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ORIGINAL ARTICLE

Subclinical left ventricular systolic dysfunction in patients with severe aortic stenosis: A speckle-tracking echocardiography study

Ciddi aort darlığı olan hastalarda sol ventrikül sistolik fonksiyonunun subklinik bozulması: Bir speckle tracking ekokardiyografi çalışması

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ABSTRACT

Objective: In patients with aortic stenosis (AS), the left ventricular (LV) geometry changes due to the increased LV afterload. However, subclinical myocardial dysfunction can develop despite a normal LV ejection fraction (EF). This study was an investigation of subclinical LV systolic dysfunction in patients with severe AS with a normal LV EF using a strain imaging method, speckle-tracking echocardiography (STE), and an evaluation of its correlation with novel indices to assess the severity of AS.

Methods: A total of 45 asymptomatic patients with severe AS and 25 age- and sex-matched controls without any cardiac disease and with preserved LV EF (EF ≥60%) were studied. In addition to performing conventional echocardiography and STE-based strain imaging, novel indices (energy loss index [ELI], valvulo-arterial impedance, systemic arterial compliance) were also measured.

Results: The LV EF, and the LV end-diastolic and end-systolic diameters were similar in the 2 groups. The LV longitudinal peak systolic strain (10.66±1.15% to 19.66±2.62%; p=0.0001) and strain rate (0.32±0.07 s^{-1} to 1.85±0.32 s^{-1}; p=0.0001) were significantly impaired in the study patients compared to the controls, demonstrating subclinical ventricular systolic dysfunction. A significant positive correlation was observed between the ELI and the LV strain/strain rate (r=0.45, p=0.002; r=0.55, p=0.0001, respectively).

Conclusion: Patients with severe AS develop subclinical LV systolic dysfunction, despite a preserved EF. Novel strain imaging-based echocardiographic techniques may provide additional data that can detect early myocardial systolic deterioration in these patients.

ÖZET

Amaç: Aort darlığı olan hastalarda, sol ventrikül (SV) ardyükündeki artışa bağlı olarak SV geometrisi değişir. Bununla beraber normal SV ejeksiyon fraksiyonuna (EF) rağmen subklinik miyokart işlev bozukluğu gelişebilir. Bu çalışmada, SVEF'si normal olup ciddi aort darlığığı bulunan hastalarda strain görüntüleme yöntemi, speckle tracking ekokardiyografi (STE), ile subklinik SV sistolik işlev bozukluğu araştırıldı ve aort darlığının derecelendirilmesinde kullanılan yeni parametreler ile ilişkisinin değerlendirilmesi amaçlandı.

Yöntemler: Çalışmaya, başka kardivasküler hastalığı olmayan ve LV EF'si normal (≥%60) 45 semptomsuz ileri aort darlıklı hasta ile yaş ve cinsiyet açısından benzer 25 sağlıklı katılımcı alındı. Geleneksel ekokardiyografi (EKO) ve STE yöntemlerinin yanısıra, "energy loss index", valvuloarteriyel empedans, sistemik arteriyel kompliyans gibi yeni parametreler de kullanıldı.

Bulgular: Sol ventrikül diyastol sonu ve sistol sonu çapları ve SV EF her iki grupta benzer bulundu. Subklinik ventrikül işlev bozukluğunun bir göstergesi olarak, SV longitudinal pik sistolik strain (%10.66±1.15 ve %19.66±2.62, p=0.0001) ve strain rate (0.32±0.07 1/s ve 1.85±0.32 1/s, p=0.0001) değerleri, hasta grubunda kontrol grubuna göre belirgin olarak bozulmuştu. Sol ventrikül strain/strain rate değerleri ile "energy loss index" arasında anlamlı pozitif korelasyon saptandı (sırasıyla, r=0.45, p=0.002; r=0.55, p=0.0001).

Sonuç: Aort darlığı olan hastalarda, korunmuş EF'ye rağmen subklinik SV sistolik işlev bozukluğu görülebilir. Strain görüntüleme-bazlı yeni ekokardiyografi teknikleri, bu hastalarda miyokardın sistolik işlevlerindeki bozulmayı erken dönemde saptayarak ek veri sağlayabilir.

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Aortic stenosis (AS) is the most common heart valve disease in the older population and is associated with higher mortality and morbidity rates than diseases involving other heart valves.[1,2] Increased afterload caused by the stenotic valve eventually leads to systolic and diastolic left ventricular (LV) dysfunction.[3] The timing of an aortic valve operation depends on the severity of the stenosis, the presence of symptoms, and LV dysfunction.[4] Patients with AS may remain asymptomatic for a long period of time.[5,6] In asymptomatic patients, the risk of sudden cardiac death is less than 1% per year. However, 30% of asymptomatic patients develop symptoms within 2 years.[7,8] After the progression of mild symptoms caused by severe AS, the outcome is extremely poor without an intervention.[4] Because of an increased risk for sudden cardiac death in some of the patients, the timing of intervention is challenging in asymptomatic patients with severe AS and normal LV ejection fraction (EF).[9] Besides LVEF, another important prognostic marker to make a decision for intervention in such patients is LV systolic functions. The development of LV systolic dysfunction is associated with a poor prognosis.[10,11] The LV EF recommended by the current guidelines as a method to assess LV systolic function is not sufficient to assess subclinical LV systolic dysfunction; more sensitive methods are needed to fully assess LV function. Quantitative techniques such as global longitudinal strain (GLS) analysis have been used to accurately characterize global myocardial systolic function and to detect subtle changes in LV performance before EF is decreased.[12,13]

Abbreviations:

AS	*Aortic stenosis*
AVA	*Aortic valve area*
AVR	*Aortic valve replacement*
BSA	*Body surface area*
DBP	*Diastolic blood pressure*
EF	*Ejection fraction*
ELI	*Energy loss index*
EOA	*Effective orifice area*
GLS	*Global longitudinal strain*
IVS	*Interventricular septum*
LV	*Left ventricular*
LVEDD	*LV end-diastolic diameter*
LVESD	*LV end-systolic diameter*
MPG	*Mean transaortic pressure gradient*
PW	*Posterior wall*
SAC	*Systemic arterial compliance*
SBP	*Systolic blood pressure*
STE	*Speckle-tracking echocardiography*
SVI	*Stroke volume index*
Zva	*Valvulo-arterial impedance*

In patients with AS, the occurrence of symptoms and LV dysfunction do not always correlate with the classical markers of hemodynamic severity (effective orifice area [EOA], transvalvular pressure gradients, etc.).[14] Novel indices like the energy loss index (ELI), systemic arterial compliance (SAC), and valvulo-arterial impedance (Zva) can provide a more accurate estimation of the severity of AS by considering the energy loss and increased workload caused by the stenosis.[15]

The aim of the present study was to evaluate subclinical LV systolic dysfunction in patients with severe AS, without any cardiovascular disease, and with a normal LV EF, using a strain imaging method, speckle-tracking echocardiography (STE) and to investigate the correlations with novel indices used to estimate the severity of AS.

METHODS

Study design and patient population

The study included 45 consecutive asymptomatic patients (60% male; mean age: 73.15±6.36 years) who were found to have severe AS after an echocardiographic evaluation (aortic valve area [AVA] <1 cm^2 using the continuity equation and mean transaortic pressure gradient [MPG] >40 mmHg) and without significant coronary artery disease as documented by coronary angiography. A total of 25 age- and sex-matched healthy controls were recruited. All of the patients had preserved LV systolic function (LV EF ≥60%) and sinus rhythm. Patients with significant coronary artery disease, hypertension, diabetes mellitus, moderate-severe aortic regurgitation or significant mitral valve disease, heart failure, cardiomyopathy, prosthetic heart valve, renal failure, congenital or acquired aortic disease, aortic aneurysm, history of cardiovascular or aortic surgery, connective tissue disorder, pulmonary hypertension, low quality echocardiographic images, conduction abnormalities or atrial fibrillation observed on an electrocardiogram were excluded.

The study protocol was approved by local Ethics Committee, and a detailed, written, informed consent was obtained from each patient. The study was conducted according to the Declaration of Helsinki.

Echocardiographic measurements

Transthoracic echocardiography was performed on the patients using a Matrix iE33 system (Philips Healthcare, Andover, MA, USA) with a 2.3–3.5 MHz transducer. LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), interventricular sep-

tum (IVS) thickness and posterior wall (PW) thickness were measured from the parasternal long-axis view in M-mode. LV EF was calculated from the apical 4-chamber view using the modified Simpson's method.[16]

Speckle-tracking echocardiography

LV apical 4-chamber, 2-chamber, and 3-chamber views were acquired in grayscale using a frame rate of 60 to100 frames per second[17] for images of 3 consecutive cardiac cycles at end-expiration breath-holding, and were stored digitally on a hard disk for offline analysis. Imaging analysis was performed on a PC work-station using QLAB analysis software, version 8.1 (Philips Healthcare, Andover, MA, USA). The LV endocardial border of the end-systolic frame was manually traced. On the basis of this line, the computer automatically created a region of interest including the entire transmural wall for all of the patients, and the software selected natural acoustic markers moving with the tissue. Automatic frame-by-frame tracking of these markers during the cardiac cycle (2-dimensional [2D] systolic time interval method) yielded a measure of strain, and strain rate at any point of the myocardium. LV GLS and strain rate (GLSR) were measured by averaging the values of all of the segments.

Severity of aortic valve stenosis

Transvalvular velocity was measured using continuous-wave Doppler from the apical 5-chamber and apical long-axis windows. The maximal and mean pressure gradients across the aortic valve were calculated using a modified Bernoulli equation.[18] Left ventricular outflow tract (LVOT) diameter was measured in mid-systole from the parasternal long-axis view after the outflow tract had been magnified. The transvalvular aortic velocity time integral was obtained using continuous wave Doppler. AVA was determined using the continuity equation method as previously described[19] and was divided by body surface area (BSA) to calculate indexed AVA.

Energy loss index

The ELI, i.e., the EOA corrected for pressure recovery, was calculated using the following formula:

ELI = (EOA x Aa)/(Aa–EOA)/BSA, where Aa is the aortic cross-sectional area calculated from the diameter of the aorta measured at the sinotubular junction.[14,15,20]

Systemic arterial compliance

Systolic and diastolic blood pressures (SBP, DBP) were measured using an arm-cuff sphygmomanometer at the time of the echocardiographic examination. The ratio of the stroke volume index (SVI) to the brachial pulse pressure (the difference between the SBP and the DBP) was used as an indirect measure of the total SAC.[21]

Valvulo-arterial impedance

As a measure of global LV hemodynamic load, Zva was calculated as follows: Zva = (MPG+SBP)/SVI, where Zva represents the valvular and arterial factors that oppose ventricular ejection by absorption of the mechanical energy developed by the LV.[14]

Reproducibility

For assessment of intraobserver variability, a sample of 10 2D strain measurements was randomly selected and examined by the same observer on 2 different days.[22]

Statistical analysis

The statistical data were analyzed using SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA) software. The Shapiro-Wilks test was used to determine normal distribution of the data. The results were expressed as mean and SD. One-way analysis of variance was used to compare the patients with severe AS to the control group. Correlation analyses were derived using Pearson's correlation coefficient. A value of r between 0 and 0.25 represented a very weak correlation, between 0.25 and 0.50 a weak correlation, between 0.50 and 0.69 moderate, between 0.70 and 0.89 strong, and a value between 0.90 and 1 indicated a very strong correlation. The results were considered significant when the p value was less than 0.05.

RESULTS

The demographic data and clinical characteristics were similar in the AS patients and the control group (Table 1). There were no significant differences between the groups with respect to LVEDD, LVESD, or EF. IVS and PW thickness was greater in patients with AS compared with the controls (1.25±0.06 cm to 0.97±0.76 cm, p=0.0001; 1.22±0.17 cm to 0.93±0.07 cm, p=0.0001, respectively), as expected. In the patient group, the ELI and the SAC were sig-

Table 1. Demographic and clinical characteristics of the study groups

Parameter	Aortic stenosis group (n=45)	Control group (n=25)	*p*
Age	73.15±6.36	72.88±5.4	NS
Male (%)	60	60	NS
Systolic blood pressure (mmHg)	123± 10.3	122±11.5	NS
Diastolic blood pressure (mmHg)	80±5.5	79±5.8	NS
Heart rate (bpm)	76±2.7	74±2.6	NS
Body surface area (m^2)	1.82±0.25	1.80±0.21	NS

Table 2. Echocardiographic measurements in patients with severe AS and in control subjects

Parameter	Aortic stenosis group (n=45)	Control group (n=25)	*p*
Left ventricular end diastolic diameter (cm)	5.08±0.28	5.04±0.22	NS
Left ventricular end systolic diameter (cm)	3.45±0.28	3.36±0.21	NS
Left ventricular ejection fraction (%)	60.75±1.14	61.08±1.25	NS
Interventricular septum (cm)	1.25±0.06	0.97±0.76	0.0001
Posterior wall (cm)	1.22±0.17	0.93±0.07	0.0001
Maximal aortic gradient (mmHg)	73.35±11.17	6.92±2.32	0.0001
Mean aortic gradient (mmHg)	45.8±8	3.43±0.86	0.0001
Aortic valve area (cm^2)	0.77±0.11	2.96±0.56	0.0001
Indexed aortic valve area (cm^2/m^2)	0.43±0.07	1.56±0.08	0.0001
Energy loss index (cm^2/m^2)	0.45±0.07	0.86±0.16	0.0001
Systemic arterial compliance ($mL/m^2/mmHg$)	0.56±0.10	0.98±0.27	0.0001
Valvulo-arterial impedance ($mmHg/mL/m^2$)	6.38±1.30	2.84±0.36	0.0001
Left ventricular strain (%)	10.63±1.41	19.88±2.88	0.0001
Left ventricular strain rate (1/sn)	0.26±0.07	1.71±0.46	0.0001

Table 3. Correlation between left ventricular global longitudinal strain and aortic stenosis severity indices

Variables	r	*p*
Energy loss index	0.45	0.002
Systemic arterial compliance	0.05	0.57
Valvulo-arterial impedance	-0.22	0.41
Aortic valve area	0.36	0.014
indexed aortic valve area	0.25	0.09
Maximum gradient	-0.26	0.074
Mean gradient	-0.25	0.086

r: Correlation coefficient.

nificantly lower, while the Zva was higher than that of the control group. The LV GLS (10.66±1.15%–19.66±2.62%; p=0.0001) and the GLSR (0.32±0.07 s^{-1} to 1.85±0.32 s^{-1}; p=0.0001) were significantly impaired in the AS patients compared with the controls, demonstrating subclinical LV systolic dysfunction (Table 2).

In the patient group, a significant positive correlation was observed between the ELI and the LV GLS/GLSR (r=0.45, p=0.002; r=0.55, p=0.0001, respectively) (Figure 1). The LV GLS was also positively correlated with the AVA (r=0.36; p=0.01). No significant correlation was found between the LV GLS/GLSR and the SAC, Zva, or the other AS severity parameters (Table 3).

Reproducibility

The intraclass correlations for intra-observer variability were good for the STE parameters (GLS: 0.90, 95% confidence interval [CI]: 0.75-0.98; GLSR: 0.86, 95% CI:).

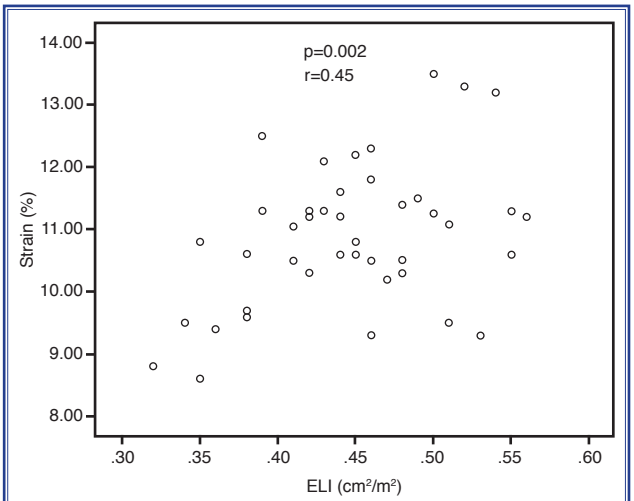

Figure 1. The correlation between left ventricular global longitudinal strain and energy loss index in the patient group.

DISCUSSION

In the present study, we demonstrated that the LV GLS and GLSR values were impaired in patients with severe AS with preserved LV EF. LV strain was also correlated with the AS severity indexes of AVA and ELI.

In patients with AS, LV hypertrophy as a compensatory mechanism for pressure overload accompanied by interstitial myocardial fibrosis beginning in the sub-endocardial layer.[23] Myocardial fibrosis leads to a reduction in ventricular compliance, hence LV diastolic dysfunction, and eventually LV systolic dysfunction.[3,24,25] Weidemann et al.[26] demonstrated that LV myocardial fibrosis in patients with severe AS and a preserved LV EF varied widely from minimal to severe, and that the severity of fibrosis was negatively correlated with LV GLS and GLSR. Fibrotic changes induced by AS mainly affect LV longitudinal function, while the EF is determined mainly by radial myocardial function and decreases in the very advanced phase of the disease, when both radial function and longitudinal function are compromised.[3] These pathophysiological mechanisms can explain why some patients are at higher risk of sudden death, even though they are asymptomatic with a preserved EF. Asymptomatic AS patients are generally not referred for aortic valve replacement (AVR) surgery until the development of symptoms or LV dysfunction (unless concurrent coronary artery bypass grafting is required) and a "watchful waiting" strategy is recommended for those patients.[27] However, it has been postulated that watchful waiting until symptom onset may result in irreversible myocardial fibrosis, ultimately compromising the AVR surgical outcomes.[28] Obviously, AVR should be considered before this end-stage of the disease. Patients with severe AS should be evaluated with more sensitive echocardiographic techniques than EF for the assessment of LV systolic function. GLS analysis as a novel quantitative method that has been used to determine a detailed analysis of global myocardial contraction and provides early detection of impairment in LV systolic function.[12,13] Cramariuc et al.[29] demonstrated that a greater degree of LV hypertrophy and the presence of symptoms were associated with decreased LV longitudinal deformation assessed with 2D STE in patients with AS. In the same study, LV radial and circumferential strain were also measured but no significant difference was found between geometric groups. A lower average LV GLS was related to more severe AS, a larger LV mass, and concentric geometry.

Another important issue while assessing AS patients is accurate evaluation of the severity of AS. Patients who have similar aortic valve EOA measurements may have different clinical outcomes.[5,30] Recent studies have emphasized the importance of taking into account the pressure recovery phenomenon that occurs downstream from heart valves.[31–33] Garcia et al.[15] indicated that the ELI has the potential to reflect the severity of stenosis better than the EOA with the cut-off point for severe stenosis of ≤0.5–0.6 cm^2/m^2. In our study, the mean ELI in the patient group was 0.45±0.07 cm^2/m^2 and a significant positive correlation was seen between the ELI and the LV GLS/GLSR rate. Although, the AVA was also positively correlated with the LV GLS, the significance of the correlation between the ELI and the LV GLS was stronger.

Other novel parameters used to assess the significance of AS are SAC and Zva. Briand et al.[14] showed that a reduced SAC (<0.6 $mL/m^2/mmHg$) independently contributed to increased afterload and decreased LV function. Also, Zva as a reflection of global LV afterload was found to be significantly increased (>4.5 $mmHg/mL/m^2$) in the severe AS and reduced SAC group and independently associated with LV diastolic and systolic dysfunction. Banovic et al.[34] demonstrated that Zva was the best predictor of mor-

tality in asymptomatic patients with severe AS. In our study, though the mean SAC and Zva values indicated hemodynamically significant AS, no significant correlation was found between the LV systolic function parameters and SAC and Zva, which was presumably related to having a more homogeneous patient group by excluding patients with coronary artery disease and hypertension, in contrast to the relevant studies. Hypertension and atherosclerosis in patients with AS have an additive effect on reduced arterial compliance by increasing arterial stiffness.

In conclusion, the present study demonstrated that LV longitudinal strain analysis provided reliable information about LV systolic function in patients with severe AS, despite having a normal EF. In addition, an association between the ELI and GLS may be useful to identify patients at higher risk for the development of myocardial dysfunction. These novel indices may help to determine the optimal timing of intervention in asymptomatic severe AS patients and take a place in the algorithm of the management of AS with further studies that include a larger patient population.

Limitations and strengths

The homogeneity of our study group with regard to the severity of the AS is a strength of this study. In addition, newer quantitative technics were used to evaluate LV function and the severity of the AS. The main limitation of this study is the small size of the study group. Further studies with a large sample size of participants are warranted in order to be able to evaluate AS patients and determine the optimal time for surgery.

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Keywords: Aortic stenosis; energy loss index; left ventricular strain imaging.

Anahtar sözcükler: Aort darlığı; enerji loss index; sol ventrikül strain görüntülemesi.