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Relation of global longitudinal strain to left ventricular geometry in aortic valve stenosis

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Abstract

Background: *In patients with aortic stenosis (AS), increased afterload induces changes in left ventricular (LV) geometry to preserve a normal ejection fraction (EF). Nevertheless, myocardial dysfunction may occur in spite of a normal EF. Global longitudinal strain (GLS) analysis can detect subtle contractile dysfunction at a pre-clinical stage. The aim of our study was to assess LV function deteriorations with GLS analysis and the association with geometric changes in patients with AS and normal EF.*

Methods: *Forty four patients with moderate to severe AS and 40 controls were enrolled. All patients underwent echocardiography, including two-dimensional strain imaging. The relative wall thickness and LV muscle mass measurements were performed with magnetic resonance imaging and patients were subdivided into four groups: Group 1 with normal LV, Group 2 with concentric remodeling, Group 3 with eccentric hypertrophy, and Group 4 with concentric hypertrophy.*

Results: *The total group of patients with AS showed a GLS of –15.3 ± 3.6% while the control group reached –18.9 ± 3.2% ($p < 0.001$). GLS was lower in the hypertrophy Groups 3 and 4 compared to Groups 1 and 2 (12.9 ± 3.4%* vs *17.2 ± 2.5%, $p < 0.05$, respectively). Splitting the patients into Groups 1 to 4, the GLS was –17.2 ± 2.4%, –17.2 ± 2.7%, –12.4 ± 3.8% and –13.1 ± 3.3, respectively ($p = 0.002$).*

Conclusions: *In subjects with AS, lower GLS is related to LV hypertrophy, but not to the presence of concentric remodeling. Assessment of GLS can identify subtle contractile dysfunction independent of a preserved EF, and might be useful in identifying patients at high risk for the transition from compensatory to pathological remodeling.* (Cardiol J 2011; 18, 2: 151–156)

Key words: strain, aortic stenosis, magnetic resonance imaging, remodeling, hypertrophy

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Introduction

Myocardial systolic function is usually assessed by left ventricular ejection fraction (LVEF). Nevertheless, an abnormal EF is a late consequence of chronically increased afterload such as it appears in degenerative aortic stenosis (AS). Newer quantitative techniques such as global longitudinal strain (GLS) analysis and tissue Doppler imaging [1] have been used to better characterize global myocardial systolic function and detect subtle signs of myocardial dysfunction before bold changes in EF occur [2, 3].

In general, in patients with AS, the onset of LV systolic dysfunction determines a poor prognosis [4, 5]. Recent guidelines only focus on the LVEF to define systolic function [6]. Despite this, there is compelling evidence to suggest that even in the presence of preserved or supranormal EF, myocardial performance may be severely dysfunctional in AS patients. Specifically, LV hypertrophy (LVH) triggered by an increased afterload can maintain a normal ejection performance despite decreased intrinsic longitudinal function [7, 8]. In addition, LVH, a very common finding in hypertension and AS, has been proven to be an adverse prognostic marker [9, 10].

Therefore, LVH can be beneficial in some respects and harmful in others. The challenge for the clinician is to detect contractile dysfunction at an early subclinical point so as to prevent irreversible myocardial function deterioration.

In AS, differences in the adaptive remodeling of the LV have been described, but the influence of LV geometry on the longitudinal systolic function is not widely appreciated. We investigated the impact of LV geometry on intramyocardial longitudinal mechanics with magnetic resonance imaging (MRI) and two-dimensional (2D) myocardial strain ('speckle tracking') echocardiography.

Methods

This study was designed for patients with moderate to severe AS who underwent conventional and 2D speckle tracking echocardiography as part of a clinical trial protocol. A total of 44 patients were enrolled. We included 40 age-matched control patients in order to establish normal GLS values for our echo laboratory.

All patients gave their written informed consent. The study protocol was approved by the local ethics committee.

In subjects with AS, MRI was performed to assess LV muscle mass, geometry and function. Exclusion criteria were: concomitant mitral valve disease, severe low gradient AS, EF < 35%, hypertrophic obstructive cardiomyopathy, uncontrolled hypertension, severe ventricular arrhythmias, and the general exclusion criteria for MRI.

Standard and tissue Doppler echocardiography were done with a commercially available system (Vingmed Vivid 7, General Electric, Milwaukee, Wisconsin, USA). LVEF was calculated by the biplane Simpson's method. Deformation analysis of the datasets was performed off-line using EchoPac PC8.0 (General Electric-Vingmed). Longitudinal strain measurements from the individual three apical standard views were averaged to obtain a GLS value [3].

MRI was done with a 1.5-Tesla Achieva scanner (Philips Medical Systems, Netherlands) equipped with a 5-element cardiac synergy coil. Cine-Images were acquired in breath hold SSFP sequences (TE 3.43; TR 1.72). Images were evaluated with the cmr 42 research edition toolkit (Circle Cardiovascular Imaging, Calgary, Canada) combining long and short axis views. The program calculated end- and end-systolic volumes, as well as stroke volume, EF and finally LV muscle mass, indexed for body surface area. The relative wall thickness was calculated from the posterior wall thickness*2/LV end-diastolic diameter and considered increased if > 0.42 [11]. Hypertrophy was defined as LV mass index > 115 g/m^2 body surface area in men and > 95 g/m^2 in women, whereas a relative wall thickness > 0.42 was used as a cut-off for concentric or ≤ 0.42 for the eccentric remodeling or hypertrophy, respectively.

The LV geometry was assessed from the LV mass index and the relative wall thickness combination, and patients were subsequently subdivided into four groups: normal geometry (Group 1), concentric remodeling (Group 2), eccentric hypertrophy (Group 3) and concentric hypertrophy (Group 4).

Statistical analysis

All analyses were performed using SPSS statistical software (SPSS 17.0, Chicago, Illinois, USA). The data is presented as mean ± SD unless otherwise specified. A p-value < 0.05 was considered statistically significant. Comparison of the two groups of subjects for various parameters was performed by one-way analysis of variance (ANOVA), and Fisher-test was used for categorical variables. When normality and/or equal variance testing conditions were not met, the Kruskal-Wallis rank test was used. Pearson's linear correlation coefficients were calculated for pairs of continuous variables.

Table 1. Demographics, clinical and laboratory characteristics.

Variable	Aortic stenosis *vs* controls			Aortic stenosis				
	Aortic stenosis (n = 38)	Controls (n = 40)	P	Group 1 (n = 8)	Group 2 (n = 13)	Group 3 (n = 6)	Group 4 (n = 11)	P
Age (mean ± SD)	73 ± 9	71 ± 8	0.31	74 ± 6	75 ± 4	70 ± 13	70 ± 13	0.49
Female	42%	50%	0.31	50%	46%	17%	45%	0.58
CAD	66%	67%	0.53	50%	54%	83%	81%	0.28
History of MI	10%	37%	0.005*	0%	8%	17%	18	0.57
Hypertension	87%	97%	0.09	88%	92%	83%	82%	0.88

CAD — coronary artery disease; MI — myocardial infarction; SD — standard deviation; *significant ($p < 0.05$); Group 1 — normal geometry; Group 2 — concentric remodeling; Group 3 — eccentric hypertrophy; Group 4 — concentric hypertrophy

We first analyzed associations without any adjustments, and then with adjustments for potential confounders by multiple linear regression for continuous and logistic regression for categorical variables.

Results

Study population

Forty four patients with moderate to severe AS and 40 age-matched controls without valvular heart disease and with normal EF were included. In two subjects with AS, MRI measurements were not performed because of technical artefacts or claustrophobia. Furthermore, the echocardiographic image quality was not sufficient to analyze longitudinal myocardial strain in four subjects with AS (5%). Therefore, both MRI measurements of LV geometry and muscle mass in addition to echocardiographic determination of GLS were sufficient in 38 subjects. Standard echocardiography including 2D strain imaging was successfully performed in all control patients. The baseline demographics and clinical characteristics are highlighted in Table 1. Demographics and clinical characteristics which might have had an impact on LV geometry (i.e. prevalence of hypertension) did not differ between AS and controls.

Echocardiographic and MRI measurements

Echocardiographic and MRI measurement results are summarized in Table 2. In addition, GLS values were obtained in a control group (n = 40). According to the aortic valve area, 32 (84%) patients were classified as having severe AS (aortic valve area < 1.0 cm^2), whereas the remaining six (16%) subjects were identified with moderate AS (aortic valve area 1–1.5 cm^2). LV muscle mass measurement by MRI reveals a normal LV muscle mass in 55% of subjects with AS (Groups 1 and 2). By subdividing these patients according to the relative wall thickness, 22% showed a normal LV geometry (Group 1), whereas 34% were classified as having concentric LV remodeling (Group 2). Increased LV mass index was detected in 45% of the study group: 16% with eccentric hypertrophy (Group 3) and 29% with concentric hypertrophy (Group 4).

One-way ANOVA analysis demonstrated that the total group of patients with AS had significantly reduced GLS values (–15.2 ± 3.6%), compared to controls (–18.9 ± 3.7%, $p < 0.001$). Splitting subjects with AS into Groups 1, 2, 3 or 4, the GLS was –17.0 ± 2.4, –17.2 ± 2.7, –12.4 ± 3.8 and –12.4 ± ± 2.9%, respectively (Fig. 1, $p = 0.002$). The post-hoc analysis (Bonferroni) showed a significant difference between Group 1 *vs* Group 3 ($p = 0.041$) and between Group 1 *vs* Group 4 ($p = 0.045$) as well as between Group 2 and Group 3 and Group 4 ($p = 0.02$ and $p = 0.017$), respectively. LV muscle mass and GLS correlated significantly ($r = 0.62$, $p < 0.001$) in subjects with moderate to severe AS.

The aortic valve area, mean pressure gradient, EF and degree of diastolic dysfunction did not differ between Groups 1–4, respectively. In a multiple linear regression analysis including age, gender, history of hypertension, the presence of coronary artery disease, LVEF or the history of myocardial infarction and the mean transvalvular pressure gradient, only LV geometry remained a significant predictor variable for the GLS impairment ($\beta = 0.36$, $p = 0.029$). LVEF (determined with MRI) and GLS ($r = –0.42$, $p = 0.14$) were not significantly correlated.

Discussion

This is the first study to report a significant association between echocardiographic analysis of longitudinal myocardial function and the LV geo-

Table 2. Echocardiographic and magnetic resonance imaging (MRI) measurements in subjects with aortic valve stenosis summarized. Left ventricular mass geometry measures were based on MRI measurements.

Variable	All patients (n = 38)	Group 1 (n = 8)	Group 2 (n = 13)	Group 3 (n = 6)	Group 4 (n = 11)	P
LVM [MRI, g/m^2 BSA, SD]	86.2 ± 23	88 ± 12	85 ± 12	125 ± 14	120 ± 15	< 0.001*
Relative wall thickness	0.46 ± 0.1	0.35 ± 0.05	0.52 ± 0.09	0.38 ± 0.04	0.52 ± 0.07	< 0.001*
GLS baseline [%]	–15.3 ± 3.6	–17.2 ± 2.4	–17.2 ± 2.7	–12.4 ± 3.9	–13.1 ± 3.3	0.002*
Vmax [cm/s]	434 ± 71	404 ± 41	443 ± 83	411 ± 65	457 ± 71	0.33
Pmax [mm Hg]	77 ± 26	65 ± 13	81 ± 31	69 ± 23	85 ± 26	0.33
Pmean [mm Hg]	45 ± 18	36 ± 8	47 ± 19	40 ± 17	51 ± 20	0.25
AVA [cm^2]	0.85 ± 0.23	0.96 ± 0.16	0.85 ± 0.19	0.86 ± 0.24	0.78 ± 0.31	0.45
AVA index [cm^2/m^2 BSA]	0.47 ± 0.12	0.53 ± 0.76	0.47 ± 0.09	0.47 ± 0.14	0.43 ± 0.17	0.41
Severe AS [AVA < 1 cm^2]	84%	88%	92%	83%	73%	0.61
E/A	1.1 ± 0.8	2.1 ± 0.5	0.9 ± 0.54	1.2 ± 1.4	1.2 ± 0.9	0.91
Smax [cm/s]	4.8 ± 1.3	5.1 ± 1.1	5.2 ± 1.4	4.1 ± 1.0	4.6 ± 1.4	0.31
E′ [cm/s]	4.5 ± 1.2	5.0 ± 1.3	4.8 ± 1.1	3.6 ± 1.6	4.4 ± 0.8	0.12
E/E′	20.4 ± 8.6	17.6 ± 3.7	22.5 ± 10.6	22.3 ± 10.9	19.1 ± 7.1	0.56
CO [ECHO, L/min]	5.5 ± 1.3	5.6 ± 0.9	5.9 ± 1.3	4.8 ± 0.5	5.3 ± 1.9	0.41
SV [MRI, mL/min]	86 ± 22	94 ± 28	78 ± 20	90 ± 21	87 ± 20	0.44
EF [ECHO, %]	64 ± 12	67 ± 9	67 ± 9	53 ± 15	64 ± 14	0.09
EF [MRI, %]	68 ± 28	68 ± 9	80 ± 43	49 ± 11	63 ± 12	0.12

A — late mitral inflow velocity; AS — aortic stenosis; AVA — aortic valve area; BSA — body surface area; CO — cardiac output; E — early mitral inflow velocity; E´ — early tissue Doppler velocity at the septal mitral annulus; EF — ejection fraction; GLS — global longitudinal strain; LVM — left ventricular mass index; MRI — magnetic resonance imaging; P — pressure; S — systolic tissue Doppler velocity at the septal mitral annulus; SV — stroke volume; V — velocity; Group 1 — normal geometry; Group 2 — concentric remodeling; Group 3 — eccentric hypertrophy; Group 4 — concentric hypertrophy; *statistically significant ($p < 0.05$)

metry measured with MRI techniques in patients with degenerative AS. LVH and reduced GLS were significantly associated irrespectively of a preserved EF, whereas the relative wall thickness (concentric *vs* eccentric remodeling) did not have an impact on the extent of longitudinal myocardial function impairment. Furthermore, 2D GLS analysis seems to be more sensitive than EF in detecting early myocardial impairment, irrespective of the severity of AS.

Our findings align with the published literature concerning this matter [12]. In a study of sub-clinical patients with cardiovascular risk factors, LV myocardial contraction was first impaired in the longitudinal direction [13]. Particularly in patients with severe AS, increased LV afterload induced changes in LV geometry. As a consequence, LV wall thickness increases to compensate for the elevated wall stress, maintaining normal EF [14].

In addition, an increased LV mass index was found to be an independent predictor for the development of symptoms in patients with asymptomatic AS [10]. Nevertheless, most publications on LV geometry have been based on studies determining LV geometry on echocardiographic measurements. A major limitation on echocardiographic measurement of the LV geometry and muscle mass is that the reproducibility of these measurements is prone to imaging artefacts [1]. MRI is considered the standard method for the determination of LV geometry because of its high spatial resolution and generally good image quality [15, 16]. Therefore, we performed LV geometry measurements with MRI [1] and GLS analysis with 2D echocardiography because of its higher temporal resolution and angle independency [17]. Combining the advantages of both methods, we believe that our results are reproducible with minor measurement artefacts.

We found that patients with concentric or eccentric hypertrophy had the lowest average longitudinal strain values, whereas there was no significant difference between controls and patients with concentric remodeling. These findings were independent of gender, EF, history of hypertension, age or severity of AS, indicating that increased LV muscle mass is a stronger covariate of impaired longitudinal myocardial function than these variables. In subjects with hypertension, concentric LVH has been associated with depressed myocardial contractility, as well as worse clinical outcomes [18]. In patients with AS, concentric hypertrophy has been

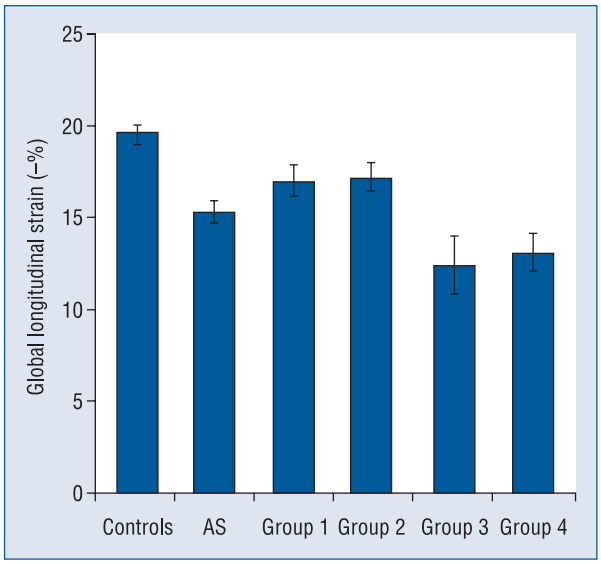

Figure 1. Global longitudinal strain values (%) in relation to left ventricular geometry in controls and patients with aortic stenosis (AS). Figure 1 illustrates the range of average peak longitudinal strain (%) in controls without AS, in the whole study group with AS (n = 38), and in the study group subdivided into normal geometry (Group 1), concentric remodeling (Group 2), eccentric remodeling (Group 3) and concentric remodeling (Group 4). Left ventricular geometry measurements were done with magnetic resonance imaging; $p < 0.001$ for comparison between all groups by full-factorial ANOVA analysis of variance; $p < 0.001$ for comparison between average peak longitudinal strain in controls and Group 3 and Group 4; $p = 0.041$ and $p = 0.045$ for the comparison between Group 2 and Groups 3 and 4, respectively.

found to be an independent predictor of higher in-hospital mortality after aortic valve replacement [19]. Despite the fact that hypertrophy helps to maintain a normal EF, it also impairs coronary blood flow reserve, which first occurs in the subendocardial layers, which has been associated with increased mortality [20, 21].

How can these results be interpreted? Since the subendocardial myocardial fibers are oriented longitudinally, and the impairment of myocardial blood flow first occurs in the subendocardium, the selective impairment in longitudinal myocardial function observed in our study might be due to the increase in subendocardial wall stress, leading to ischemia and consecutive fibrosis. LVH develops first as an adaptive response to maintain a normal EF despite high LV afterload. While progressive hypertrophy in AS has deleterious physiological effects, concentric remodeling possibly reflects an earlier phase in the remodeling process without impairments of myocardial contractile function. Although the compensatory response to increased LV afterload is initially beneficial, incipient hypertrophy leads to impairments in myocardial function, which cannot be detected with EF in the early stages.

Limitations of the study

There are several limitations to our study. Firstly, MRI determination of LV geometry was not done in the control group. Nevertheless, the control group only serves to provide a basis to obtain normal GLS values in subjects without AS and comparable age and co-morbidities. Also, the impact of antihypertensive treatment on deformation parameters could not be assessed in the study.

Conclusions

Analysis of GLS provides a powerful means of unmasking subtle myocardial dysfunction that is not detected by EF in the early stages. This is of practical importance, since recent guidelines only focus on LVEF in management decisions in patients with degenerative AS. Our findings, in addition to previous works focusing on deformation analysis, justify the assessment of GLS in patients with AS, and may identify patients who are in transition from compensatory hypertrophy to myocardial failure.

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