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Assessment of left ventricle function in patients with symptomatic and asymptomatic aortic stenosis by 2-dimensional speckle-tracking imaging

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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Summary

Background:

Global longitudinal peak strain (GLPS) quantifies left ventricle (LV) long-axis contractility. Early detection of LV systolic dysfunction is pivotal in diagnosis and treatment of patients with aortic stenosis (AS). This study was performed to assess LV longitudinal systolic function by GLPS derived from 2-dimensional speckle tracking imaging (2D-STI) in AS patients in comparison to standard echocardiographic parameters.

Material/Methods:

Laboratory tests, standard echocardiography, tissue Doppler imaging (TDI) and 2D-STI examinations with GLPS calculation were performed in 49 consecutive patients with moderate to severe AS with LV ejection fraction $\geq 50\%$ and 18 controls.

Results:

While LVEF do not differentiate AS patients from controls, GLPS was significantly decreased in the AS group ($-15.30 \pm 3.25\%$ vs. $-19.60 \pm 2.46\%$ in controls, $p < 0.001$). GLPS was significantly reduced in symptomatic AS patients as compared to the asymptomatic AS group [-15.5 (11.8–16.8) vs. -17.5 (14.7–18.9)%, $p = 0.02$].

Conclusions:

In aortic stenosis patients, despite normal left ventricle ejection fraction, long-axis left ventricular function is impaired, which manifests in global longitudinal peak strain reduction. GLPS reveals that LV function impairment is more pronounced in symptomatic as compared to asymptomatic AS patients. Further studies are needed to determine the prognostic significance of early LV function impairment in aortic stenosis patients showed by GLPS.

key words:

aortic stenosis • speckle tracking echocardiography • global longitudinal peak strain • left ventricle function

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BACKGROUND

Aortic stenosis (AS) is the most common acquired heart defect, present in 2% of people over 75 years old and in 8% of those over 85 years old [1,2]. Patients with AS remain asymptomatic over a long period [3,4]. The prognosis in the asymptomatic AS period is much better than in the symptomatic, but there is still a 1% risk of sudden cardiac death despite the lack of symptoms [3,4]. Deterioration of left ventricle (LV) systolic function is a predictor of poor outcome after aortic valve replacement (AVR) [5]. However, the traditional method commonly used to assess LV systolic function – the ejection fraction (EF) – seems to lack sufficient precision. The myocardial strain and strain-rate analysis is an echocardiographic technique that enables the detection of mild LV systolic dysfunction. Non-Doppler 2-dimensional speckle tracking imaging (2D-STI) is an angle-independent method showing the deformation of LV muscle in 3 directions: longitudinal, circumferential and radial [6–8].

According to the guidelines, patients with symptomatic severe AS should be scheduled for AVR. Asymptomatic patients with severe AS should be treated surgically when left ventricle systolic function is impaired (LVEF <50%) or there is an abnormal exercise test result revealing symptoms (indications in IC class) [9]. However, LVEF can be preserved in AS for a long time, in spite of the deterioration of LV systolic function. Thus, more sensitive methods should be used for the assessment of LV function.

This study was performed to assess LV longitudinal systolic function by means of global longitudinal peak strain (GLPS) examination in AS patients compared to standard echocardiographic parameters.

MATERIAL AND METHODS

Patients

This study was performed in 49 consecutive patients with moderate or severe AS, admitted to the Cardiac and Vascular Diseases Department, Jagiellonian University Medical College, Cracow, Poland. Moderate AS was defined as aortic valve area (AVA) 1.0–1.5 cm², and severe AS as AVA <1.0 cm². The control group consisted of 18 patients referred to our Department. Exclusion criteria for study group and control group were as follows: unstable coronary artery disease (CAD), impaired left ventricular systolic function defined as LVEF <50%, regional LV wall motion abnormalities, concomitant moderate or severe valvular disease, atrial fibrillation, and severe chronic renal or hepatic injury.

All patients underwent routine physical examination, blood analysis and transthoracic echocardiography. Medical histories were taken, including the presence of AS symptoms (chest pain, dyspnea, syncope). The study was performed in accordance with the actual version of the Helsinki Declaration. All patients gave their informed consent for participation in the study.

Echocardiography

Echocardiographic examinations were performed using Vivid Seven GE Medical Systems equipment (Horton,

Norway). Offline analysis was performed on the EchoPAC version 108.1.12 (GE Healthcare). Standard measurements were made in parasternal long and short axes, as well as in 4- and 5-chamber apical views. LV end-systolic, end-diastolic volume and ejection fraction were measured by the modified bi-plane Simpson method, and LV mass was calculated using the ASE formula [10]. The mean and the peak trans-aortic gradients were measured by continuous wave Doppler method. Aortic valve opening area (AVA) was calculated using the standard continuity equation [11]. LV mass, left atrial volume and AVA were indexed to body surface area. Peak early velocity of mitral inflow (E) was obtained using the pulsed-wave Doppler method. Peak systolic (S') and peak early diastolic (E') mitral annular velocities were measured at the lateral side of the mitral annulus by means of pulsed wave tissue Doppler imaging (TDI). E/E' ratio was calculated. LV longitudinal strain was measured using 2-D speckle tracking imaging and automated function imaging (AFI) application. The ECG-gated images were obtained in apical long-axis, 4- and 2-chamber views at the frame rate of 60–70 per second, stored digitally and analyzed offline. The endocardial border of the myocardium was automatically traced and corrected manually, if needed. Segmental strains were determined offline and presented as a bullseye map. GLPS was automatically calculated as the mean value obtained from 17 segments (Figure 1).

Statistical analysis

Statistical analysis was performed using STATISTICA 9.0 software. The Shapiro-Wilk test was used to determine normal distribution. Continuous variables are shown as mean ± standard deviation (SD) or interquartile range [IQR]. Categorical variables are presented as number of patients and percentage. Comparisons between the groups were made by t-test for continuous variables and χ^2 test for categorical variables. The Spearman correlation was used to examine linear correlation between the numerical variables. The value of $p < 0.05$ was considered statistically significant.

RESULTS

The demographic and clinical characteristics of aortic stenosis patients and control subjects are shown in Table 1.

By definition, AS patients had higher peak and mean transvalvular pressure gradients, with lower AVA and AVAI as compared to controls. Left ventricle mass and mass index were higher in AS patients as compared to controls (Table 2). Interestingly, although the LV ejection fraction did not significantly differ between groups, the GLPS was reduced in AS patients ($-15.30 \pm 3.25\%$ vs. $-19.60 \pm 2.46\%$, $p < 0.001$). Moreover, S' and E' velocities were reduced in the AS group, with E/E' ratio increased in AS patients (Table 2). Figure 1 shows an example of normal GLPS recorded in a control subject and reduced GLPS obtained in an aortic stenosis patient.

Among AS patients, 29 were symptomatic and 19 asymptomatic. The symptoms of 1 patient were not typical for AS, and he was excluded from the analysis. Subgroups did not differ significantly with regard to their demographics or clinical status, despite AS symptoms (Table 3).

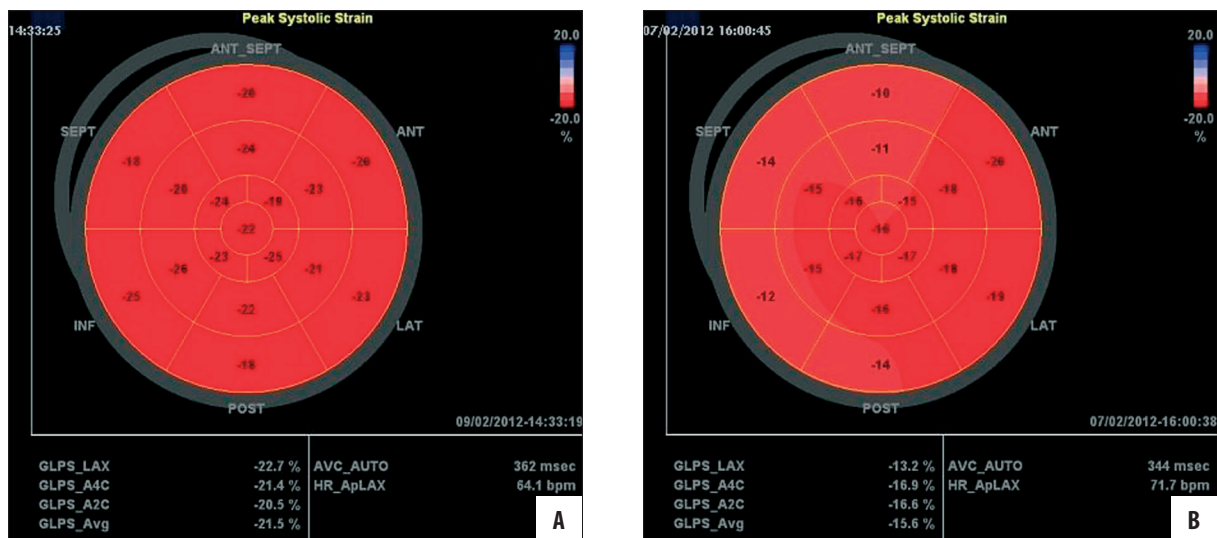


Figure 1. Segmental strain and average global longitudinal peak strain (GLPS_Avg) in a 17-segmental model presented as a “bull-eye” in control group subject (A) and in a symptomatic aortic stenosis patient (B).

Table 1. Demographic and clinical characteristics of the patients with aortic stenosis and in control subjects.

	Patients with aortic stenosis (n=49)		Control group (n=18)		p
Age (years)	68	(60–78)	52	(31–63)	<0.001
Males, n (%)	28	(57)	8	(44)	0.36
Smoking, n (%)	7	(14)	6	(35)	0.06
Hypertension, n (%)	38	(78)	6	(35)	<0.01
Diabetes, n (%)	11	(22)	3	(18)	0.94
Coronary artery disease, n (%)	20	(41)	5	(29)	0.40

Symptomatic patients had significantly higher transvalvular peak and mean pressure gradients and a lower aortic valve area. Importantly, GLPS and E' velocity were significantly lower in the symptomatic patients as compared to the asymptomatic group [-15.5 (11.8–16.8) vs. -17.5 (14.7–18.9)%, p=0.02 and 0.06 (0.04–0.08) vs. 0.08 (0.06–0.11) m/s, p=0.02, respectively]. S' velocity was insignificantly lower in the symptomatic subgroup (Table 4). Left ventricle ejection fraction, LV volumes and masses did not differ between symptomatic and asymptomatic patients.

While there was no correlation between GLPS and left ventricle ejection fraction, GLPS correlated positively with S' and E' velocities (r=0.41, p=0.004 in both cases).

DISCUSSION

We demonstrated that LV long-axis systolic function is impaired in AS patients despite normal left ventricle ejection fraction. Aortic stenosis leads, as an adaptation to the long period of chronic pressure overload, to LV concentric hypertrophy [1,2,12]. However, increased myocardial mass results in a higher request for oxygen. Marcus et al. found decreased coronary reserve in AS subjects [13]. The disproportion between the request and the supply of the oxygen leads to ischemia and fibrosis. The most affected region

of the myocardium is the subendocardial layer, where longitudinally directed fibres dominate. Interstitial fibrosis is one of the mechanisms of LV diastolic dysfunction [14]. Weidemann et al. [15] demonstrated reduction of the longitudinal strain in patients with advanced fibrosis. This may be an important factor worsening the outcome of patients after aortic valve replacement.

2D-STI is a new modality that enables quantification of myocardial deformation. The most important advantage of this technique compared to TDI is its angle independency. It enables offline measurements of the longitudinal, radial and circumferential strain and strain rate [6–8]. Because of the high sensitivity of this method, it is used to detect mild LV function abnormalities. It was shown that segmental and global longitudinal strain is decreased in coronary artery disease [16], hypertrophic cardiomyopathy [17] and dilated cardiomyopathy [18].

The Doppler-derived analysis of the segmental longitudinal, radial and circumferential strain is time consuming and requires advanced medical staff. In contrast, GLPS is an easy to obtain parameter that may be helpful in everyday clinical practice. Marwick et al. [19] examined 250 healthy volunteers (44% men, age 51±12 years) to assess the normal range of average peak systolic strain, showing no influence

Table 2. Echocardiographic parameters in patients with aortic stenosis and in control subjects.

	Patients with aortic stenosis (n=49)		Control group (n=18)		p
Global longitudinal peak strain (GLPS) [-%]	15.30	(±3.25)	19.60	(±2.46)	<0.001
Ejection fraction (EF) [%]	61.53	(±6.55)	63.11	(±4.17)	0.34
Left ventricle mass [g]	258	(215–339)	186	(135–216)	<0.001
Left ventricle mass index [g/m ²]	145	(122–185)	93	(84–111)	<0.001
Peak aortic gradient [mmHg]	68.16	(±28.30)	6.61	(±2.34)	<0.001
Mean aortic gradient [mmHg]	41.04	(±17.81)	3.29	(±0.95)	<0.001
Aortic valve area (AVA) [cm ²]	0.860	(0.710–1.200)	2.850	(2.600–3.100)	<0.001
Indexed aortic valve area (AVAL) [cm ² /m ²]	0.510	(0.386–0.651)	1.588	(1.462–1.791)	<0.001
Early velocity of mitral inflow -E [m/s]	0.689	(±0.251)	0.768	(±0.221)	0.25
E/E' ratio	9.09	(7.00–14.50)	6.11	(5.42–8.63)	<0.01
Systolic peak annular velocity (S') [m/s]	0.07	(0.06–0.08)	0.08	(0.07–0.11)	0.02
Early diastolic annular velocity (E') [m/s]	0.07	(0.05–0.09)	0.12	(0.08–0.15)	<0.001

Table 3. Demographic and clinical characteristics of the patients with asymptomatic aortic stenosis vs. those with symptomatic aortic stenosis.

	Asymptomatic aortic stenosis (n=19)		Symptomatic aortic stenosis (n=29)		p
Age	68	(49–79)	70	(62–78)	0.35
Males, n (%)	7	(37)	20	(69)	0.03
Smoking, n (%)	3	(16)	4	(14)	0.82
Hypertension, n (%)	13	(68)	24	(83)	0.25
Diabetes, n (%)	4	(21)	6	(21)	0.74
Coronary artery disease, n (%)	5	(26)	14	(48)	0.13
hs C-reactive protein [mg/l]	1.20	(0.92–2.49)	1.37	(0.61–2.31)	0.81
Total cholesterol [mmol/l]	4.84	(±1.30)	4.97	(±1.04)	0.69
LDL cholesterol [mmol/l]	2.85	(±1.02)	3.03	(±1.04)	0.56
HDL cholesterol [mmol/l]	1.57	(±0.29)	1.55	(±0.33)	0.82
Glucose [mmol/l]	5.65	(5.40–6.80)	5.50	(5.30–5.80)	0.36
Triglycerides [mmol/l]	0.93	(0.79–1.36)	1.11	(0.84–1.36)	0.80
Creatinine [μmol/l]	79	(74–86)	80	(76–94)	0.46
Alanine transaminase (ALT) [U/L]	22	(16–28)	25	(17–30)	0.55

hs – high sensitivity.

of age, and only mild influence of blood pressure and heart rate on average longitudinal strain values. Previous studies showed that GLPS, decreased in AS, is even more affected in severe as compared to moderate AS [20-22]. Zito et al. [23], in a prospective study of 52 asymptomatic AS patients, showed that GLPS decrease is an independent predictor of the occurrence of the symptoms, need for AVR, or death. Moreover, the increase of longitudinal LV contractility

expressed by GLPS is lower during exercise in patients with abnormal exercise test results [21]. After AVR followed by inverse left ventricle remodeling, the long-axis LV function and GLPS may improve [24,25].

In our study, GLPS (but not S' velocity) was significantly lower in the symptomatic subgroup compared to asymptomatic patients. This finding is consistent with those obtained

Table 4. Echocardiographic parameters in the patients with asymptomatic aortic stenosis vs. in those with symptomatic aortic stenosis.

	Asymptomatic aortic stenosis (n=19)		Symptomatic aortic stenosis (n=29)		P
Global longitudinal peak strain (GLPS) [-%]	17.5	(14.7–18.9)	15.5	(11.8–16.8)	0.02
Ejection fraction (EF) [%]	61.63	(±4.14)	61.28	(±7.84)	0.84
Left ventricle end-diastolic volume (LVEDV) [ml]	115	(81–143)	133	(104–157)	0.17
Left ventricle end-systolic volume (LVESV) [ml]	47	(43–70)	56	(40–73)	0.78
Left ventricular mass [g]	249	(178–323)	276	(252–349)	0.05
Left ventricular mass index [g/m²]	141	(101–158)	167	(131–196)	0.04
Left atrial area (LAA) [cm²]	20.44	(±5.19)	23.86	(±5.93)	0.05
Left atrial volume (LAV) [ml]	62.20	(±23.40)	73.76	(±29.38)	0.16
Aorta ascending [mm]	36.26	(±6.26)	36.17	(±4.75)	0.95
Peak aortic gradient [mmHg]	53	(38–66)	71	(62–93)	0.01
Mean aortic gradient [mmHg]	30	(21–43)	45	(35–56)	0.004
Aortic valve area (AVA) [cm²]	1.10	(0.85–1.30)	0.75	(0.64–0.92)	0.004
Indexed aortic valve area (AVAI) [cm ² /m ²]	0.608	(0.486–0.739)	0.404	(0.373–0.651)	0.07
Early velocity of mitral inflow (E) [m/s]	0.77	(±0.26)	0.63	(±0.24)	0.06
E/E'	8.89	(6.43–14.50)	9.80	(7.17–14.67)	0.48
Systolic peak annular velocity (S') [m/s]	0.07	(0.06–0.08)	0.06	(0.05–0.08)	0.06
Early diastolic annular velocity (E') [m/s]	0.08	(0.06–0.11)	0.06	(0.04–0.08)	0.02

by Tongue et al. [26]. Despite left ventricle long-axis systolic function disturbances, LV diastolic dysfunction was also more pronounced in patients presenting clinical symptoms.

Limitations of the study

The control group consisted of patients referred to our Department who did not meet the inclusion criteria described above. This group was significantly younger than the study patients, because aortic stenosis occurs predominantly in older subjects. This, however, does not influence our results, as it was shown that strain and strain rate do not change significantly with increasing age [27]. While ischemia obviously has an influence on LV function, the frequency of coronary artery disease in the study patients and in the control group was comparable. Moreover, there were no patients with regional wall motion abnormalities, thus LV function impairment in our groups were mainly caused by valvular disease, not by regional left ventricle ischemia.

CONCLUSIONS

In aortic stenosis patients, despite normal left ventricle ejection fraction, long-axis left ventricular function is impaired, which manifests in global longitudinal peak strain reduction. GLPS reveals that LV function impairment is more pronounced in symptomatic as compared to asymptomatic AS patients. The prognostic significance of early LV

function impairment in aortic stenosis patients showed by GLPS should be determined in further studies.

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