF is a predictor in AS; this possibly reflects that patients with LVEF<40% were excluded. The entry criterion for the study was symptomatic AS referred for AVR. Because of selection bias, it precludes applicability to asymptomatic patients. Future studies should be performed on asymptomatic patients to clarify whether our findings also apply to a general population with AS.

LV structure was assessed by echocardiography, and no histological examinations were performed; thus, we can only speculate on the degree of myocardial fibrosis. No direct hemodynamic measurements of LV end-diastolic or LA pressure were performed. However, E/e' is accepted as a well-validated surrogate in a wide range of patients with cardiac disease including AS.[27]

Conclusions

The present study demonstrates that preoperative longitudinal global strain assessed with speckle tracking analyses is significantly associated with long-term postoperative cardiac mortality and morbidity, in patients with severe aortic valve stenosis and LVEF>40% after aortic valve surgery.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Aortic valve stenosis (AS) leads to left ventricular remodeling and compromised coronary flow reserve that gradually affects systolic and diastolic function. Left ventricular ejection fraction is the most routinely used parameter when assessing left ventricular systolic function. However, it is well known that in AS, ejection fraction may remain normal despite reduced myocardial contractility. The use of speckle tracking allows assessment of systolic strain, which reflects longitudinal and radial myocardial function. As early myocardial alterations are primarily known to affect longitudinal myocardial fibers, the use of longitudinal strain analysis may be useful in AS in identifying patients with reduced contractility despite normal ejection fraction. Identification of this population is important, as reduced contractility may lead to increased long-term mortality despite aortic valve replacement. We have demonstrated that global strain is independently associated with long-term postoperative cardiac mortality and morbidity in symptomatic patients with severe aortic valve stenosis and preserved ejection after aortic valve surgery. Future studies should be performed on asymptomatic patients to clarify whether patients with reduced global strain would benefit from early surgery.

Global Strain in Severe Aortic Valve Stenosis: Relation to Clinical Outcome After Aortic Valve Replacement

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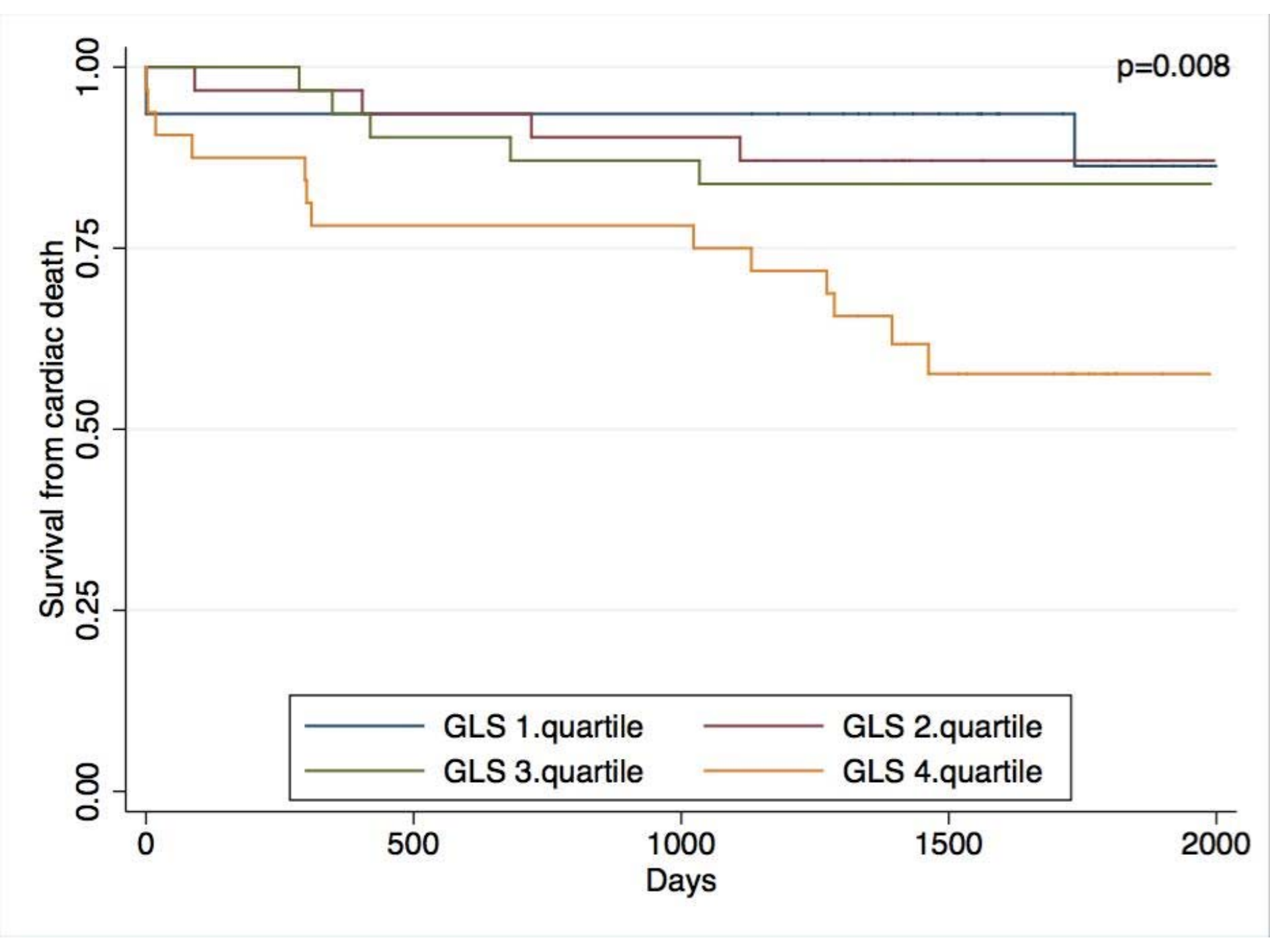
Supplemental Material

Supplemental Figure I. Cardiac survival as a function of the level of global strain

Supplemental Figure II. Incremental prognostic information of EuroScore, diabetes, left atrial volume index and global strain, in predicting cardiac mortality. Global strain also provided incremental information to ejection fraction, NT-proBNP and relative wall thickness.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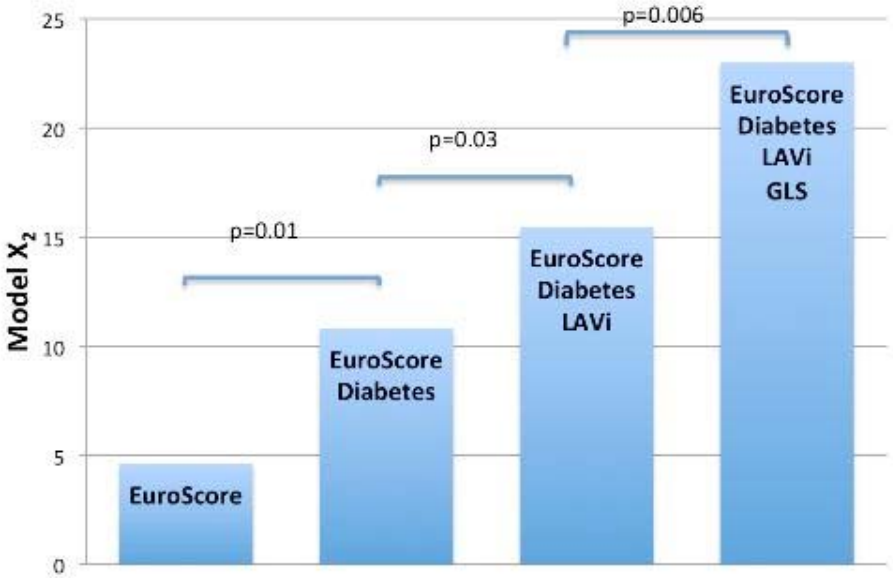
0.75
0.50
0.25
0.00
0
500
1000
1500
2000
Days
GLS 1.quartile
GLS 2.quartile
GLS 3.quartile
GLS 4.quartile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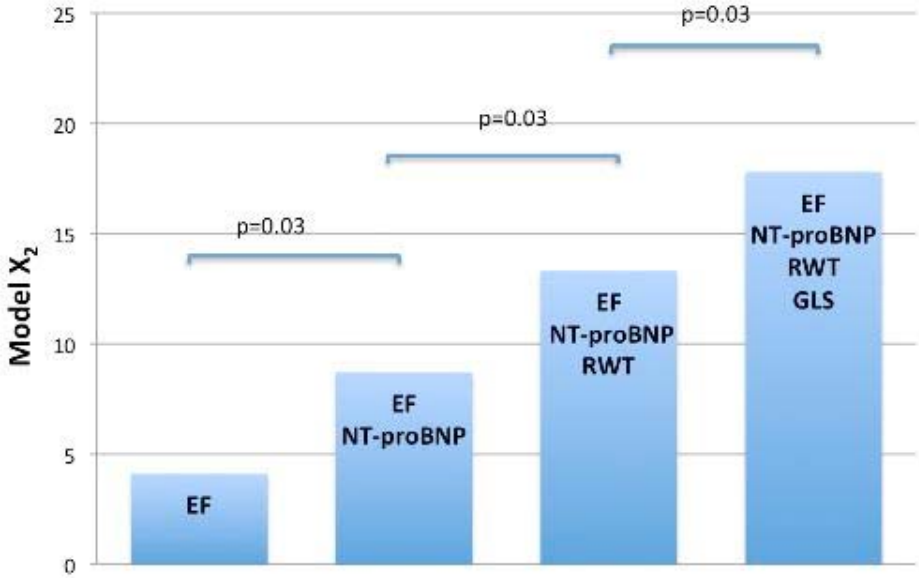
p=0.03
p=0.006
EuroScore
EuroScore Diabetes
EuroScore Diabetes LAVi
EuroScore Diabetes LAVi GLS


Model X_2
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20
15
10
5
0
p=0.03
p=0.03
p=0.03
EF
EF NT-proBNP
EF NT-proBNP RWT
EF NT-proBNP RWT GLS