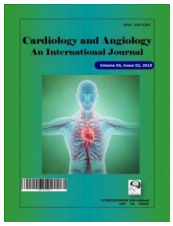

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Effect of an Increase in Global Left Ventricular Afterload on Myocardial Deformation in Patients with Aortic Stenosis, Comparison with Hypertensive Patients

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Left ventricular hypertrophy (LVH) secondary to hypertension and aortic stenosis (AS) are often considered together to be pressure overload hypertrophy. We hypothesized that important differences could exist in the myocardial function with these 2 origins of pressure-overload LVH.
Methods: Global LV longitudinal peak strain (GLS), circumferential strain (GCS) and peak left atrial (LA) longitudinal strain (PALS) were measured using speckle-tracking echocardiography in 38 hypertensive LVH (H-LVH) patients and 36 patients with severe AS and preserved LV ejection fraction. The ratio of E/Ea to PALS was used as an index of LA stiffness. To estimate the global LV afterload, we calculated the valvuloarterial impedance (Zva) as the sum of the systolic arterial pressure and the mean transvalvular pressure gradient divided by the stroke volume index.

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Results: The patients in the high Zva (n=49, Zva≥3mmHg ml/m2) were divided into two groups: AS group (n=28) and H-LVH group (n=21). GLS and PALS were significantly worsened in the AS group (p<0.0001 and p<0.0001, respectively). However, GCS was not significantly difference between two groups. LA stiffness was greater in the AS group than in the H-LVH group (p<0.0001).
Conclusions: Despite of similar global LV afterload and LV hypertrophy, myocardial LV longitudinal systolic function and LA function are impaired in patients with severe AS compared with H-LVH patients.

Keywords: Aortic stenosis; left ventricular hypertrophy; valvuloarterial impedance, myocardial strain.

1. INTRODUCTION

Aortic stenosis (AS) is the most common valvular heart disease [1]. The therapeutic management of patients with AS depends on the severity of the stenosis and the presence of symptoms or the presence of left ventricular (LV) dysfunction, because the onset of symptoms and LV dysfunction determines a poor prognosis [2-4]. In patients with AS, it has been demonstrated that increased LV pressure overload induces changes in LV geometry to compensate for elevated mid-wall stress, and LV wall thickness increases, maintaining normal LV ejection fraction (LVEF) [5]. On the other hand, LV hypertrophy (LVH) have many origins, which may include hypertension and AS. LVH secondary to hypertension and AS are often considered together to be “pressure overload” hypertrophy, although studies that directly compare hearts hypertrophied secondary these 2 causes are limited [6-7]. Because hypertension and AS place different mechanical loads on the heart, it is difficult to differentiate LVH between these 2 causes.

Recently, Briand et al. [8] have demonstrated that that systemic arterial compliance is reduced in AS patients. Reduced systemic arterial compliance additively contributes to the increased systolic load caused by the outflow obstruction; the LV facing a double load (valvular + arterial) [8]. This global LV afterload that may be assessed by valvulo-arterial impedance plays a detrimental effect on LV systolic function [9]. Briand et al. [8] proposed a new index measurable by Doppler echocardiography, valvuloarterial impedance (Zva), to estimate the global hemodynamic load imposed on the LV [8]. This index integrates the mean transvalvvular gradient, the brachial systolic blood pressure and the stroke volume index.

Recent improvement in 2-dimensional echo-cardiographic image resolution has enabled detection of tissue pixels and tracking of acoustic markers from frame-to-frame [10-11]. Recent studies using speckle-tracking echocardiography have reported that LV contraction is first impaired in the longitudinal direction in patients with cardiovascular risk factors [12-13]. Therefore, strain is a measure reflecting regional systolic function and has been used to detect subclinical myocardial dysfunction in a number of cardiac conditions.

This study aimed to assess whether the important differences exist in the myocardial function with these 2 origins of “high pressure afterload” LVH, using two-dimensional speckle tracking echocardiography.

2. METHODS

2.1 Study Population

Our study population consisted of 40 patients hypertensive LVH (H-LVH) and 40 patients with severe AS from January 2015 to November 2015. The diagnosis of H-LVH was based on conventional echocardiographic demonstration of a hypertrophic LV (maximum LVWT > 12 mm) in the absence of long-term hypertension. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥90 mmHg or receiving treatment with antihypertensive drugs. All patients were in normal sinus rhythm and had a normal LVEF. Two patients with H-LVH and 4 patients with severe AS were excluded because of poor echocardiograms. The remaining 38 patients with H-LVH and 36 patients with AS patients were enrolled. Informed consent to participate in this study was obtained from all subjects.

2.2 Echocardiography

Echocardiographic studies were performed using a standard commercial ultrasound machine (Vivid e9, General Electric, Horten, Norway) with a phased-array transducer. Single cine loops

were recorded from 2 standard apical planes consisting of 4-chamber and 2-chamber views. LV end-diastolic volume, LV end-systolic volume and ejection fraction were determined from apical 2-chamber and 4-chamber views using the modified Simpson's method. LV mass was calculated using the formula proposed by Devereux et al. [14] and corrected by the body surface areas to derive LV mass index. Conventional echocardiographic parameters were measured according to the recommendations of the American Society of Echocardiography [15]. The early diastolic transmitral velocity (E) and late diastolic transmitral velocity (A) were recorded in the apical 4-chamber view with the sample volume (5 mm) positioned in the direction of antegrade flow at the level of the mitral valve tips in diastole. The early diastolic velocity (Ea) and late diastolic velocity (Aa) of the mitral annulus in the 4-chamber view were measured. Ea and Aa were obtained at the septal and lateral sites of the annulus, and average values of these measurements were calculated for each patient.

Continuous-wave Doppler was used to measure the aortic transvalvular maximal velocities; peak and mean gradients (MG) were calculated using the simplified Bernoulli equation. Aortic valve area was calculated using the continuity equation. Stroke volume (SV) was calculated using Doppler method as follows: 0.785×(LV outflow tract)^2 ×LV outflow tract velocity time integral [16-18].

2.3 Strain Analysis with Speckle-tracking Imaging

Two-dimensional B-mode grayscale images were captured with a frame rate of 60 to 90 frames per second, and performed on 3 apical views (long-axis, 4-chamber, and 2-chamber) and short-axis view at the mid papillary level. Image analysis was performed offline on a remote workstation using custom analysis software (EchoPAC version 112.0.1; GE Vingmed Ultrasound AS). LV global longitudinal strain (GLS) and global circumferential strain (GCS) were calculated automatically (Fig. 1). After placing three endocardial markers in an end-diastolic frame, the software automatically tracks the contour on subsequent frames. Adequate tracking can be verified in real time and corrected by adjusting the region of interest or by manually correcting the contour to ensure optimal tracking. Segments that were of inadequate image quality were rejected by the software and excluded from analysis. GLS strain was assessed in three apical views, and GCS was assessed in the mid papillary level of parasternal short-axis views. Longitudinal strain represents myocardial deformation directed from the base to the apex. Circumferential strain represents LV myocardial fiber shortening along the circular perimeter, as observed on a short-axis view.

Two-dimensional grayscale images of the septal and lateral LA walls were acquired in the standard apical 4-chamber view. The LA endocardial border was traced manually and adjusted to cover the thickness of the LA walls, resulting in strain curves from a total of 6 atrial segments. From the average of all 6 resulting strain curves, we assessed peak atrial longitudinal strain during systole (PALS) as the maximum positive strain value during LV systole (Fig. 1). LA stiffness index was calculated as E/Ea/PALS, as described by Kurt et al. [19].

2.4 Systemic Arterial Hemodynamics and Global Left Ventricular Afterload

Systemic arterial pressure (SAP) was measured with the use of an arm-cuff sphygmomanometer at the time of the Doppler echocardiographic examination. The ratio of the stroke volume index to the brachial pulse pressure (the difference between the systolic and the diastolic blood pressure) was used as an indirect measure of the total systemic arterial compliance. To estimate the global LV afterload, we calculated the valvulo-arterial impedance (Zva) as the sum of the systolic arterial pressure and the mean transvalvular pressure gradient divided by the SV index [20]. The patients were divided into two groups according to the level of Zva: low Zva group (Zva<3 mmHg ml/m^2, n=25) and high Zva group (Zva≥3 mmHg ml/m^2, n=49).

2.5 Statistics

Data are expressed as mean ± standard deviation. Comparisons between the 2 groups were performed using the Student's t test for continuous variables, or chi-square test for categorical variables. The correlation between Zva and LV strain, AS severity were assessed by simple liner regression analysis. We assessed the interobserver and intraobserver variability for strain measurements from 15 randomly selected patients. For all analyses, a P value <0.05 was considered significant.

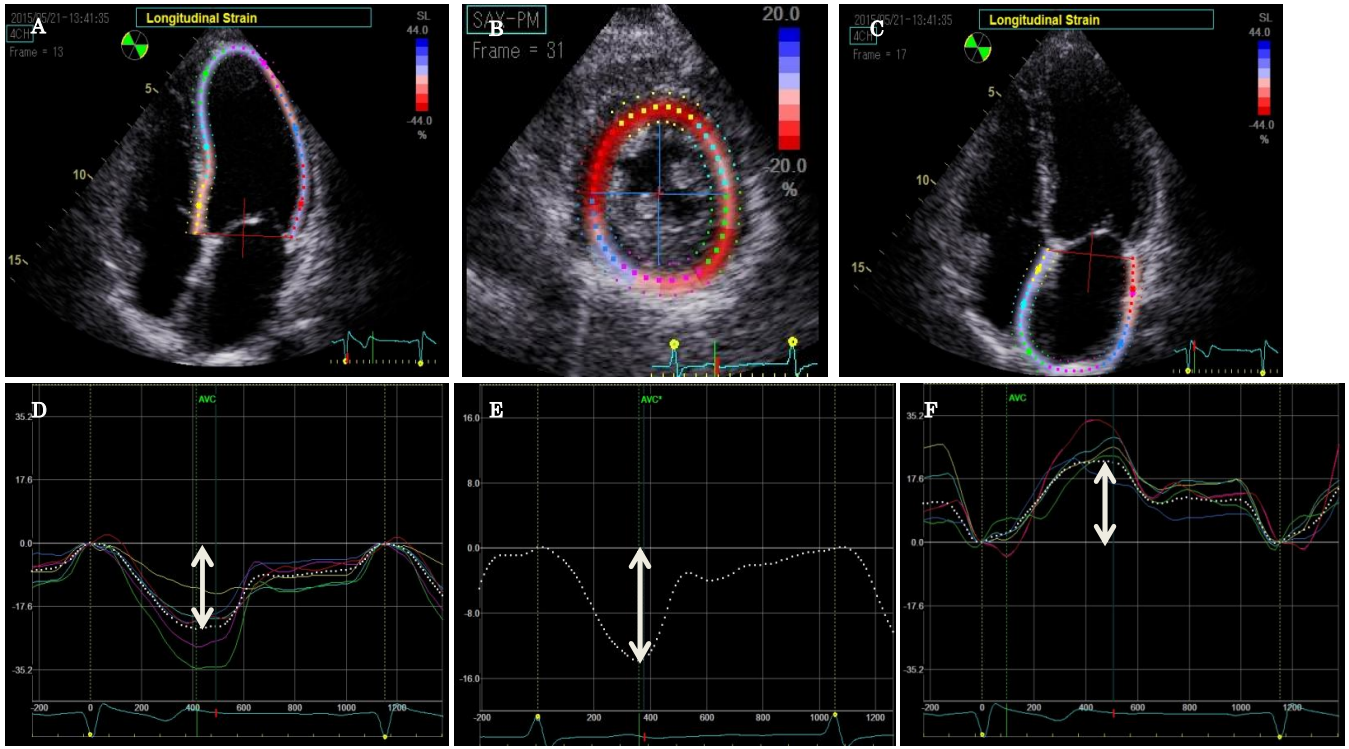

Fig. 1. Assessment of left ventricular myocardial strain patterns using 2-D speckle tracking strain imaging. The apical view (A), mid-papillary short axis view (B) and apical 4-chamber view (C) of the left ventricle are acquired. The resulting strain curves for the left ventricle and left atrium are shown with makings corresponding to global left ventricular longitudinal peak strain (GLS) (D), global left ventricular circumferential strain (GCS) (E) and peak left atrial longitudinal strain (PLAS) (F)

3. RESULTS

3.1 Patient Characteristics and Echocardiographic Measurements

Table 1 shows the baseline characteristics and echocardiographic measurements of the patients in the 2 groups. There were no significant differences in age, sex, history of diabetes, hypertension and smoking between the 2 groups. AS was significantly greater in the high Zva group than in the low Zva group ($p<0.05$). There were no significant differences in LVEF and LV mass index between the two groups. However, LV end-diastolic volume and end-systolic volume were significantly smaller in the high Zva group than in the low Zva group ($p<0.001$, and $p<0.01$, respectively). SV index was significantly smaller in the high Zva group than in the low Zva group ($p<0.0001$).

3.2 Strain Measurements

There was no significant difference in GCS between the 2 groups (Table 2). GLS and PALS were significantly worsened in the high Zva group compared with that in the low Zva group ($p<0.05$, and $p<0.01$, respectively) (Table 2). Intraobserver variability of GLS, GSC and PALS were 5.3 ± 2.8%, 4.8 ± 3.1%, and 5.8 ± 4.6%, respectively. Interobserver variability of GLS, GSC and PALS were 6.2 ± 3.7%, 5.8 ± 4.7%, and 5.9± 4.9%, respectively.

3.3 Comparison between Aortic Stenosis and Hypertensive Hypertrophy

Patients in the high Zva group were divided into two subgroups according to etiology of LV hypertrophy: the AS group (n=28) and the H-LVH group (n=21). Table 3 shows the baseline characteristics and echocardiographic measurements of the patients in the 2 groups. Systolic blood pressure was significantly higher in the H-LVH group than in the AS group ($p<0.05$). There were no significant differences in LVEF, LV posterior wall thickness, LV mass index, and Zva between the 2 groups. LV end-systolic volume and SV index were smaller in the H-LVH

Table 1. Baseline and echocardiographic characteristics

	High Zva (N=49)	Low Zva (N=25)	P
Age (yrs)	81 ± 7	81 ± 11	0.99
Male	34 (69%)	20 (80%)	< 0.0001
Body surface area (m^2)	1.61 ±0.14	1.72 ±0.16	0.011
Systolic blood pressure (mmHg)	130 ±20	121 ±18	0.085
Diastolic blood pressure (mmHg)	66 ±10	62 ±11	0.097
Heart rate (beat per minute)	71 ±10	68 ± 10	0.207
eGFR (ml/min/1.73m^2)	45 ± 20	40 ± 10	0.710
BNP (pg/ml)	480 ± 27	489 ± 78	0.963
Diabetes mellitus	8 (16%)	8 (32%)	0.099
Hypertension	42 (86%)	22 (88%)	0.377
Dyslipidemia	19 (38%)	21 (84%)	< 0.0001
Current smoker	2 (4%)	1 (4%)	0.447
Aortic valve stenosis	28 (57%)	8 (32%)	0.041
Echocardiographic parameters			
LV end-diastolic volume (ml)	59.3 ± 14.4	81.9 ± 30.1	0.001
LV end-systolic volume (ml)	20.0 ± 7.4	30.5 ± 16.1	0.004
LV ejection fraction (%)	66.9 ± 7.7	63.8 ± 8.5	0.130
LA volume index (ml/m^2)	59.5 ± 24.3	40.2 ± 22.6	0.004
LV mass index (g/m^2)	121 ± 42	133 ± 44	0.358
E/A	0.8 ± 0.3	0.9 ± 0.3	0.061
E-DT (ms)	258 ± 82	255 ± 95	0.903
Ea (cm/s)	4.5 ± 1.4	5.7 ± 2.1	0.018
Aa (cm/s)	7.8 ± 2.4	8.0 ± 2.5	0.663
E/Ea	19.3 ± 10.4	17.6 ± 14.9	0.595
Stroke volume index (ml/m^2)	47.0 ± 7.5	60.1 ± 11.1	< 0.0001

eGFR, Estimated glomerular filtration rate; BNP, Brain natriuretic peptide; LV, Left ventricular; LA, Left atrial; DT, Deceleration time

Table 2. Strain measurements

	High Zva (N=49)	Low Zva (N=25)	P
Global LV longitudinal peak strain (%)	-16.3 ± 4.3	-18.2 ± 3.5	0.047
Global LV circumferential peak strain (%)	-17.4 ± 4.8	-17.9 ± 4.6	0.638
Global LA longitudinal strain (%)	18.4 ± 7.8	24.5 ± 9.9	0.006
LA stiffness	1.55 ± 0.23	0.80± 0.17	0.012

LV, Left ventricular; LA, Left atrial

Table 3. Baseline and echocardiographic characteristics

	AS group (N=28)	H-LVH group (N=21)	P
Age (yrs)	78 ± 4	74 ± 9	0.086
Male	6 (21%)	9 (42%)	0.107
Body surface area (m^2)	1.38 ±0.16	1.58 ±0.13	0.0001
Systolic blood pressure (mmHg)	121 ±18	141 ±17	0.0001
Diastolic blood pressure (mmHg)	63 ±9	70 ±9	0.011
Heart rate (beat per minute)	70 ±10	72 ±9	0.625
eGFR (ml/min/1.73 m^2)	43 ± 28	51 ± 11	0.371
Diabetes mellitus	2 (7%)	6 (28%)	0.053
Dyslipidemia	5 (18%)	14 (66%)	0.001
Current smoker	0 (0%)	2 (9%)	0.179
Echocardiographic parameters			
LV end-diastolic volume (ml)	61.4 ± 16.0	56.5 ± 11.9	0.241
LV end-systolic volume (ml)	21.5 ± 6.7	18.0 ± 7.9	0.104
LV ejection fraction (%)	65.9 ± 7.6	68.0 ± 7.9	0.370
LA volume index (ml/m^2)	67.5 ± 21.2	32.8 ± 12.0	< 0.0001
LV posterior wall thickness (mm)	13.5 ± 1.9	13.1 ± 0.9	0.529
LV mass index (g/m^2)	128.0 ± 47.2	102.4 ± 15.2	0.176
E/A	0.9 ± 0.3	0.7 ± 0.1	0.010
E-DT (ms)	276 ± 91	235 ± 66	0.094
Ea (cm/s)	3.9 ± 1.2	5.4 ± 1.2	< 0.0001
Aa (cm/s)	6.2 ± 1.6	9.6 ± 2.1	< 0.0001
E/Ea	24.6 ± 10.2	12.8 ± 6.1	< 0.0001
Stroke volume index (ml/m^2)	48.1 ± 8.2	38.4 ± 11.1	< 0.0001
Zva (mmHg ml/m^2)	3.91 ± 0.57	4.04 ± 0.93	0.568

eGFR, Estimated glomerular filtration rate; LV, Left ventricular; LA, Left atrial; DT, Deceleration time

group than in the AS group ($p<0.01$, and $p<0.0001$, respectively). There was no significant difference in GCS between the 2 groups (-17.7±4.5% vs. -16.9±5.3, p=0.608) (Fig. 2). GLS and PALS were significantly worsened in the AS group compared with that in the H-LVH group (GLS, -13.9±4.0% vs. -19.4±2.3, $p<0.0001$, and PALS, 14.6±5.5% vs. 23.4±7.6, $p<0.0001$, respectively) (Fig. 2). LA stiffness was greater in the AS group than in the H-LVH group (2.20±1.69 vs. 0.67±0.72, $p<0.0001$) (Fig. 2).

4. DISCUSSION

The major findings of the present study were follows: (1) increased global LV afterload impairs LV myocardial LV longitudinal systolic function in patients with LV hypertrophy; (2) despite of similar global LV afterload and LV hypertrophy, myocardial LV longitudinal systolic function and LA function are impaired in patients with severe AS compared with H-LVH patients.

In general, AS results in LV systolic pressure overload and elevated wall stress [5,20]. Consequently, LV wall thickness increases in an attempt to maintain adequate wall stress [5,21]. With increasing severity of AS, LV hypertrophy progresses to minimize LV wall stress and preserve LV systolic function. Ultimately, the LV decompensates and heart failure ensues. The transition from adaptive LV hypertrophy to heart failure is characterized by myocyte death and

myocardial fibrosis. A previous study demonstrated that in patients with AS, both increased LV mass and high relative wall thickness were associated with worsened myocardial longitudinal deformation in spite of normal LVEF [22,23]. Similarly, hypertensive heart disease represents abnormalities that include altered LV morphology, LV hypertrophy, and systolic and diastolic dysfunction. The myocardial consequences of HTN include not only myocyte hypertrophy, but also perivascular and myocardial fibrosis and medial thickening of the intramyocardial coronary arteries. Recently, using speckle-tracking echocardiography, some studies reported that LV contraction was first impaired in the longitudinal direction in patients with cardiovascular risk factors [24-26]. Therefore, strain is a measure reflecting regional systolic function and it has been used to detect subclinical myocardial dysfunction in a number of cardiac conditions. The Zva is a new index, assessing the global LV hemodynamic load that can be measured by Doppler echocardiography [8]. The Zva is associated with LV myocardial dysfunction, and with longitudinal, radial, and circumferential LV deformation impairment, especially in low-flow AS patients [27]. In the present study, GLS was significantly decreased in the high Zva group compared with that in the low Zva group. The present study shows that increased global LV afterload impairs LV myocardial LV longitudinal systolic function in both patients with LV hypertrophy. We speculate that when the prolonged high LV global afterload exceeds the limit of LV compensatory mechanisms, the longitudinal myocardial dysfunction occur firstly.

In general, subendocardial longitudinal fibers are vulnerable in the presence of myocardial ischemia and hemodynamic overload, and abnormal longitudinal function can be detected at an early stage [28,29]. On the other hand, at the same stage, this phenomenon may not be present in mid-myocardial fiber layers, resulting in normal circumferential strain. Some studies reported that subendcardial fibers are more sensitive to microvascular ischemia (subendocardial blood flow maldistribution related to LV hypertrophy and increased wall

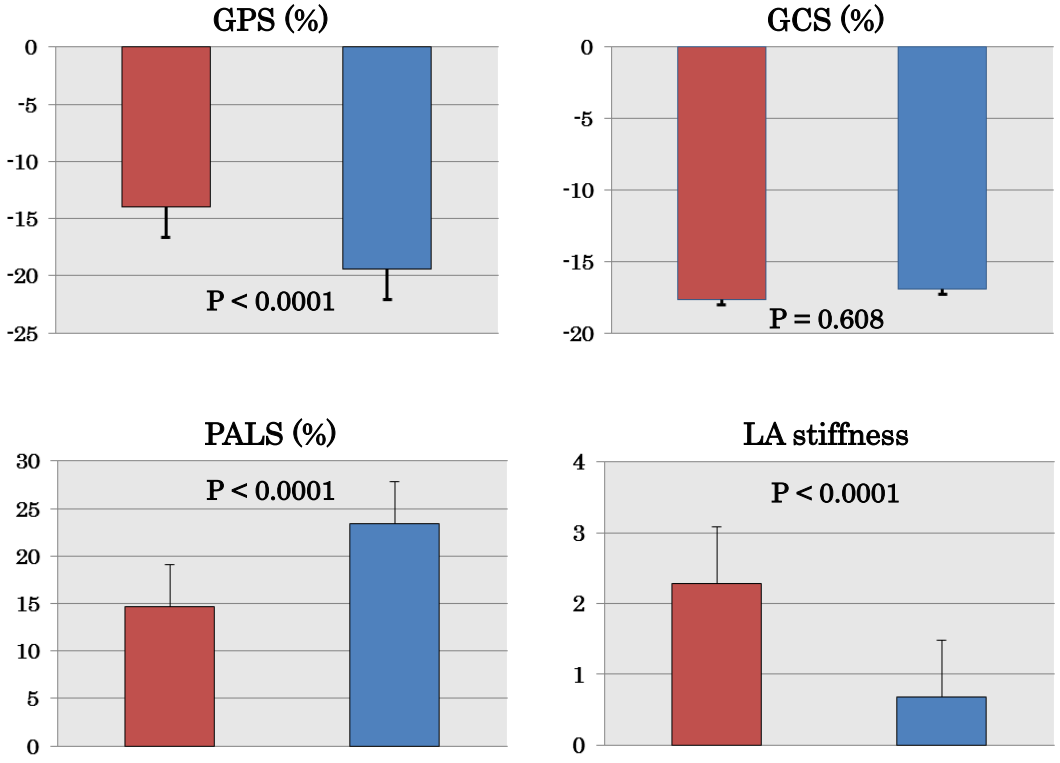

Fig. 2. Comparison of the strain measurements between AS group and H-LVH group (red bar: AS group, blue bar: H-LVH group)

AS, Aortic stenosis; H-LVH, Hypertensive left ventricle hypertrophy; GLS, Global left ventricle longitudinal peak strain; GCS, Global left ventricular circumferential strain; PALS, Peak left atrial longitudinal strain

stress) and fibrosis, and consequently, the longitudinal function is the first to be altered in AS [26,30]. In similarly, despite the normal diameter of coronary arteries in hypertrophied hearts, some predisposition to ischemia may exist, particularly in the subendocardial layers [31]. In dogs with severe LV hypertrophy, exhaustion of subendocardial blood flow reserve is associated with myocyte necrosis and fibrosis, demonstrating that structural alterations play an important role in the development of heart failure [32]. Poulsen et al. [33] showed that reduced longitudinal strain is associated with increased collagen turnover and degree of myocardial fibrosis in hypertensive patients. However, in the present study, GLS was significantly decreased in the AS group compared with that in the H-LVH group, GCS was not significantly difference between two groups, despite of similar high global LV afterload and LV hypertrophy. Saupe et al. reported that LVH secondary to hypertension protects against ischemia-induced myocardial dysfunction by minimizing the size of the region of severe acidosis in Dahl rats [34]. Although it is generally thought that hypertrophic myocardium, especially the subendocardium, has a poor tolerance to ischemia, this phenomenon may not be present in mid-myocardial fiber layers at the same stage, resulting in normal circumferential strain. We hypothesized that, during the natural history of hypertensive LVH, hypertension-induced LVH may result in improved poor tolerance to ischemia, compared with AS. This hypothesis may indicate that myocardial LV longitudinal systolic function is impaired, but circumferential systolic function is normal, in patients with severe AS compared with H-LVH patients despite of similar global LV afterload and LV hypertrophy. Moreover, in the present study, LA stiffness was greater in the AS patients than in the H-LVH patients. We previously reported that in patients with preserved longitudinal LV systolic function, LA structure and function are also preserved [35]. However, LA structure and function are rapidly impaired in patients with reduced longitudinal LV systolic function [35]. Despite of similar global LV afterload and LV hypertrophy, LA wall in the AS patients may become stiffer than that in the H-LVH patients.

5. LIMITATIONS

Several limitations should be addressed in the present study. First, the number of patients was relatively small. Second, the study population was heterogeneous including subjects with or without coronary artery disease. Although we excluded patients with evidence of coronary artery disease as indicated by electrocardiography and conventional echocardiography, and none of the study subjects complained of typical symptoms, the possibility that a small number of subjects with silent myocardial ischemia were included cannot be ruled out because of the lack of confirmation by stress testing or coronary angiography. Third, in the presence of significant aortic insufficiency, both the numerator (transvalvular gradient) and the denominator (SVI measured in the LV outflow tract) of Zva may increase, which may reduce the ability of this index to correctly quantify the severity of the hemodynamic load in patients with mixed valvular dysfunction. However, patients with more than mild aortic insufficiency were excluded from this study. Further studies are needed to examine the applicability and utility of Zva in patients with mixed valvular dysfunction. Finally, no data was available for medical therapy and hemodynamic measurement of LA and LV function. Therefore, future studies are needed to validate the findings of our study.

6. CONCLUSIONS

The magnitude of the global LV afterload as reflected by Zva is a powerful determinant of altered LV longitudinal deformation in LV hypertrophy patients with preserved LV ejection fraction. Moreover, despite of similar global LV afterload and LV hypertrophy, myocardial LV longitudinal systolic function and LA function are impaired in patients with severe AS compared with H-LVH patients.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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