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Strain and Strain Rate Echocardiography Findings in Children With Asymptomatic Congenital Aortic Stenosis

Vehbi Dogan · Burhan Öcal · Utku Arman Orun ·
Senem Ozgur · Osman Yılmaz · Mahmut Keskin ·
Özben Ceylan · Selmin Karademir · Filiz Şenocak

Abstract The aim of our study was to evaluate myocardial functions with strain/strain rate echocardiography in asymptomatic patients having congenital aortic stenosis (CAS) with normal cardiac functions as determined by conventional echocardiographic techniques and comparing them with those of healthy controls. A total of 58 patients with various degrees of isolated CAS and 52 healthy controls were enrolled in this study. Conventional and two-dimensional speckle tracking (2DSTE) echocardiography were performed. Global longitudinal strain (LS) (-23.1 ± 3.6 and -23.8 ± 4.7), and longitudinal strain rate (LSR) (-1.49 ± 0.32 and -1.76 ± 0.39) values were lower, whereas circumferential strain (CS) (-25.9 ± 4.7 and -22.8 ± 6.4) and circumferential strain rate (CSR) (-1.82 ± 0.46 and -1.69 ± 0.49) values were greater in the patient group than in the control subjects. The difference was significant for global LSR and CS ($p < 0.05$) values. Regional analysis showed lower LS values in the basal part of the left-ventricular (LV) free wall and lower LSR values in the basal parts of both of the septum and free wall in the patient group ($p < 0.05$). CS values in the anteroseptal, posterior, and inferior walls were significantly greater in the patients ($p < 0.05$). 2DSTE detects subtle alterations in myocardial function in asymptomatic children with CAS. Impairment of LV long-axis function occurred earlier and was more prominent in basal parts of the interventricular septum and the free wall of the left ventricle.

V. Dogan (✉)
Department of Pediatric Cardiology, Faculty of Medicine,
Gaziosmanpaşa University, Tokat, Turkey
e-mail: vdogan86@yahoo.com

B. Öcal · U. A. Orun · S. Ozgur · O. Yılmaz · M. Keskin ·
Ö. Ceylan · S. Karademir · F. Şenocak
Department of Pediatric Cardiology, Dr. Sami Ulus Maternity
and Children's Hospital, Ankara, Turkey

Introduction

Congenital aortic stenosis (CAS) accounts for 5 % to 10 % of all congenital heart disease. In clinical practice, the severity of stenosis is defined using the Doppler ultrasound-derived peak instantaneous aortic flow velocity or Bernoulli equation-derived pressure gradient across the stenotic segment. With this method, a peak systolic pressure gradient <25 mmHg is defined as trivial, 25–50 mmHg as mild, 50–80 mmHg as moderate, and >80 mmHg as severe [19]. Therapeutic management of patients with AS generally depends on the hemodynamic severity of the stenosis and the presence of symptoms [2]. Compared with the adult population, there is controversy concerning the timing of intervention in children with AS, especially for patients with moderate stenosis [2, 15]. The main reason for intervention in this subset of patients is to avoid further deterioration and irreversible myocardial damage.

Two-dimensional speckle tracking (2DSTE) is a relatively new echocardiographic technique to quantify myocardial strain, providing comprehensive information on left-ventricular (LV) myocardial contractility. It is based on frame-by-frame tracking of tiny echo-dense speckles within the myocardium and subsequent measurement of LV deformation. 2DSTE has been shown to be effective in detecting subclinical myocardial dysfunction in a spectrum of heart disease [12, 18].

The aim of our study was to evaluate myocardial function with 2DSTE in asymptomatic CAS patients with normal cardiac functions as determined by conventional

echocardiographic techniques and compare them with that of healthy controls.

Methods

Study Population

The study population comprised 58 asymptomathic patients with varying degrees of CAS who were visiting the outpatient clinic at the Dr. Sami Ulus Pediatric Research and Training Hospital between March 2010 and April 2011 and who were eligible for inclusion in the study. Inclusion criterion was Doppler-derived peak instantaneous aortic flow velocity of at least 2.5 m/s (corresponding to 25 mmHg peak systolic pressure gradient). Exclusion criteria were (1) associated congenital heart disease, (2) endocardial fibroelastosis, (3) moderate or severe aortic regurgitation, (4) acute or chronic illness at the time of echocardiographic evaluation, (5) low ejection fraction (EF) measurement with conventional echocardiography methods, (6) diagnosis of genetic or metabolic diseases, and (7) inappropriate echocardiographic data for off-line analysis. The patient group was divided into two subgroups: those with aortic flow velocity <3.5 m/s (peak systolic gradient <50 mmHg), which was defined as mild stenosis, and those with aortic flow velocity >3.5 m/s, which was defined as moderate to severe stenosis.

Demographic and anthropometric characteristics, including age and body weight at the time of echocardiographic study, were recorded. A complete history, physical examination, and electrocardiography were performed.

Control Group

The control consisted of 52 subjects who were routinely referred for echocardiographic evaluation of an asymptomatic, innocent heart murmur and found to have no structural heart disease or acute/chronic illness. We obtained informed consent in writing from the parents of all subjects according to the guidelines of the Institutional Review Board.

Echocardiography

Echocardiographic study was performed with a commercially available standard ultrasound scanner (Vivid 7; General Electric Medical Systems, Horten, Norway) with 3.0- and 7.5-MHz transducers. Transducer choice depended on the weight and age of the child. All echocardiographic examinations were performed by the same investigator to avoid interobserver variability.

Conventional Echocardiographic Parameters

Quantification of chamber size and LV systolic function were measured in accordance with the recommendations of American Society of Echocardiography [17]. The LV dimensions were calculated from standard M-mode images at the parasternal long-axis view and included LV diameters and end-systolic and end-diastolic thickness of the interventricular septum and posterior wall. The LV systolic functions were characterized using fractional shortening (FS) and EF. The LV end-diastolic and end-systolic volumes were measured from the apical two- and four-chamber (FC) views, and LVEF was calculated using Simpson's rule. LV mass was calculated using the formula for estimating LV mass according to Devereux and was subsequently indexed for body surface area (BSA).

2DSTE

Standard 2D multiframe B-mode gray scale images of the left ventricle were acquired at apical 4C and parasternal short-axis (SA) view (at the level of the papillary muscles). A sector scan angle of 30° to 60° was chosen, and frame rates ≥60 Hz were used. Data were stored in cine-loop format for further off-line analysis. Off-line analysis of the stored data was performed using software for echocardiographic quantification (Echopac 6.3.6; Vingmed General Electric Medical Systems). In brief, the endocardial contour was manually traced at an the end-systolic frame. The software then automatically traced a region-of-interest width and, when necessary, was manually adjusted to cover the entire myocardial wall. The tracking algorithm then followed speckles in the myocardium through the cardiac cycle. Tracking was only accepted if both visual inspection as well as dedicated software indicated adequate tracking. The software automatically divided the cross-sectional image into six segments. LV segments to be analysed were the basal, mid-, and apical segments of the septum and lateral wall of the apical 4C view as well as the anteroseptal, anterior, lateral, posterior, inferior, and septal segments of the basal SA view. Myocardial longitudinal, radial, and circumferential strain (CS) and circumferential strain rate (CSR) values of each cardiac segment were recorded. To determine global S and SR values, values of the six segments were averaged for the 4C and the basal SA views. All 2DSTE analysis were performed by the same investigator to avoid interobserver variability. Strain values are dimensionless and are expressed as a percentage. The SR is the time derivation of S and is expressed as s^{-1}. The negative S values reflect shortening, whereas positive values reflect lengthening or thickening. An example for 2DSTE images and six segments of each axis is shown in Fig. 1.
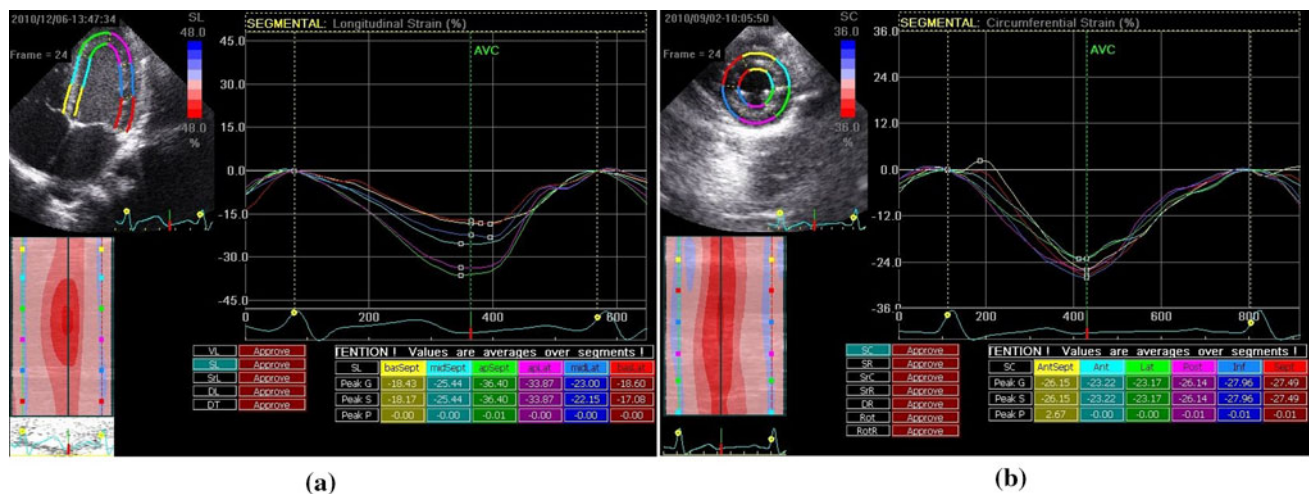
Fig. 1 2DSTE images and analysis from **a** apical 4C view and **b** parasternal SA view at the level of the papillary muscle

Statistical Analysis

All demographic, anthropometric, conventional echocardiographic, and 2D S/SR values were expressed as mean ± SD or median and range. A cohort consisting of 73 healthy children was used as a control group. Comparison between healthy controls and the patient group were performed by one-way analysis of the variance (ANOVA) and Kruskal–Wallis test as appropriate. All statistical analyses were performed with SPSS software (version 16.0; SPSS, Chicago, IL), and $p < 0.05$ was considered statistically significant.

Results

Demographic, Anthropometric, and Conventional Echocardiography Parameters

We examined 58 asymptomatic patients with CAS and 52 healthy controls with a mean age of 74.6 ± 49.8 and 76.6 ± 46.4 months and male-to-female ratio of 3.1 and 3.0, respectively. Conventional functional echocardiographic findings did not indicate systolic dysfunction, and were all in normal limits. Differences were statistically significant only in terms of end-systolic interventricular septum diameter and LV mass index between the patient and control groups ($p < 0.05$). Patient and control group demographic characteristics and anthropometric and conventional echocardiographic parameters are listed in Table 1.

Of the 58 patients, 40 were classified as having mild stenosis, and 18 were classified as having moderate to severe stenosis. Between these two groups, there were no statistically significant differences in terms of demographic, anthropometric, and conventional echocardiography parameters ($p > 0.05$).

Table 1 Demographic, anthropometric, and conventional echocardiographic findings (mean ± SD)

Findings	Control group	Patient group
No.	52	58
M/F	39/13	44/14
Age (months)	76.6 ± 46.4	74.6 ± 49.8
Weight (kg)	24.1 ± 13	23.8 ± 14.5
BSA (m²)	0.87 ± 0.32	0.85 ± 0.37
HR (bpm)	101.6 ± 26.3	103.1 ± 28.4
EF	75.7 ± 8.3	77.3 ± 8.7
FS	44.2 ± 7.7	46 ± 8.5
IVSEDD (mm)	6.6 ± 1.6	7.1 ± 2.4
IVSESD (mm)	10.7 ± 2.9	12.3 ± 2.7
LVEDD (mm)	33.8 ± 7.4	34.9 ± 8.4
LVESD (mm)	17.8 ± 5.8	19.2 ± 6.5
PWEDD (mm)	5.9 ± 1.4	6.1 ± 1.4
PWESD (mm)	10.3 ± 2.4	11.2 ± 2.4
LVMI (gr/m²)	56.1 ± 18.4	67.6 ± 25.4
ΔP_{max}	–	41.9 ± 11

HR heart rate, *IVSEDD* interventricular septum end-diastolic diameter, *IVSESD* interventricular septum end-systolic diameter, *LVEDD* LV end-diastolic diameter, *LVESD* LV end-systolic diameter, *PWEDD* posterior wall end-diastolic diameter, *PWESD* posterior wall end-systolic diameter, *LVMI* LV mass index, *ΔP_{max}* peak systolic pressure gradient

Myocardial S/SR Parameters

For the patient group, apical 4C and basal SA 2D images were stored with a mean frame rate (fps) of 69.8 ± 8.9 and 70.5 ± 11.1, respectively. These values were 68.9 ± 6.1 and 69.5 ± 6.4 fps in the control group. There were no analyses with a frame rate <50 fps.

Table 2 Global strain and strain rate findings (mean ± SD)

Parameter	Control group	Patient group	p
Global LS	−23.8 ± 4.7	−23.1 ± 3.6	0.098
Global LSR	−1.76 ± 0.39	−1.49 ± 0.32	0.033
Global CS	−22.8 ± 6.4	−25.9 ± 4.7	0.000
Global CSR	−1.69 ± 0.49	−1.82 ± 0.46	0.066
Global RS	34.5 ± 22.1	35.8 ± 21.9	0.935
Global RSR	2.26 ± 0.67	2.3 ± 0.97	0.442

LS longitudinal strain, *LSR* longitudinal strain rate, *CS* circumferential strain, *CSR* circumferential strain rate, *RS* radial strain, *RSR* radial strain rate

Global LS (−23.1 ± 3.6 and −23.8 ± 4.7) and LSR (−1.49 ± 0.32 and −1.76 ± 0.39) values were lower, whereas CS (−25.9 ± 4.7 and −22.8 ± 6.4) and CSR (−1.82 ± 0.46 and −1.69 ± 0.49) values were greater, in the patient group than in controls. The differences were significant in terms of LSR and CS values. RS and RSR values were similar, with a slightly greater values in the patient group. Global S and SR measurements are listed in Table 2.

Regional S and SR analysis from apical 4C view showed lower LS and LSR values in all segments of the septum and posterior free wall in the patient group than control group. However, the difference were statistically significant for LS values of the basal segments of the septum and free wall and the LSR values from basal segment of the posterior free wall ($p < 0.05$). Regional LS and LSR analysis findings are listed in Table 3. Regional LS and LSR values were lower in all segments in the moderate-to-severe stenosis group than mild-stenosis group, but the difference was not statistically significant ($p > 0.05$).

Table 3 Regional LS/LSR analysis findings (mean ± SD)

Region of analysis	Parameter	Control group	Patient group	p
SB	LS	−20.4 ± 3.2	−19.6 ± 3.2	0.076
	LSR	−1.47 ± 0.35	−1.31 ± 0.24	0.006
SM	LS	−23.8 ± 3.4	−23.1 ± 3.2	0.269
	LSR	−1.63 ± 0.4	−1.53 ± 0.27	0.273
SA	LS	−28.4 ± 5.3	−28.5 ± 5.9	0.951
	LSR	−2.07 ± 0.6	−1.98 ± 0.5	0.458
LVB	LS	−23.5 ± 5.6	−19.6 ± 7.2	0.003
	LSR	−1.92 ± 0.51	−1.68 ± 0.5	0.023
LVM	LS	−23.1 ± 4.7	−21.9 ± 4.9	0.201
	LSR	−1.61 ± 0.4	−1.55 ± 0.3	0.133
LVA	LS	−23.5 ± 6.1	−19.6 ± 7.2	0.003
	LSR	−1.87 ± 0.43	−1.68 ± 0.5	0.023

SB basal segment of interventricular septum, *SM* mid-septum, *SA* apical septum, *LVB* basal segment of free wall, *LVM* mid segment of free wall, *LVA* apical segment of free wall

Table 4 Regional SA S/SR analysis findings (mean ± SD)

Region of analysis	Parameter	Control group	Patient group	p
Anteroseptal	CS	−33.2 ± 5.6	−37.2 ± 6.5	0.002
	CSR	−2.73 ± 0.8	−2.9 ± 0.7	0.133
	RS	31.9 ± 19.5	32.1 ± 19.2	0.827
	RSR	2.16 ± 0.6	2.2 ± 0.9	0.488
Anterior	CS	−24.2 ± 7.1	−26.4 ± 8.1	0.114
	CSR	−2.1 ± 0.67	−2.1 ± 0.76	0.428
	RS	35.9 ± 24.1	37.1 ± 20.5	0.692
	RSR	2.1 ± 0.7	2.3 ± 0.9	0.375
Lateral	CS	−17.1 ± 6.7	−17.6 ± 8.4	0.072
	CSR	−1.53 ± 0.65	−1.59 ± 0.8	0.617
	RS	38.2 ± 23.2	40.4 ± 23.5	0.643
	RSR	2.15 ± 0.53	2.3 ± 1	0.328
Posterior	CS	−12.7 ± 5.8	−16.1 ± 7.9	0.019
	CSR	−1.53 ± 0.62	−1.61 ± 0.6	0.421
	RS	36.4 ± 23.4	38.9 ± 24.5	0.485
	RSR	2.2 ± 0.9	2.2 ± 1.1	0.918
Inferior	CS	−17.6 ± 7.5	−21.9 ± 7.9	0.004
	CSR	−1.81 ± 0.6	−1.87 ± 0.5	0.441
	RS	34.1 ± 23.2	33.9 ± 22.9	0.960
	RSR	2.2 ± 1.1	2.1 ± 1	0.742
Septal	CS	−32.2 ± 6.1	−34.2 ± 5.8	0.063
	CSR	−2.56 ± 0.72	−2.6 ± 0.6	0.743
	RS	30.7 ± 18.9	32.1 ± 21.5	0.568
	RSR	2.2 ± 0.9	2.1 ± 0.8	0.759

CS circumferential strain, *CSR* circumferential strain rate, *RS* radial strain, *RSR* radial strain rate

Basal SA views at the level of mitral valve were analysed for circumferential and radial S and SR measurements. CS values were greater in the patient group in all segments, whereas a statistically significant difference was present between two groups in terms of measurements from the anterioseptal, posterior, and inferior segments ($p < 0.05$). There was no significant difference between the two groups according to CSR, RS, and RSR measurements in all segments ($p < 0.05$) (Table 4). According to disease severity, CS and CSR values were greater in the moderate-to-severe stenosis group in all segments, but the difference was statistically significant only for the CSR values of the anteroseptal and septal segments ($p < 0.05$). RS and RSR were also greater in the moderate-to-severe stenosis group, with statistically significant results for the RS values of all segments except the anterior segment ($p < 0.05$).

Discussion

Obstruction to LV outflow results in LV pressure overload and concentric LV hypertrophy to maintain cardiac output.

The increase in wall thickness initially leads to normalization of wall stress; therefore, LV contractility is preserved. However, concentric hypertrophy compromises ventricular tissue compliance as well as subendocardial perfusion, thus leading to ischemia. This combination, with ischemia-induced replacement of contractile tissue by fibrous tissue, lead to diastolic and finally to systolic ventricular dysfunction [6, 7, 9].

In clinical practice, the severity of AS is defined using the Doppler ultrasound-derived peak instantaneous aortic flow velocity or the Bernoulli equation-derived pressure gradient across the stenotic segment. The therapeutic management of patients generally depends on the hemodynamic severity of the stenosis and the presence of symptoms. The rationale for intervention in children with severe AS is obvious when the patient is symptomatic and intervention/surgery will most likely improve the outcome. The decision is controversial when patients are asymptomatic, which is often the case in the pediatric population, even in cases of severe stenosis.

Doppler ultrasound-derived peak velocity flow, which is commonly used to indicate the severity of stenosis, is strongly dependent on hemodynamic status and does not provide any information on the impact of stenosis on the condition of the myocardium. Other traditional methods, such as 1D M-mode technique and 2D imaging (e.g., EF), are the most widely used clinical tools to quantify LV systolic function in various conditions. However, various studies have reported that subclinical alterations occur in systolic and diastolic myocardial functions in patients with AS and preserved EF. Furthermore, they do not provide information about regional alterations in ventricular myocardial contraction. Even more importantly, in the case of LV hypertrophy, these conventional indices appear to be relatively insensitive to impaired myocardial performance [12, 18].

Cardiac remodelling occurs early in the chronically pressure-overloaded heart. In children with AS, the total amount of myocardial collagen was significantly increased despite normal LV myocardial contractility and diastolic function as assessed by means of standard echocardiographic techniques. LV remodelling was abnormal in approximately one quarter of the patients, and none had more than mild hypertrophy despite significant fibrosis [14]. Derumeaux et al. [5] showed early regional systolic dysfunction in artificially pressure-loaded rats with normal conventional EF measurements.

Because the harmful effects of AS precede the symptoms and low EF values, it would be desirable to be able to detect myocardial changes at an early stage to optimize timing of the intervention and hopefully prevent permanent damage to the cardiac muscle. Kiraly et al. [8] showed that tissue Doppler strain imaging (TDI) indicated LV dysfunction in the longitudinal direction in children with various degrees of AS and normal conventional indices of ventricular function. However, TDI is limited by its inherently 1D nature and is strongly dependent on the angle of insonation. 2DSTE, with less angle dependence, has emerged as a new index of local myocardial function. Furthermore, various studies have shown that 2DSTE can detect subtle changes in regional myocardial function in a wide spectrum of myocardial diseases at an earlier stage compared with traditional methods [1, 4, 11, 16].

S/SR echocardiography studies of patients with AS in the literature mostly consist of adult patients with severe stenosis [3, 4, 13, 16]. Studies involving subjects of younger ages and mild stenosis had been rarely reported. However, the degree of regional impairment is closely related to collagen accumulation depending on the severity and duration of the pressure load. Furthermore, much current knowledge on pressure overload is from studies of subjects with acquired disease in whom a structurally normal LV is gradually exposed to greater pressures. However, in the case of CAS, pressure challenge is already present at some stage of intrauterine growth.

In our study, we found lower global LS and LSR values and greater circumferential and radial S/SR values. The differences were statistically significant only for LSR and CS values. Regional S/SR analysis showed lower LS and LSR values in all six segments and was statistically significant for only LS and LSR values from the basal segment of free wall and LSR measurement from the basal segment of septum. Circumferential S values were significantly greater in anteroseptal, posterior, and inferior segments in the patient group. These finding showed that a decrease in LV longitudinal systolic performance, especially in the basal segments of the interventricular septum and the LV free wall, precedes that in other directions, which is in agreement with previous reports performed in pressure-overloaded patients with AS and hypertension [3, 10, 13].

Delgado et al. [4] reported impaired systolic performance in all directions (longitudinal, circumferential, and radial) in elderly patients with severe AS. After aortic valve replacement (AVR), significant improvement in S/SR in all three directions was observed. Although improvement in longitudinal function was detected at 17 months after AVR, LS and LSR values were still lower than those of the control group. Carasso et al. [3] studied left ventricle mechanics in patients with severe AS with preserved and low EF values. They found lower LS values in all patients, whereas CS and CSR values were greater in patients with preserved EF and lower in patients with subnormal EF values. In another study including 420 adult patients with mild, moderate, or severe AS, S and SR values were found to be decreasing in all three directions parallel to disease severity. These investigators found that myocardial dysfunction begins in subendocardial layers in

cases of mild stenosis (longitudinal), involves the mid-wall (circumferential) in cases of moderate stenosis, and, finally, involves the transmural (radial) layer in cases of severe AS [13]. Marcus et al. [10] found an inverse relationship between global peak systolic strain parameters in all directions and degree of AS severity in a group of children with congenital valvar AS. They also determined that longitudinal systolic impairment precedes that in other directions and that local peak systolic strain in the interventricular septum was most affected.

The subendocardial myocardial fibers responsible for longitudinal function are more vulnerable to increased wall stress, stress-induced ischemia, and microvascular dysfunction associated with LV pressure overload [6, 9, 14]. Increased tissue pressure in the subendocardium results in impaired coronary perfusion during systole. Because they perform the greatest work in the development of tension during the cardiac cycle, increased energy requirements and impaired perfusion accounts for the vulnerability of the these subendocardial fibers to ischemia. In addition, the difference in regional impairment may be due to the distinct structural geometry and unequally exposure to increased wall stress. We found greater global and regional CS, CSR, and RS values in the patient group than control group. The mechanisms underlying the maintenance of normal or supra-normal LV radial function in the early stages of myocardial affectation by AS are thought to be related to the augmented LV wall thickness [3, 10]. It is possible that the increase in radial and CS values shown in mild cases of stenosis compensates for a decrease in longitudinal strain. In this light, a decrease of circumferential and radial strain in the more advanced stages of AS could be regarded as a form of decompensation.

We have shown that the decrease in LV longitudinal systolic performance, especially in basal parts of the septum and free wall, precedes that in other directions, which is in agreement with previous reports performed in pressure-overloaded adults with AS and hypertension. As mostly seen in adult patients with long-standing or severe stenosis, decreased radial function should be regarded as an alarming sign of decompensation.

Limitations

We analysed only an instantaneous measurements and we did not perform a validation study. Because of the small number of patients in the moderate-to-severe stenosis group, we could not analyse the condition with increasing disease severity. Assessment of radial deformation with 2DSTE is less reliable compared with longitudinal or circumferential deformation. Because disease severity and duration are determinative in LV systolic performance impairment, serial examination and long-term follow-up

with 2DSTE will give more information to understand the pathophysiology, and then it will be more appropriate to adopt the findings into clinical application.

Conclusion

In conclusion, we found differences in terms of S and SR echocardiography values between patients with normal cardiac functions as determined by conventional methods and healthy control subjects. Compatible with previous studies, impairment of the LV long-axis function occurred earlier and was more prominent in the basal parts of the interventricular septum and the free wall of the left ventricle. According to these findings, S/SR echocardiography, in addition to conventional methods, for evaluating LV functions and determining subtle alterations in CAS patients will be helpful in the management and timing of treatment.

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