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Association between aortic stenosis severity and contractile reserve measured by two-dimensional strain under low-dose dobutamine testing

Uticaj težine aortne stenoze na procenu kontraktilne rezerve procenjene pomoću dvodimenzionalnog naprezanja tokom niskodoznog dobutaminskog testa

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Abstract

Background/Aim. Early detection of left ventricle (LV) systolic dysfunction could be a clue for surgical treatment in patients with significant aortic stenosis (AS). Therefore, we evaluated LV peak of global longitudinal strain (PGLS) using speckle tracking imaging at rest and during low-dose dobutamine infusion in asymptomatic patients with moderate and severe AS and preserved LV ejection fraction (EF). **Methods.** All the patients underwent coronary angiography and had no obstructive coronary disease (defined as having no stenosis greater than 50% in diameter). The patients were divided into two groups: above and below median of 0.785 cm² aortic valve area (AVA). PGLS was measured from acquired apical 4-chamber and 2-chamber cine loops using a EchoPac PC-workstation at rest and during 5 μg/kg/min, 10 μg/kg/min, and 20 μg/kg/min dobutamine infusion, respectively. The global strain was the average of segment strains from the apical views. **Results**: A total of 62 patients with moderate and severe AS (AVA < = 1.5 cm²), the mean age 66.12 ± 9.91, (57.14% males), were enrolled in this prospective study. At rest, mean gradient was 43.57 ± 0.29 mmHg and mean EF was 72.24 ± 0.45%. When divided according to median AVA, both groups had decreased average PGLS at rest (-9.33 ± 4.46% *vs* -8.95 ± 3.08%; p = ns). During dobutamine both groups increased their average PGLS, but only the group with AVA > median reached the statistical significance (-8.71 ± 2.68% *vs* -11.93 ± 3.74%, p = 0.002). In addition, PGLS increase was also significant in 4-chamber view in the patients with AVA above median, but only when comparing baseline to peak 20 μg/kg/min (-10.72 ± 3.07% *vs* -13.14 ± 4.79%; p = 0.034). Conversely, in both groups the increase of PGLS in 2-chamber view did not reach significance. **Conclusion.** Two-dimensional strain speckle tracking analysis of myocardial deformation with measurement of peak systolic strain during dobutamine infusion is a feasible and accurate method to determine myocardial longitudinal systolic function and contractile reserve and may contribute to clinical decision making in patients with significant AS.

Key words:
ventricular function, left; myocardial contraction; aortic value stenosis; dobutamine; heart function tests; ultrasonography.

Apstrakt

Uvod/Cilj. Rano otkrivanje sistolne disfunkcije leve komore kod bolesnika sa znatnom aortnom stenozom (AS) je važno, jer nam može na vreme ukazati na potrebu da se bolesnik uputi na hirurško lečenje. Iz tog razloga, koristeći dvodimenzionalnu *speckle tracking* tehniku, ispitali smo kolika je vrednost maksimalnog globalnog longitudinalnog naprezanja (*maximal global longitudinal strain* – MGLS) u miru i kako se menja tokom niskodoznog dobutaminskog testa kod bolesnika sa umerenom i tesnom AS i očuvanom ejekcionom frakcijom (EF) u miru. **Metode.** Svim bolesnicima je urađen koronarni angiogram i nijedan bolesnik nije imao suženje veće od 50% prečnika epikardnog koronarnog krvnog suda. Bolesnici su na osnovu medijane površine aortnog ušća (PAŠ) koja je iznosila 0,785 cm² podeljeni u dve grupe: iznad i ispod medijane. MGLS je meren iz apikalnog četvoro i dvošupljinskog preseka, pomoću EchoPac PC-radne stanice u miru i tokom niskodoznog dobutaminskog testa koji je obuhvatao tri nivoa: 5, 10, i 20 μg/kg/min. Ukupno globalno naprezanje izračunato je kao srednja vrednost naprezanja izračunatog iz četiri i dve

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šupljine. **Rezultati.** Ukupno 62 bolesnika sa umerenom i tesnom AS (PAŠ ≤ 1,5 cm²), prosečne starosti 66.12 ± 9.91 godine, (57.14% muškarci), bile su uključena u ovu prospektivnu studiju. U miru, srednji gradijent preko aortnog ušća iznosio je 43.57 ± 0.29 mmHg, a srednja vrednost EF bila je 72.24 ± 0.45%. Obe grupe bolesnika imale su sniženu prosečnu vrednost MGLS u miru (-9.33 ± 4.46% *vs* -8.95 ± 3.08%, *p* = ns). Tokom dobutaminskog testa obe grupe bolesnika povećale su prosečnu vrednost MGLS, ali je samo u grupi bolesnika čija je PAŠ bila iznad medijane taj porast bio statistički značajan (-8,71 ± 2,68% *vs* -11,93 ± 3,74%, *p* = 0,002). Takođe, u ovoj grupi bolesnika statistički značajan bio je i porast MGLS u apikalnom preseku četiri šupljine (-10,72 ± 3,07% *vs* -13,14 ± 4,79%, *p* = 0,034). Sa druge strane, nijedna grupa bolesnika nije dostigla statistički značajan porast MGLS u apikalnom preseku dve šupljine. **Zaključak.** Dvodimenzionalna *speckle tracking* analiza miokardne deformacije sa merenjem MGLS u miru i tokom niskodoznog dobutaminskog testa sigurna je, izvodljiva i precizna metoda za određivanje longitudinalne sistolne funkcije leve komore u miru i njene kontraktilne rezerve i može doprineti boljem kliničkom rasuđivanju kod bolesnika sa hemodinamski značajnom AS.

Ključne reči:
srce, funkcija leve komore; miokard, kontrakcija; zalistak aorte, stenoza; dobutamin; srce, funkcijski testovi; ultrasonografija.

Introduction

Speckles are natural acoustic markers due to interference patterns caused by backscattered signals from small structures in myocardium [1]. Long axis systolic left ventricular (LV) function is governed by the subendocardial myocardial fibres that can be reliably quantified by the measurement of longitudinal myocardial deformation using the two dimensional, 2D speckle tracking imaging [2]. Dobutamine is a potent beta-agonist which increases heart rate and contractility of the heart, but, in low dose, the effect is more pronounced on increasing myocardial contractility than heart rate [3].

LV response to chronic pressure overload and increased wall stress in aortic stenosis (AS) is a concentric hypertrophy – an increase in mass due to increased wall thickness without chamber dilatation [4]. This mechanism enables left ventricle ejectin fraction (LVEF) to remain preserved until late in the disease course. However, revealing the progression from compensatory hypertrophy to heart failure, in timely manner, may be important because once symptoms start to occur and LVEF to decrease, outcome becomes significantly worse [5]. Thus, early detection of diminished or absent LV long-axis myocardial deformation, as a marker of LV systolic dysfunction in AS, could be helpful for better decision-making in these patients [6].

The aim of this study was to evaluate the impact of AS on LV longitudinal systolic function by using 2D-speckle tracking of myocardial deformation at rest and during low-dose dobutamine infusion, in asymptomatic patients with moderate and severe AS and preserved LVEF.

Methods

A cohort of 70 patients with AS (effective orifice area of 1.5 cm^2 or less) and preserved EF at rest (EF > 50%), as calculated by Doppler and 2D echocardiography, used to be enrolled consecutively from May 2009 to September 2010 in the clinical echocardiography laboratory of the University Clinical Center, Belgrade, Serbia. All the patients underwent coronary angiography and had no obstructive coronary disease (defined as having no stenosis greater than 50% in diameter). Due to insufficient image quality at rest and during dobutamine testing (DBT) (of the 2D-strain especially), 8 patients were excluded forming the final group of 62 patients. According to the median aortic valve area (AVA) of 0.785 cm^2 the patients were divided into two groups: below and above the median level. Exclusion criteria were atrioventricular block or bradycardia with heart rate (HR) below 50 beats per minute, other significant valvular disease and uncontrolled hypertension (> 180/100 mmHg). The Ethics Committee of the University Clinical Center approved the study, and all the patients gave written informed consent.

Echocardiography

Transthoracic echocardiography exam was performed with an General Electric, Vivid 4 cardiac ultrasound system (BTO6, 1.5–3.6 MHz; GE Healthcare Technologies, Waukesha, WI, USA). The subjects were studied in the left lateral decubitus. Left ventricular internal dimension, posterior wall thickness (PWT) and interventricular septum thickness (IVST) were measured at end-diastole, at a level immediately apical to the mitral valve leaflet tips, in two-dimensional parasternal long-axis view [7]. The LV mass was calculated using the corrected formula of the American Society of Echocardiography and was indexed for body surface area (BSA) [8]. Relative wall thickness (RWT) was calculated with the formula: RWT = (PWT + IVST)/LVEDD. Significant LV hypertrophy was defined as LV mass index > 134 g/m^2 for men and > 110 g/m^2 for women and as RWT > 0.5 [9]. AS was graded using the continuity equation[10] calculated as moderate (AVA from 1.0 cm^2 to 1.5 cm^2) or severe (AVA 1.0 cm^2 or less). The subaortic diameter was measured from inner edge to inner edge at the level of the base of the aortic cusps in a parasternal long axis frame frozen in mid-systole. Pulsed Doppler recordings were made in apical 5-chamber view with the sample volume moved axially from the aortic annulus, usually 0.5 cm to 1 cm below the valve, recording maximal velocity and velocity-time integral. Continuous wave recordings were made from the apex and right intercostal positions and the optimal signal was traced to obtain peak velocity, velocity-time integral, systolic ejection time and peak and mean pressure difference, using the on-line software.

After echocardiography exam at rest, patients underwent low dose DBT with three levels, starting from 5 μg/kg/min, than 10 μg/kg/min and peak 20 μg/kg/min, re-

spectively. Each level was lasting for 3 minutes. All standard echocardiographic measures were recorded during the last minute of each level and analysed off-line.

Strain measurement

Strain measurement was based on the speckle tracking approach: the global longitudinal myocardial deformation was evaluated from the standard 2D images. The image acquisition frame rate was 60–90 Hz (mean value 75 Hz). Peak strain was measured from acquired apical 4-chamber and 2-chamber cine loops using an EchoPac PC-workstation at rest and during 5 μg/kg/min, 10 μg/kg/min, and 20 μg/kg/min DBT. In brief, by tracing the endocardial borders on an end-systolic frame, the software automatically tracked the contour on the subsequent frames. Adequate tracking was verified in real-time and was manually corrected, if necessary. The peak global longitudinal deformation was the average of segment strains from apical 4- and 2- chamber view. The inter-observer reproducibility of measurements was tested by random selection of 10 patients. Inter-observer agreement was 90%.

Statistical analysis

The data were expressed as mean values and standard deviations or percentages, and analyzed with the paired samples *t*-test. The median split method was used to divide patients into two equal cohorts: the cohort of patients below median level representing patients with severe AS and the cohort of patients above median level, representing patients with moderate AS. A p value < 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS statistical software (SPSS for Windows, release 17.0, SPSS, Chicago, IL).

Results

A total of 537 cine loops were analyzed in the cohort of 62 asymptomatic AS patients, mean age 66.12 ± 9.91 years; range from 33 to 83 years; 54.8% were males. Dobutamine infusion was generally well-tolerated, no adverse event was registered during or after the testing. Table 1 presents the echocardiographic data of our patient cohort. All the patients had normal end-systolic and end-diastolic LV measures, and, by definition, AVA was reduced and mean and peak gradients increased. However, the signs of LV hypertrophy and diastolic dysfunction were present, with relatively high E/E' relationship indicating increased LV end-diastolic pressure.

Heart rate was increasing under DBT ($p < 0.05$) parallel with dobutamine dose increase. All parameters describing the severity of AS and systolic LV function, and when analyzing according to AVA median level, significantly changed in all patients ($p < 0.05$) during DBT (Table 2).

Table 1

Echocardiographic parameters describing diastolic function and left ventricle (LV) hypertrophy in all the patients

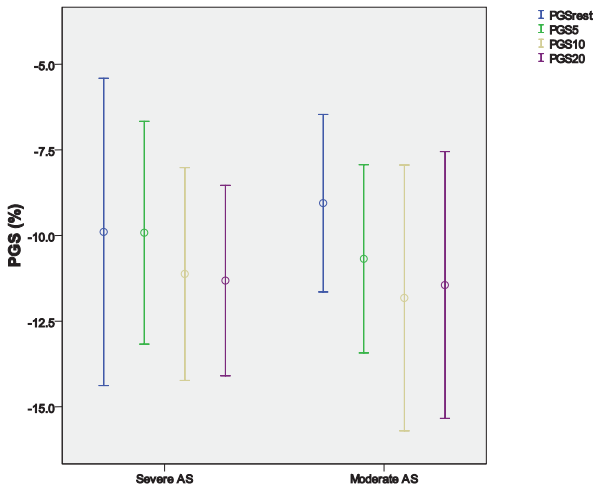
Parameters	$\bar{x}$ ± SD
LV mass index (g/m^2)	141.62 ± 33.52
Relative wall thickness	0.51 ± 0.08
Septum (cm)	1.31 ± 0.13
Posterior wall (cm)	1.24 ± 0.13
Isovolumetic relaxation time (ms)	94.00 ± 39.06
Deceleration time (ms)	243.88 ± 73.17
E/E' (index of left ventricular filling pressure) (cm/s)	14.10 ± 7.21
LV end-diastolic volume (mL)	88.07 ± 22.35
LV end-systolic volume (mL)	25.04 ± 10.14

Table 2

Clinical and echocardiographic parameters at rest and during peak dobutamine infusion for all the patients and according to aortic value area (AVA) median level

Parameters	All patients			AVA < median			AVA > median		
	rest ($\bar{x}$ ± SD)	peak dobutamine level ($\bar{x}$ ± SD)	p	rest ($\bar{x}$ ± SD)	peak dobutamine level ($\bar{x}$ ± SD)	p	rest ($\bar{x}$ ± SD)	peak dobutamine level ($\bar{x}$ ± SD)	p
Heart rate (bpm)	69.91± 11.51	100.98 ± 18.13	0.000	73.38 ± 11.11	107.58 ± 18.43	0.000	66.45 ± 11.02	94.38 ± 15.02	0.000
Systolic arterial pressure (mmHg)	147.58 ± 20.40	140.72 ± 20.18	0.001	146.12 ± 21.04	139.83 ± 21.19	0.016	149.03 ± 19.97	141.61 ± 19.42	0.002
Diastolic arterial pressure (mmHg)	88.79 ± 10.14	85.32 ± 11.76	0.014	88.70 ± 9.65	83.87 ± 10.93	0.026	88.87 ± 10.77	86.77 ± 12.55	ns
Aortic valve area (cm^2)	0.83 ± 0.23	1.01 ± 0.30	0.000	0.65 ± 0.10	0.81 ± 0.16	0.000	1.01 ± 0.19	1.20 ± 0.27	0.000
Maximal velocity (m/s)	4.28 ± 0.45	4.96 ± 0.55	0.000	4.40 ± 0.43	5.12 ± 0.53	0.000	4.16 ± 0.43	4.81 ± 0.52	0.000
Mean gradient (mmHg)	43.57 ± 10.92	57.42 ± 14.93	0.000	46.43 ± 10.49	61.84 ± 15.43	0.000	40.70 ± 9.40	52.99 ± 13.21	0.000
Indexed stroke volume (mL/m^2)	39.81 ± 10.98	45.78 ± 10.92	0.000	34.32 ± 9.62	41.31 ± 7.50	0.001	45.31 ± 9.46	50.24 ± 12.04	0.001
Ejection Fraction (%)	72.24 ± 6.31	78.23 ± 8.52	0.000	71.19 ± 5.05	79.00 ± 7.68	0.000	73.29 ± 7.29	77.46 ± 9.36	0.006
S' (systolic mitral annulus tissue Doppler) (cm/s)	7.01 ± 1.49	9.63 ± 2.60	0.000	6.75 ± 1.34	8.87 ± 1.93	0.000	7.27 ± 1.61	10.40 ± 2.75	0.000
E/E' (index of left ventricular filling pressure) (cm/s)	14.10 ± 7.21	9.95 ± 6.14	p = ns	19.20 ± 5.43	14.20 ± 4.93	0.000	9.00 ± 3.22	5.60 ± 2.84	0.000

When divided according to median AVA, both groups of patients had a decreased average peak of global longitudinal strain (PGLS) at rest. No significant difference was found between them (p = ns), although patients with moderate AS had somewhat lower baseline values. However, during DBT both groups increased their average PGLS, but only the group with AVA > median level reached the statistical significance, during both 10 μg/kg/min and 20 μg/kg/min infusion (p = 0.012 and p = 0.020), while the increase during 5 μg/kg/min infusion was very close to statistical significance (p = 0.053) (Figure 1). In addition, PGLS increase was also significant in 4-chamber view in the patients with AVA above median level, but only when comparing baseline to peak 20 μg/kg/min DBT. In contrast, the patients with AVA below the median did not reach a significant increase in PGLS during DBT (Table 3). Conversely, in both groups the



AVA < median value (0.785 cm^2)		AVA > median value (0.785 cm^2)
PGSrest - PGS5;	p = ns	p = 0.053
PGSrest - PGS10;	p = ns	p = 0.012
PGSrest - PGS20;	p = ns	p = 0.020

Fig. 1 – Peak average global longitudinal strain (PGS) at rest and during dobutamine infusion according to median aortic value area (AVA) level.

Table 3

Peak global longitudinal strain (PGLS) at rest and during dobutamine infusion from apical 4- and 2- chamber view according to median aortic value area (AVA) level

AVA	x̄ ± SD (%)	p
< median value (0.785 cm^2)		
PGLS 4-chamber view at rest	-10.65 ± 3.96	ns
PGLS 4-chamber view at DBT 5 μg/kg/min	-10.33 ± 4.04	
PGLS 4-chamber view at rest	-10.94 ± 3.91	ns
PGLS 4-chamber view at DBT 10 μg/kg/min	-10.77 ± 3.42	
PGLS 4-chamber view at rest	-11.16 ± 4.09	ns
PGLS 4-chamber view at DBT 20 μg/kg/min	-11.40 ± 3.36	
> median value (0.785 cm^2)		
PGLS 4-chamber view at rest	-10.00 ± 3.05	ns
PGLS 4-chamber view at DBT 5 μg/kg/min	-9.89 ± 3.67	
PGLS 4-chamber view at rest	-9.98 ± 3.10	ns
PGLS 4-chamber view at DBT 10 μg/kg/min	-10.96 ± 4.52	
PGLS 4-chamber view at rest	-10.72 ± 3.07	0.034
PGLS 4-chamber view at DBT 20 μg/kg/min	-13.14 ± 4.79	
< median value (0.785 cm^2)		
PGLS 2-chamber view at rest	-9.55 ± 3.45	ns
PGLS 2-chamber view at DBT 5 μg/kg/min	-8.86 ± 3.57	
PGLS 2-chamber view at rest	-9.46 ± 3.63	ns
PGLS 2-chamber view at DBT 10 μg/kg/min	-10.08 ± 3.99	
PGLS 2-chamber view at rest	-9.52 ± 3.69	ns
PGLS 2-chamber view at DBT 20 μg/kg/min	-10.59 ± 3.07	
> median value (0.785 cm^2)		
PGLS 2-chamber view at rest	-9.17 ± 2.88	ns
PGLS 2-chamber view at DBT 5 μg/kg/min	-10.16 ± 3.62	
PGLS 2-chamber view at rest	-9.02 ± 2.77	ns
PGLS 2-chamber view at DBT 10 μg/kg/min	-10.16 ± 3.62	
PGLS 2-chamber view at rest	-9.48 ± 2.77	ns
PGLS 2-chamber view at DBT 20 μg/kg/min	-10.40 ± 3.56	

increase of PGLS in 2-chamber view did not reach significance. When analyzing mean LVEF at rest, we found, in contrast, that both groups have normal LVEF at rest (71.19 ± 5.05% *vs* 73.29 ± 7.29%, p = ns), and significant increase during DBT (71.19 ± 5.05% *vs* 79.00 ± 7.68%, $p < 0.01$, for AVA < median value and 73.29 ± 7.29 cm^2 *vs* 77.46 ± 9.36 cm^2, $p < 0.01$, for AVA > median level).

Discussion

The present study showed that 2D-speckle tracking analysis of myocardial deformation with measurement of PGLS during dobutamine infusion is a feasible and accurate method to determine myocardial systolic function and contractile reserve and may contribute to decision making in patients with moderate or severe AS. When compared to normal subjects, extensively investigated in the HUNT[11] study (in which authors reported normal PGLS around 16%), patients with AS have reduced longitudinal systolic function in spite of preserved LVEF at rest. This finding was recently showed by Donal et al. [6] who used exercise testing for estimating contractile reserve, and was confirmed with DBT in our study. To the best of the author's knowledge, this is the first study that used low-dose DBT for estimating longitudinal systolic function contractile reserve.

In hemodynamically significant AS, when chronically increased LV global afterload exceeds the limit of LV compensatory mechanism, intrinsic impairment of myocardial function can occur. However, despite the presence of myocardial dysfunction, often associated with disturbed myocardial architecture, LVEF is commonly normal in patients with AS. This might be due to the fact that LVEF is influenced not only by intrinsic myocardial function, but LV cavity geometry, also [2, 12, 13]. In AS, wall thickening as an adaptive mechanism to pressure overload, can thus mask subtle LV dysfunction [5]. Subclinical LV dysfunction is classically detected by a decrease in longitudinal myocardial function which, as we confirmed, can be reliably quantified by the measurement of myocardial deformation using 2D-speckle tracking analysis [14, 15]. Longitudinal function is governed by the subendocardial myocardial fibres which are aligned longitudinally and more sensitive to microvascular ischaemia [16, 17]. This may lead to progressive myocardial fibrosis that participates to reduce longitudinal myocardial function. In asymptomatic AS patients reduced subendocardial function has been showed to be associated with changes in symptomatic status during follow-up and adverce outcomes [14]. However, when the reactive subendocardial fibrosis becomes distinct, irreversible myocardial damage may occur. Therefore, early detection of intrinsic myocardial dysfunction in AS patients with preserved EF could be of help for risk assessment.

The present study showed that both patients with moderate and severe AS had impaired longitudinal myocardial function at rest. However, changes in longitudinal function during DBT were not homogenous, with the patients with AVA > 0.785 cm^2 (thus considered as moderate stenosis) having more increase (becomes more negative) in PGLS. The present observation suggest that patients with moderate stenosis better adapt to acute change in LV load, by recruiting LV contractile reserve to the increased afterload. Both inotropic contractile reserve and rise in transaortic pressure gradients are thus concomitant. Conversely, when the aortic valve is no longer compliant, or in case of a significant myocardial damage (*ie* ischaemia), mismatch between afterload and contractility can occur, which is often the case in more advanced stage of a disease [6]. Hence, limited longitudinal contractile reserve during DBT probably reflects a more advanced disease process with more extensive myocardial fibrosis, myocytes degeneration and exhausted coronary flow reserve.

Identification of subclinical LV dysfunction in hemodynamically significant AS is challenging and of clinical importance. The results of the present study show that the magnitude of DBT-induced changes in LVEF are not equal to changes in PGLS (as a measurement of LV long-axis function) and that different categories of asymptomatic AS patients can be identified according to changes in longitudinal function. In addition, PGLS, in contrast to LVEF, is decreased even during maximal DBT. This emphasizes that in AS, the assessment of myocardial contractile function by 2D-speckle tracking is more appropriate than by changes in LVEF in the setting of pressure overload. Also, the role of mitral annulus pulse tissue Doppler in distinguishing patients with limited contractile reserve, according to Van Pelt et al. [18], is less accurate.

Conclusion

2D-speckle tracking analysis of PGLS during DBT is a feasible and accurate method to determine subnormal myocardial systolic function and contractile reserve and may contribute to decision making in asymptomatic moderate and severe AS patients with preserved LVEF. However, a decrease in LV longitudinal systolic function in a significant AS cannot simply be related to the severity of valve obstruction and needs to be evaluated in comparison with control groups.

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