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Alterations in multidirectional myocardial functions in patients with aortic stenosis and preserved ejection fraction: a two-dimensional speckle tracking analysis

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Aims To identify changes in multidirectional strain and strain rate (SR) in patients with aortic stenosis (AS).

Methods and results A total of 420 patients (age 66.1 ± 14.5 years, 60.7% men) with aortic sclerosis, mild, moderate, and severe AS with preserved left ventricular (LV) ejection fraction [(EF), ≥50%] were included. Multidirectional strain and SR imaging were performed by two-dimensional speckle tracking. Patients were more likely to be older ($P < 0.001$) and at a worse New York Heart Association functional class ($P < 0.001$) with increasing AS severity. There was a progressive stepwise impairment in longitudinal, circumferential, and radial strain and SR with increasing AS severity (all $P < 0.001$). The myocardial dysfunction appeared to start in the subendocardium with mild AS, to mid-wall dysfunction with moderate AS, and eventually transmural dysfunction with severe AS. Aortic valve area, as a measure of AS severity, was an independent determinant of multidirectional strain and SR on multiple linear regressions.

Conclusions Patients with AS have evidence of subclinical myocardial dysfunction early in the disease process despite normal LVEF. The myocardial dysfunction appeared to start in the subendocardium and progressed to transmural dysfunction with increasing AS severity. Symptomatic moderate and severe AS patients had more impaired multidirectional myocardial functions compared with asymptomatic patients.

Keywords Aortic stenosis • Aortic valve • Left ventricle • Echocardiography

Introduction

In patients with aortic stenosis (AS), there is progressive left ventricular (LV) hypertrophy in response to pressure overload. With severe AS, patients may develop a reduced LV ejection fraction (EF) due to afterload mismatch or from true impairment of myocardial contractility secondary to reduced myocardial perfusion and increased myocardial oxygen consumption.[1] Previous anatomical study has shown that the LV myocardial architecture is a complex array of longitudinally and circumferentially orientated fibres located predominately in the epicardium/endocardium and mid-wall, respectively.[2] Furthermore, the subendocardial fibres are more susceptible to increased wall stress and reduced myocardial perfusion.[3,4] Conventional global measures of LV systolic function such as LVEF can be preserved until end-stage disease as it often lacks accuracy in identifying changes in myocardial

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contractility and cannot ascertain the transition from compensatory hypertrophy to myocardial dysfunction and heart failure. In contrast, strain and strain rate (SR) imaging are more sensitive indices of myocardial function. In addition, multidirectional analyses of longitudinal, circumferential, and radial strain/SR provide insights into regional myocardial functional changes with increasing AS severity. However, human studies examining the relationship between multidirectional myocardial functions and increasing AS severity have been limited. Thus, the aims of the present evaluation were to describe changes in multidirectional LV strain and systolic SR with increasing AS severity in patients with normal LVEF by 2-dimensional (2D) speckle tracking echocardiography, and to identify independent determinants of multidirectional myocardial functions.

Methods

Patient population

Four hundred and fifty-seven consecutive patients diagnosed with aortic sclerosis and varying degrees of AS severity were included. All patients underwent a history, physical examination, and transthoracic echocardiography. Exclusion criteria included rhythm other than sinus rhythm, LVEF <50%, moderate or severe co-existing aortic regurgitation, moderate or severe mitral regurgitation, subvalvular or supravalvular AS, dynamic subaortic obstruction, active endocarditis, history of myocardial infarction, and presence of regional wall motion abnormalities. A total of 37 patients (8%) were excluded due to suboptimal images resulting in the inability to perform speckle tracking analyses, and thus the final patient population consisted of 420 patients.

All clinical data were retrieved from the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center) as permitted by the Institutional Review Board.

All echocardiograms were divided into four groups (aortic sclerosis, mild AS, moderate AS, and severe AS) based on the calculated aortic valve area (AVA), mean gradient, and peak velocity as recommended by the European Association of Echocardiography and American Society of Echocardiography.[5] Changes in multidirectional LV strain and SR with increasing AS severity were examined. Finally, independent determinants of multidirectional LV strain and SR were identified. As asymptomatic AS patients constitute a special population of interest, all multivariate analyses were repeated whereby only asymptomatic AS patients were selected.

Echocardiography

Transthoracic echocardiography was performed with the subjects at rest using commercially available ultrasound systems (System 5 and Vivid 7, GE-Vingmed, Horten, Norway). All images were digitally stored on hard disks for off-line analysis (EchoPAC version 108.1.5, GE-Vingmed, Horten, Norway). A complete 2D, colour, pulsed, and continuous-wave Doppler echocardiogram was performed according to standard techniques.[6,7] Left ventricular end-diastolic volume index (EDVI) and end-systolic volume index (ESVI) were calculated using Simpson's biplane method of discs and corrected for body surface area (BSA).[8] Left ventricular ejection fraction was calculated and expressed as a percentage. Left ventricular mass index was calculated by using the area–length method as recommended by the American Society of Echocardiography and corrected for BSA.[9] Maximal left atrial volume index was measured at LV end-systole (just before mitral valve opening) using Simpson's biplane method of discs and corrected to BSA. Left ventricular afterload was quantified by end-systolic circumferential wall stress as previously described[10]:

$$\text{End-systolic circumferential wall stress} = \text{LV peak pressure} \times a^2 \times \left(\frac{1+b^2}{c^2}\right) \times \frac{1}{(b^2-a^2)}$$

where LV peak pressure = systolic blood pressure + peak AS gradient, a = (LV end-systolic dimension/2), b = (LV end-systolic dimension/2) + (end-systolic posterior wall thickness), and c = (LV end-systolic dimension/2) + (end-systolic posterior wall thickness/2).

Definitions of aortic sclerosis and stenosis were based on recommendations by the European Association of Echocardiography and American Society of Echocardiography.[5] Aortic stenosis aetiologies were defined as congenital, rheumatic, or degenerative as previously published.[5,11] Classifications of AS severity were based on AVA peak velocity and mean gradient. AVA was calculated by the continuity equation using velocity time integrals of the aorta and LV outflow tract.[5] Peak and mean aortic transvalvular gradients were calculated using the modified Bernoulli equation.

Mitral inflow velocities were recorded using conventional pulsed-wave Doppler echocardiography in the apical four-chamber view using a 2 mm sample volume. Transmitral early (E-wave) and late (A-wave) diastolic velocities as well as deceleration time were recorded at the mitral leaflet tips.

Two-dimensional speckle tracking

Two-dimensional speckle tracking analyses were performed on grey scale images of the LV obtained in the apical two-, three-, and four-chamber views, and short-axis mid-ventricular views. As the LV myocardial architecture consists of longitudinally and circumferentially orientated fibres located predominately in the epicardium/endocardium and mid-wall, respectively, longitudinal, circumferential, and radial strain/SR are reflective of subendocardial, mid-wall, and transmural myocardial functions, respectively.[2] Left ventricular radial and circumferential functions were determined in the mid-ventricular short-axis view, and longitudinal function was determined in the three apical views. During analysis, the endocardial border was manually traced at end-systole and the width of the region of interest adjusted to include the entire myocardium. The software then automatically tracks and accepts segments of good tracking quality and rejects poorly tracked segments, while allowing the observer to manually override its decisions based on visual assessments of tracking quality. Peak strain and SR for the three orthogonal myocardial functions were determined. Mean global longitudinal strain/SR were calculated from the three individual apical global longitudinal strain/SR curves, respectively, whereas mean global circumferential strain/SR and mean radial strain/SR were obtained from the mid-ventricular short-axis view. All strain and SR measurements were exported to a spreadsheet (Microsoft® Excel 2002, Microsoft Corporation, Redmond, WA, USA).

Variability analysis

Previous work has reported the intra- and inter-observer variabilities in our laboratory as expressed by the mean absolute difference for longitudinal strain (1.2 ± 0.5 and $0.9 \pm 1.0\%$) and SR (0.10 ± 0.06 and $0.09 \pm 0.08\ s^{-1}$), circumferential strain (1.2 ± 1.0 and $2.3 \pm 2.4\%$) and SR (0.08 ± 0.08 and $0.16 \pm 0.09\ s^{-1}$), and radial strain

Table 1 Clinical characteristics of the total population and according to severity of aortic stenosis

Variable	Total population ($n = 420$)	Aortic sclerosis ($n = 118$)	Mild aortic stenosis ($n = 81$)	Moderate aortic stenosis ($n = 109$)	Severe aortic stenosis ($n = 112$)	*P*-value*
Demographic characteristics						
Age, (years)	66.1 ± 14.5	60.8 ± 14.9	67.6 ± 14.2	66.5 ± 15.0	70.2 ± 12.0	<0.001
Male gender, (%)	60.7	59.3	69.1	61.5	55.4	0.28
Body mass index, (kg/m^2)	26.0 ± 4.3	26.0 ± 3.7	25.9 ± 3.8	26.8 ± 5.5	25.3 ± 3.9	0.10
Body surface area, (m^2)	1.90 ± 0.21	1.90 ± 0.21	1.92 ± 0.21	1.92 ± 0.21	1.85 ± 0.19	0.065
Medical history						
New York Heart Association class, (%)						
I	71.1	94.1	81.0	59.6	50.5	<0.001
II	18.1	5.1	10.1	26.6	29.4	
III	10.8	0.8	8.9	13.8	20.1	
IV	0	0	0	0	0	
Hypertension, (%)	51.1	50.8	44.3	56.0	51.4	0.48
Diabetes, (%)	16.4	17.8	13.9	17.4	15.6	0.88
Hyperlipidaemia, (%)	29.0	28.8	20.3	27.5	37.0	0.092
Current smoker, (%)	16.2	16.9	12.8	20.2	13.9	0.44
Systolic blood pressure, (mmHg)	147 ± 26	145 ± 24	146 ± 26	150 ± 28	146 ± 27	0.51
Diastolic blood pressure, (mmHg)	81 ± 12	80 ± 11	81 ± 12	82 ± 12	79 ± 14	0.59
Medications						
β-blocker, (%)	37.2	30.8	34.2	42.2	41.3	0.23
ACE-inhibitor/ARB, (%)	38.9	35.0	32.9	46.8	39.4	0.19
Diuretic, (%)	23.5	17.2	20.3	32.1	23.9	0.58
Statins, (%)	39.6	33.3	34.2	41.3	48.6	0.081

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
*P-value by ANOVA for continuous variables and by χ^2 test for categorical variables.

(4.3 ± 2.3 and 6.5 ± 5.4%) and SR (0.27 ± 0.18 and 0.34 ± 0.24 s^{-1}), respectively.[12]

Statistical analysis

All continuous variables were tested and confirmed to be of Gaussian distribution as determined by the Kolmogorov–Smirnov test and presented as mean ± 1 SD. Categorical variables were presented as frequencies and percentages, and were compared using the χ^2 test. The independent *t*-test was used to compare two groups of continuous data, whereas one-way analysis of variance (ANOVA) was used to compare more than three groups of continuous variables of Gaussian distribution. Post hoc analyses for significant results were performed using Bonferroni correction. Multiple linear regression analyses were then performed to identify independent clinical and echocardiographic determinants of longitudinal, circumferential, and radial strain and SR. To build the multivariable models, end-systolic circumferential wall stress was first entered as the first block, followed by AVA as the second block, and finally age, gender, heart rate, LV mass index, LVESVI, and left atrial volume index entered as the third block. To avoid multicolinearity between the univariate predictors, a tolerance of >0.5 was set. A two-tailed *P*-value of <0.05 was considered significant. All statistical analyses were performed using SPSS for Windows (SPSS Inc., Chicago), version 17.

Results

A total of 420 patients were evaluated. *Table 1* summarizes the clinical and echocardiographic characteristics of the patients. It was found that 118 (28.0%), 81 (19.3%), 109 (26.0%), and 112 (26.7%) patients had aortic sclerosis, mild stenosis, moderate stenosis, and severe stenosis, respectively. A total of 45 (10.7%) patients had bicuspid aortic valves. The mechanisms underlying AS were degenerative in 91.9%, congenital in 6.2%, rheumatic in 1.0%, and uncertain in 1.0%. Patients were more likely to be older ($P < 0.001$) and at a worse New York Heart Association functional class ($P < 0.001$) with increasing AS severity. However, there were no significant differences in the prevalence of cardiac risk factors and usage of cardiac medication between the four groups of patients. No patients had evidence of wall motion abnormalities on echocardiography by virtue of the exclusion criteria.

Echocardiography

Table 2 summarizes the echocardiographic characteristics of the patients. The mean LVEDVI, LVESVI, and LVEF were 47.5 ± 13.2 mL/m^2, 18.6 ± 6.4 mL/m^2, and 61.1 ± 6.0%, respectively.

Table 2 Echocardiographic characteristics of the total population and according to severity of aortic stenosis

Variable	Total population ($n = 420$)	Aortic sclerosis ($n = 118$)	Mild aortic stenosis ($n = 81$)	Moderate aortic stenosis ($n = 109$)	Severe aortic stenosis ($n = 112$)	*P*-value*
Heart rate (b.p.m.)	72 ± 13	69 ± 12	74 ± 14	73 ± 13	73 ± 12	0.035
AVA (cm^2)	1.58 ± 0.74	2.41 ± 0.67	1.81 ± 0.33†	1.30 ± 0.24†	0.81 ± 0.19†	<0.001
Mean gradient (mmHg)	22.9 ± 18.0	7.9 ± 4.5	12.4 ± 5.0†	22.6 ± 7.5†	46.7 ± 15.5†	<0.001
Peak gradient (mmHg)	37.9 ± 28.6	13.9 ± 7.4	21.1 ± 7.7†	37.6 ± 11.4†	75.4 ± 25.1†	<0.001
LV mass index (g/m^2)	113.0 ± 27.1	105.4 ± 20.9	107.5 ± 21.1	110.8 ± 26.3	127.9 ± 32.2†	<0.001
LVEDVI (mL/m^2)	47.5 ± 13.2	47.2 ± 12.7	46.3 ± 11.2	47.6 ± 14.6	48.5 ± 13.4	0.71
LVESVI (mL/m^2)	18.6 ± 6.4	18.2 ± 6.2	19.1 ± 5.5	18.2 ± 6.9	19.2 ± 6.5	0.54
LVEF (%)	61.0 ± 6.0	61.7 ± 5.8	58.9 ± 5.8	62.0 ± 6.1	60.8 ± 5.8	0.003
LV end-systolic circumferential wall stress ($kdyne/cm^2$)	184.2 ± 54.6	168.2 ± 49.4	174.2 ± 44.2	182.3 ± 49.2	210.4 ± 62.5†	<0.001
Transmitral E/A ratio	0.96 ± 0.47	1.00 ± 0.31	0.83 ± 0.33	1.03 ± 0.55†	0.95 ± 0.59	0.024
Transmitral deceleration time (ms)	241.3 ± 78.9	231.6 ± 60.6	251.6 ± 95.4	230.4 ± 74.1	255.2 ± 84.8	0.038
Maximal left atrial volume index (mL/m^2)	33.8 ± 13.5	32.8 ± 11.0	31.2 ± 12.8	32.4 ± 13.7	38.4 ± 15.5†	0.003
Multidirectional myocardial function						
Longitudinal strain (%)	−17.7 ± 2.8	−20.3 ± 1.9	−18.0 ± 1.7†	−17.1 ± 2.0†	−15.1 ± 2.4†	<0.001
Longitudinal SR (s^{-1})	−0.92 ± 0.19	−1.05 ± 0.15	−0.96 ± 0.16†	−0.89 ± 0.16†	−0.77 ± 0.16†	<0.001
Circumferential strain (%)	−20.1 ± 3.9	−22.2 ± 3.3	−21.1 ± 3.7	−19.7 ± 3.3†	−17.9 ± 4.0†	<0.001
Circumferential SR (s^{-1})	−1.15 ± 0.28	−1.29 ± 0.30	−1.23 ± 0.31	−1.13 ± 0.21†	−0.98 ± 0.21†	<0.001
Radial strain (%)	47.8 ± 15.9	53.7 ± 14.8	50.3 ± 17.5	47.4 ± 13.2	41.1 ± 15.7†	<0.001
Radial SR (s^{-1})	1.89 ± 0.52	1.97 ± 0.54	2.03 ± 0.61	1.94 ± 0.51	1.69 ± 0.40†	<0.001

AVA, aortic valve area; LV, left ventricular; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; EF, ejection fraction; SR, strain rate.
**P*-value by ANOVA.
†$P < 0.05$ vs. preceding aortic stenosis category with Bonferroni correction.

Patients with severe AS had significantly higher LV mass index ($P < 0.001$) and end-systolic circumferential wall stress ($P < 0.001$) compared with patients with lesser degrees of AS. However, LV volumes and LVEF did not significantly change with increasing AS severity. Similarly, there were no significant differences in transmitral diastolic E/A ratio and deceleration time with increasing AS severity. However, patients with severe AS had significantly larger maximal left atrial indexed volume compared with others.

Changes in multidirectional myocardial function with increasing aortic stenosis severity

Table 2 summarizes the changes in multidirectional myocardial function with increasing AS severity. One-way ANOVA showed significantly greater impairment of longitudinal myocardial function with increasing AS severity ($P < 0.001$). Post hoc analysis with Bonferroni correction demonstrated that with each categorical increase in the grade of AS severity from sclerosis to severe stenosis, there was an associated progressive impairment of longitudinal strain and SR (*Figure 1*).

Similarly, circumferential strain and SR progressively declined with increasing AS severity ($P < 0.001$, *Table 2*). Post hoc analysis showed that there was no significant difference in LV circumferential functions between aortic sclerosis and mild AS. However, circumferential strain and SR progressively worsened from moderate to severe AS (*Figure 2*).

Finally, there was a significant difference in radial strain and SR with increasing AS severity ($P < 0.001$). Post hoc analysis showed that radial strain and SR were only impaired in the presence of severe AS (*Table 2* and *Figure 3*).

Figures 1–3 demonstrate a progressive stepwise impairment in longitudinal, circumferential, and radial myocardial functions with increasing AS severity. As multidirectional strain and SR analyses reflect regional functions at different layers of the myocardium, *Figures 1–3* show that myocardial dysfunction appears to start from the subendocardium with mild AS, progresses to mid-wall impairment with moderate AS, and eventually transmural impairment with severe AS.

Independent associations of multidirectional myocardial function

To identify independent associations of multidirectional myocardial strain and SR, end-systolic circumferential wall stress was first entered as the first block, followed by the AVA as the second block, and finally age, gender, heart rate, LV mass index, LVESVI,

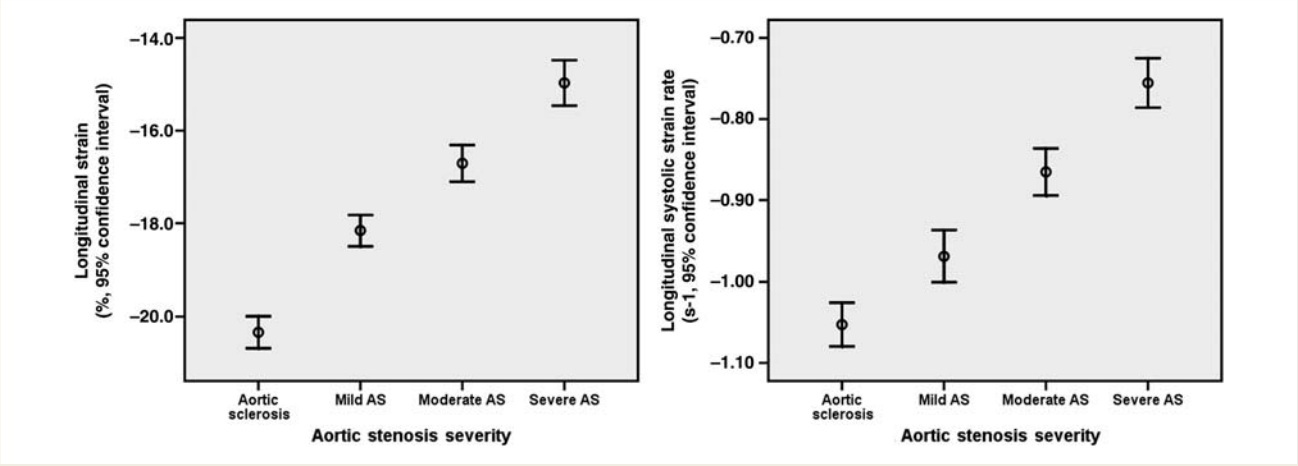

Figure 1 Impairment of left ventricular longitudinal strain and systolic strain rate with increasing aortic stenosis severity ($P < 0.001$ by ANOVA). Left ventricular longitudinal function progressively decline from mild to severe aortic stenosis. Post hoc analysis with Bonferroni correction showed that with each categorical increase in aortic stenosis severity grade from sclerosis to severe stenosis, there was an associated progressive impairment of longitudinal strain and strain rate (all $P < 0.05$).

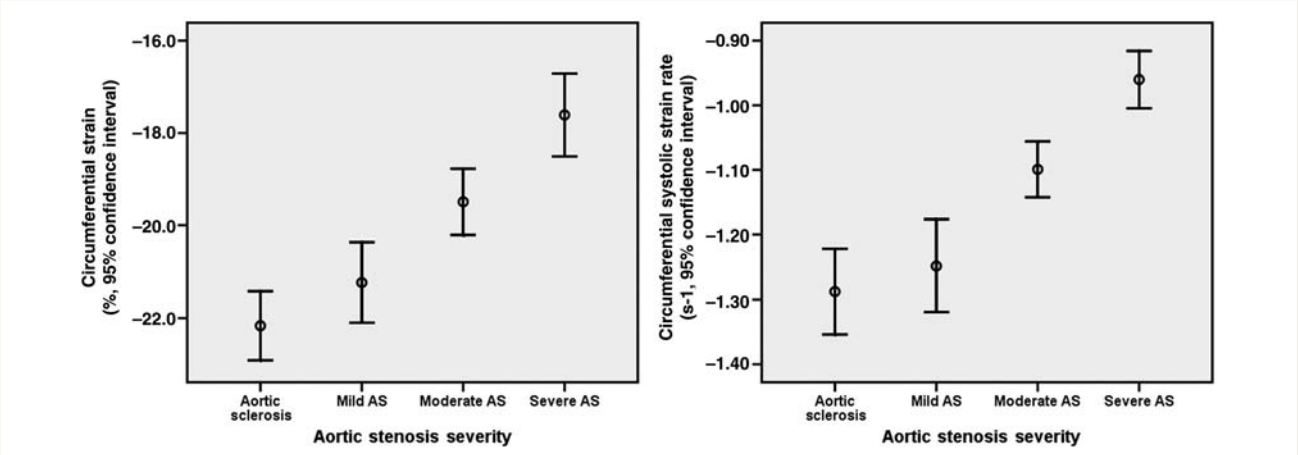

Figure 2 Impairment of left ventricular circumferential strain and systolic strain rate with increasing aortic stenosis severity ($P < 0.001$ by ANOVA). Post hoc analysis with Bonferroni correction showed that there was no significant difference in left ventricular circumferential strain/strain rate between sclerosis and mild stenosis, but progressively worsened from mild to moderate ($P < 0.05$), and from moderate to severe aortic stenosis ($P < 0.05$).

and left atrial volume index entered as the third block into the multiple linear regression models. Blood pressure and aortic transvalvular gradients were not included in the multivariate models due to significant colinearity with end-systolic circumferential wall stress (which is a measure of LV afterload). *Table 3* showed that the AVA was independently associated with an impaired LV longitudinal, circumferential, and radial strain and SR, even after correcting for age, gender, heart rate, LV mass index, LVESVI, left atrial volume index, and LV afterload by end-systolic circumferential wall stress.

As asymptomatic AS patients constitute a population of interest, all multivariate analyses were repeated whereby only asymptomatic AS patients were selected ($n = 295$). Similarly, the AVA was independently associated with impaired LV longitudinal strain ($\beta = -0.488$, $P < 0.001$) and SR ($\beta = -0.440$, $P < 0.001$), circumferential strain ($\beta = -0.267$, $P = 0.001$) and SR ($\beta = -0.290$, $P < 0.001$), despite correcting for age, gender, heart rate, LV mass index, LVESVI, left atrial volume index, and LV end-systolic circumferential wall stress.

Comparisons between symptomatic and asymptomatic patients

A total of 58.7% of moderate and severe AS patients were symptomatic at baseline. Compared with asymptomatic patients, symptomatic patients had more impaired longitudinal strain (-15.7 ± 2.5 vs. $-16.8 \pm 2.2\%$, $P = 0.001$), longitudinal SR (-0.80 ± 0.16

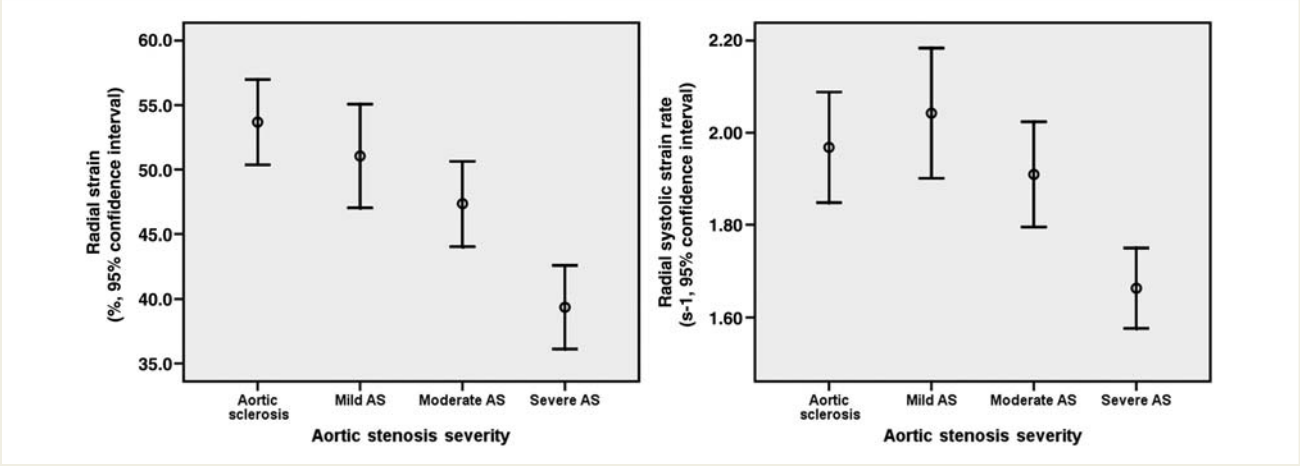

Figure 3 Impairment of left ventricular radial strain and systolic strain rate with increasing aortic stenosis severity ($P < 0.001$ by ANOVA). Post hoc analysis with Bonferroni correction suggested no significant differences in radial strain/strain rate between aortic sclerosis, mild and moderate aortic stenosis. However, radial strain and strain rate were significantly impaired in the presence of severe aortic stenosis ($P < 0.05$).

Table 3 Univariate and multivariate linear regression models for multidirectional myocardial functions in patients with aortic stenosis

Variable	Univariate		Multivariate		Univariate		Multivariate	
	β	*P*-value	*β*	*P*-value	*β*	*P*-value	*β*	*P*-value
	Longitudinal strain				Longitudinal systolic strain rate			
LV wall stress	0.281	<0.001	0.043	0.30	0.369	<0.001	0.122	0.007
AVA	−0.613	<0.001	−0.527	<0.001	−0.537	<0.001	−0.502	<0.001
Age	0.239	<0.001	0.104	0.015	0.148	0.002	0.062	0.17
Gender	0.078	0.11	0.120	0.004	−0.010	0.83	−0.021	0.63
Heart rate	0.163	0.001	0.126	0.001	−0.199	<0.001	−0.169	<0.001
LV mass index	0.437	<0.001	0.262	<0.001	0.328	<0.001	0.115	0.022
LVESVI	0.153	0.002	0.038	0.42	0.276	<0.001	0.155	0.002
Left atrial volume index	0.154	0.004	−0.039	0.37	0.170	0.001	−0.007	0.89
	Circumferential strain				Circumferential systolic strain rate			
LV wall stress	0.211	<0.001	0.035	0.58	0.307	<0.001	0.105	0.081
AVA	−0.401	<0.001	−0.308	<0.001	−0.431	<0.001	−0.370	<0.001
Age	0.081	0.16	0.022	0.73	0.068	0.24	0.011	0.86
Gender	0.022	0.70	−0.004	0.95	−0.004	0.95	−0.034	0.57
Heart rate	0.215	<0.001	0.194	0.001	−0.156	0.007	−0.140	0.013
LV mass index	0.226	<0.001	0.145	0.044	0.261	<0.001	0.115	0.10
LVESVI	0.123	0.037	0.104	0.13	0.253	<0.001	0.161	0.015
Left atrial volume index	0.023	0.71	−0.099	0.14	0.134	0.033	−0.019	0.77
	Radial strain				Radial systolic strain rate			
LV wall stress	−0.081	0.16	−0.007	0.92	−0.073	0.21	0.064	0.32
AVA	0.264	<0.001	0.142	0.042	0.223	<0.001	0.190	0.005
Age	−0.141	0.015	−0.101	0.13	0.007	0.90	0.017	0.79
Gender	0.026	0.65	0.009	0.89	0.033	0.57	0.043	0.51
Heart rate	−0.118	0.041	−0.105	0.09	0.233	<0.001	0.211	0.001
LV mass index	−0.228	<0.001	−0.181	0.019	−0.244	<0.001	−0.154	0.040
LVESVI	−0.076	0.20	−0.057	0.44	−0.204	<0.001	−0.132	0.06
Left atrial volume index	−0.075	0.23	0.050	0.48	−0.175	0.005	−0.049	0.47

BP, blood pressure; LV, left ventricular; ESVI, end-systolic volume index; AVA, aortic valve area.

vs. $-0.87 \pm 0.18\ s^{-1}$, $P = 0.002$), circumferential strain (-18.3 ± 3.8 vs. $-19.4 \pm 3.7\%$, $P = 0.09$), circumferential SR (-1.02 ± 0.20 vs. $-1.10 \pm 0.24\ s^{-1}$, $P = 0.016$), radial strain (41.5 ± 13.9 vs. $48.4 \pm 15.4\%$, $P = 0.003$), and radial SR (1.73 ± 0.40 vs. $1.94 \pm 0.53\ s^{-1}$, $P = 0.007$).

Discussion

The present analyses demonstrated that LV myocardial function was impaired in the presence of AS despite preservation of the LVEF. Furthermore, there was progressive multidirectional impairment of myocardial strain and the SR with increasing AS severity, starting from subendocardial dysfunction with mild AS, to mid-wall dysfunction with moderate AS, and eventually transmural dysfunction with severe AS. The AVA, as a measure of AS severity, was independently associated with impaired multidirectional LV myocardial strain and SR. Finally, symptomatic moderate and severe AS patients had more impaired multidirectional strain/SR compared with asymptomatic patients.

Pathophysiology of left ventricular dysfunction in patients with aortic stenosis

Left ventricular outflow obstruction secondary to AS often progresses slowly over a period of years. During this period of chronic pressure overload, the LV adapts by replicating sarcomeres in parallel and thereby increasing wall thickness with development of concentric hypertrophy. Early in the course of the disease, this concentric hypertrophy is adaptive as the increase in LV wall thickness with maintenance of normal chamber volume is enough to counterbalance the increased LV pressures and thus preserves LVEF.[1,13] However, chronic pressure overload may eventually lead to a depressed LVEF in some patients either due to 'afterload mismatch' or from true depression of myocardial contractility. Normally, there is an inverse relationship between LV systolic wall stress and the LVEF.[14] Afterload mismatch occurs in the context of inadequate 'compensatory' ventricular hypertrophy in response to elevated ventricular pressures, thereby resulting in increased wall stress and consequently a reduced LVEF. However, patients may also develop a true depression in myocardial contractility due to alterations in myocardial perfusion, ischaemia, and fibrosis. Previous studies on patients with AS and normal coronary arteries showed reduced coronary flow reserve and thus a diminished myocardial oxygenation.[15,16] Furthermore, myocardial oxygen consumption in patients with AS is increased due to an increased LV muscle mass, elevated systolic pressures, and prolonged ejection period. This imbalance between reduced coronary perfusion and increased oxygen consumption results in subendocardial hypoperfusion and ischaemia.[16] Consequently, myocardial fibrosis in patients with severe AS often begins in the subendocardium,[3,4] and corrective surgery may be less beneficial in patients with impaired myocardial contractility compared with patients with a depressed LVEF due to afterload mismatch.[17]

Changes in multidirectional myocardial function in patients with aortic stenosis

Despite its widespread clinical utility as a measure of LV systolic function, the LVEF is relatively insensitive in identifying subclinical myocardial dysfunction. In patients with AS, application of the LVEF as a surrogate marker of myocardial contractility may potentially lead to misinterpretations of the pathophysiology of the underlying myocardial dysfunction. An impaired LVEF could be secondary to afterload mismatch while the underlying myocardial contractility is still normal.[14] Conversely, patients with concentric LV hypertrophy can have a normal LVEF but impaired myocardial contractility. In these patients, despite abnormal sarcomere shortening, the physical presence of a greater number of sarcomeres laid down in parallel results in preserved myocardial thickening and LVEF. Thus, the presence of myocardial contractile dysfunction can be masked by a normal LVEF.[18] In the present evaluation, all patients had a preserved LVEF by virtue of the inclusion criteria. However, strain and SR imaging demonstrated impaired myocardial contractility despite a normal LVEF.

To examine if impaired multidirectional strain and SR were solely due to an increased afterload or represented a true depression of myocardial contractility, LV afterload was quantified by end-systolic circumferential wall stress. As expected, patients with severe AS had significantly higher wall stress compared with patients with less severe AS. However, the AVA was still an independent determinant of multidirectional myocardial functions despite after correcting for LV afterload on multivariable analysis. Similarly, differences in baseline clinical and echocardiographic characteristics could have potentially confounded the present results. For example, patients with severe AS were significantly older on univariate analysis. However, the AVA continues to be an independent determinant of multidirectional myocardial functions after adjusting for differences in baseline characteristics such as age. Furthermore, previous studies on normal healthy subjects have demonstrated that myocardial strain and systolic SR by 2D speckle tracking echocardiography do not significantly change with increasing age.[19] Thus, the observed impairment in multidirectional myocardial functions likely represents a true depression of myocardial contractility not solely explained by an increased afterload with increasing AS severity or differences in baseline patient characteristics. Importantly, symptomatic moderate and severe AS patients had significantly more impaired multidirectional myocardial functions compared with asymptomatic patients.

Although previous studies have reported impaired longitudinal myocardial function in patients with AS,[20–22] few have examined changes in all three multidirectional myocardial functions with increasing AS severity. As the LV myocardial fibre architecture is a complex array of longitudinally and circumferentially orientated fibres located predominately in the epicardium/endocardium and mid-wall, respectively,[2] their functional changes in relation to increasing AS severity could be quantified by multidirectional myocardial strain and SR analyses. A recent animal study observed an earlier impairment of longitudinal function with relatively preserved radial function in a pig model of acute pressure overload.[23] Similarly, the present analyses demonstrated the presence of subtle myocardial dysfunction that occurred early in the disease process

as reflected by an impaired longitudinal strain and SR. Moreover, analyses of multidirectional strain and the SR suggested a progressive subendocardial to transmural impairment of myocardial function with increasing AS severity and chronic pressure overload.

A recent publication from our group assessed multidirectional strain and the SR in severe AS patients before and after aortic valve replacement surgery.[24] Delgado *et al.*[24] demonstrated that severe AS patients with a normal LVEF had significantly more impaired longitudinal, circumferential, and radial functions compared with normal controls. Importantly, although circumferential and radial functions returned to normal after aortic valve replacement surgery, longitudinal strain and the SR failed to normalize compared with normal controls. The results suggested persistent subendocardial dysfunction at long-term follow-up. In contrast, Rost *et al.*[25] demonstrated improvements in multidirectional strain 6 months after aortic valve replacement. However, the study was limited by a smaller number of patients ($n = 33$), and a lack of control group.

Clinical implications

Patients with mild and moderate AS are normally years away from requiring aortic valve replacement surgery. However, patients can demonstrate evidence of myocardial dysfunction that starts long before the need for surgery. Weidemann *et al.*[4] recently assessed myocardial functions and fibrosis in patients with severe AS. The study demonstrated evidence of progressively greater impairment of longitudinal function with increasing degrees of myocardial fibrosis. In addition, myocardial fibrosis persisted at 9 months follow-up after aortic valve replacement. Similarly, Delgado *et al.*[24] demonstrated persistent subendocardial dysfunction after aortic valve replacement surgery in severe AS patients with a normal LVEF. Therefore, earlier detection of subclinical myocardial dysfunction by speckle tracking echocardiography may permit earlier identification of patients at risk of irreversible myocardial damage.

Similarly, patients with asymptomatic AS constitute a special population of interest. Subgroup analyses showed that the AVA was still an independent determinant of impaired myocardial function despite correcting for baseline age, gender, heart rate, LV mass index, LVESVI, and LV afterload in this patient population. Recently, Lancellotti *et al.*[26] evaluated multidirectional strain in 173 asymptomatic severe AS patients. Patients with high global LV afterload and/or low-flow AS had significantly lower multidirectional strain compared with their counterparts. However, the study did not evaluate multidirectional strain in mild or moderate AS patients, and independent determinants of impaired multidirectional strain were not identified.[26] Thus, the potential prognostic value of multidirectional strain/SR analyses needs to be examined in future studies.

Study limitations

Although the present cross-sectional observational analyses described the changes in multidirectional myocardial function in patients with increasing AS severity, we did not assess their long-term prognostic implications such as time to symptom onset and post-operative survival. Thus, long-term prognostic studies will be needed to determine the survival outcome of patients with severe AS who have reduced transmural function vs. only subendocardial dysfunction. This may have significant implications for the optimal timing of aortic valve surgery. Similarly, the contributory role of myocardial fibrosis causing impaired myocardial function was also not examined. In addition, although patients with a history of myocardial infarction and the presence of regional wall motion abnormalities were excluded, the presence of undiagnosed significant underlying coronary artery disease could have influenced strain and SR measurements.

Conclusions

Patients with AS have evidence of subclinical myocardial dysfunction early in the disease process despite a normal LVEF. Furthermore, there was a progressive subendocardial to transmural impairment of myocardial function with increasing AS severity. Symptomatic moderate and severe AS patients had more impaired multidirectional myocardial functions compared with asymptomatic patients.

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