Assessment of cardiac function in absence of congenital and acquired heart disease in patients with Down syndrome

Sevket Balli, Ilker Kemal Yucel, Ayse Esin Kibar, Ibrahim Ece, Eylem Sen Dalkiran, Sukru Candan

Istanbul, Turkey

Background: **Extra genetic material in patients with Down syndrome (DS) may affect the function of any organ system. We evaluated cardiac functions using conventional tissue Doppler and two-dimensional speckle tracking echocardiography in patients with DS in the absence of congenital and acquired heart disease in patients.**

Methods: **A total of 115 patients with DS between 6 and 13 years of age with clinically and anatomically normal heart and 55 healthy children were included in this cross-sectional study. DS was diagnosed by a karyotype test. Patients with mosaic type were not included in this study. Systolic and diastolic functions were evaluated by echocardiography.**

Results: **Pulsed waved Doppler transmitral early/late inflow velocity (E/A), tissue Doppler mitral annular early/late diastolic peak velocity (Ea/Aa), transtricuspid E/A and tricuspid valve annulus Ea/Aa, pulmonary venous Doppler systolic/diastolic (S/D) wave ratio were lower in patients with Down syndrome than in the control group (P=0.04, P=0.001, P<0.05, P<0.001, P<0.001, respectively). Mitral and tricuspid annular Ea were lower in patients with DS (P<0.001). The right and left ventricular myocardial performance indexes were higher in patients with DS than in the controls (P<0.01). They had significantly higher left ventricular mass, ejection fraction, the mitral annular plane systolic excursion values. However, the Down syndrome group compared with the controls had a lower strain values examined by two-dimensional longitudinal speckle-tracking strain echocardiography.**

Conclusion: **These findings suggest conventional tissue Doppler and two-dimensional longitudinal speckle-tracking strain echocardiography were useful methods of investigating ventricular function and identifying a higher incidence of biventricular dysfunction in patients with Down syndrome compared with the healthy controls.**

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Original article

Introduction

Down syndrome (DS) is one of the most common genetic birth defects, affecting approximately one in 700 live births.[1,2] Among live-born babies, DS is the most common chromosomal anomaly. Heart defects are the most common birth defect in children with DS. It is characterized by the whole chromosomal aneuploidy in about 95% of cases. The remaining 5% is in the form of translocations and mosaics.[3,4] Approximately 40% to 60% of children with DS have heart defects.[5,6] Even in the absence of congenital and acquired heart defects in patients with DS, there may also be a risk for problems with the myocardial fibrillar structure and autonomic nervous system.[7,8]

Patients with DS are at an increased risk of developing pulmonary hypertension due to abnormal pulmonary vasculature growth. Cardiac function is also affected due to pulmonary hypertension.[9-13]

Patients with DS can often live up to adulthood who have reduced exercise capacity in daily life and sports activities. But, we do not have enough knowledge about their cardiac capacity. Patients with DS can experience Left ventricle (LV) myocardial deformation later in life,

Author Affiliations: Department of Pediatric Cardiology, Balikesir Ataturk Hospital, Balikesir, Turkey (Balli S); Department of Pediatric Cardiology, Siyami Ersek Education and Research Hospital, Istanbul, Turkey (Yucel IK); Department of Pediatric Cardiology, Children's Hospital, Mersin, Turkey (Kibar AE); Department of Pediatric Cardiology, Yuzuncu Yil University of Medicine, Van, Turkey (Ece I); Department of Pediatrics, Balikesir Ataturk Hospital, Balikesir, Turkey (Dalkiran ES); Department of Medical Genetics, Balikesir Ataturk Hospital, Balikesir, Turkey (Candan S)

Corresponding Author: Sevket Balli, Department of Pediatric Cardiology, Balikesir Ataturk Hospital, Acibadem Mahallesi Almondhill Sitesi B3 D22 Uskudar/Istanbul, Turkey (Tel: +902165424444; Fax: +902164183317; Email: drsevketballi@hotmail.com)

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which can progressively lead to heart failure. Recently, tissue Doppler imaging and two-dimensional (2D) speckle-tracking echocardiography (STE) have been utilized to evaluate cardiac functions. More sensitive echocardiographic modalities were reported to be appropriate for evaluating early changes in systolic and diastolic myocardial dysfunction, detecting very small areas of the ventricular myocardial dysfunction. These parameters are much less affected by cardiac rotation and passive cardiac motion, and are a true measure of local deformation.[14]

The aim of this study was to evaluate the cardiac function of children with DS in the absence of congenital or previously diagnosed acquired heart disease. Examination of cardiac function in this vulnerable population may be critical to identify risk for decreased exercise capacity and increased risk for morbidity.

Methods

Patients

The study was conducted as a cross-sectional study. A total of 115 children with DS between 6 and 13 years of age with clinically and anatomically normal heart were treated from October 2011 to May 2014 in Balikesir Ataturk State Hospital, and age- and sex-matched 55 healthy controls were included in the study. DS was diagnosed by a karyotype test. Children with mosaic type DS were not included in this study. Any congenital or acquired disease was excluded by clinical and echocardiographic examination. B-type natriuretic peptide (BNP) levels were evaluated in all patients. Hypothyroidism and anemia were excluded by blood analysis.[15] Patients with upper airway obstruction and chronic lung disease were not included in this study. Twenty-four patients with upper airway obstruction, 12 with anemia, 11 with hypothyroidism, and 3 with chronic lung disease were excluded from the study. Informed written consent was obtained from all parents. The study protocol was approved by the ethics committee of our hospital.

Echocardiography

Each patient underwent a complete baseline echocardiographic examination in the supine position. All echocardiography examinations were performed with a commercially available echocardiographic machine (GE, Vivid S6 System form Vingmed General Electric, equipped with 4 and 6-Megahertz transducers, Horten, Norway) and simultaneous electrocardiogram. The analyses were performed using commercially available computer software program (Echopac 2008, GE Vingmed) and the mean values of three consecutive measurements were recorded.

LV end-diastolic and end-systolic dimensions, posterior wall thickness, interventricular septal thickness, and LV ejection fraction were evaluated by M-mode echocardiography in parasternal long axis. Measurement of left atrial volume from the Simpson method used apical 4-chamber and apical 2-chamber views at ventricular end systole. Left atrial volume index was calculated by dividing left atrial volume by body surface area. Pulmonary arterial flow was measured with pulsed-wave Doppler, placing the sample volume centrally between the leaflets of the pulmonary valve in a short-axis view at the base of the heart. The mitral and tricuspid Doppler signals were evaluated in the apical four-chamber view, with the Doppler sample volume placed at the tip of the mitral or tricuspid valve.[16] The variables obtained included: early diastolic peak velocity (peak E, cm/s), mitral deceleration time of early filling (E-DT, millisecond), late diastolic peak velocity (peak A, cm/s) and early to late diastolic peak velocity ratio (E/A). The pulmonary artery systolic pressure was measured via tricuspid regurgitation jet using the Bernoulli equation. Pulmonary venous flow velocities were assessed from the apical four chamber view. The pulsed wave Doppler sample volume was placed 1 cm upstream in the right upper pulmonary vein. Sample volume positioning was always guided by colour Doppler imaging. Systolic (S), diastolic (D) and smaller end-diastolic waves (AR) were obtained by pulse wave Doppler. Mitral annular plane systolic excursion (MAPSE) was assessed with M-mode in apical four-chamber view, placing the examination beam on the lateral mitral annulus. Tricuspid annular plane systolic excursion (TAPSE) was assessed with M-mode in apical four-chamber view, placing the examination beam on the lateral mitral annulus.[17]

Calculating left ventricular mass

The most commonly used formulas to estimate LV mass are all variations of the same mathematical principle, based on the volume formulas stated above. The left ventricular mass (LVM, g) was calculated using the predefined Devereux and Reishek formula. LVM was divided by the body surface area to obtain the left ventricular mass index (LVMI, g/m^2).[18]

Tissue Doppler imaging

Tissue Doppler imaging was obtained from an apical 4-chamber view to obtain longitudinal annular velocities (VEL) at the lateral mitral wall, septum, and lateral tricuspid wall adjacent to the atrioventricular valve hinge points. Filters and gains were adjusted to allow a clear tissue signal and minimize background noise. Systolic (Sa), early diastolic (Ea), and late diastolic (Aa) tissue

Doppler velocities were measured at the lateral mitral, septal, and lateral tricuspid walls and subsequently averaged over 3 cardiac cycles in accordance with previous reports. The myocardial performance index (MPI) defined as the sum of isovolumic contraction and relaxation times divided by LV ejection time, was calculated as reported previously.[19,20] The electrocardiogram was connected and traced simultaneously to define the timing of cardiac cycle events. The beginning of QRS complex was used as a reference point. Transmitral and transtricuspid E/Ea ratios were calculated for each patient.[19]

Analysis of regional and global myocardial deformation using 2D strain speckle-tracking echocardiography (STE)

2D strain data were stored in digital format and analyzed offline with the workstation (Echopac, PC 2008, GE, Horten, Norway). 2D harmonic image cine-loops recordings (video clips) of apical 4C view (including the septum and lateral wall), with good quality electrocardiography (ECG) signal and frame rate between 40-100 frames/sn were acquired and stored in digital cineloop format. All the echocardiographic assessments taken were digitally recorded (DVD-CD) to enable later investigation. The analyses were performed using commercially available computer software program by Echopac software. Sample volumes were placed using the 2D strain software at the mitral valve septal and lateral annulus. The cardiac motion is determined from a user-defined tracing along the endocardial-myocardial border. After manual tracing of the endocardial border in the end-systolic frame of a 2D image and selecting the appropriate wall thickness, the software automatically (speckle tracking) determined 6 segments for longitudinal function: apical, mid, and basal segments in the septum and LV lateral wall from apical views.[21] Data were approved when the values for all six segments were considered acceptable by the software or when a value of any one segment had poor tracking (fewer than two segments) and was rejected by the software but tracking of that segment was determined to be acceptable.[22] Each representative value was obtained from the average of three measurements. Because radial function was scored as poor image quality in obese children, we calculated longitudinal function. By using the speckle tracking algorithm, we measured peak systolic (VEL_{sys}), early diastolic (VEL_E) and late diastolic (VEL_A) myocardial velocities, longitudinal peak systolic strain (%), peak systolic SR (SR_{sys}) (s^{-1}), peak early diastolic (SR_E) and late diastolic (SR_A) SR at the septal and lateral attachments of the mitral valve in patients with DS.

Statistical analysis

All analyses were performed using SPSS version 15.0 (SPSS, Inc. Chicago IL) statistical software. Data are presented as mean (standard deviation) values. Pearson's product-moment correlation coefficient analysis and the Chi-square analysis for comparison of frequencies of findings, unpaired Student's *t* test for comparison of mean values of groups were used. *P* value <0.05 was considered to be statistically significant.

Results

The demographic and clinical characteristics of children with DS and the control group are shown in Table 1. There was no significant difference between the children with DS and controls in terms of age, gender and BMI. Systemic and pulmonary blood pressure were similar in the two groups ($P>0.05$). BNP levels and left atrial volume were similar in both groups.

Left ventricular echocardiographic data of the children with DS and the controls are shown in Table 2. LV ejection fraction and MAPSE were higher in patients with DS ($P=0.03$, $P<0.01$). LV mass index was higher in children with DS ($P<0.01$). The transmitral E/A ratio and the mitral annulus tissue Doppler Ea/Aa ratio were lower in the DS group compared with the control group ($P=0.04$, $P<0.001$, respectively). Mitral annulus Ea velocity was significantly lower in children with DS ($P<0.001$). There was no significant difference in terms of isovolumic contraction time in both groups ($P>0.05$). LV E/Ea ratio was similar in both groups ($P>0.05$). Deceleration time ($P<0.01$) and isovolumic relaxation time were longer in the DS group than in the control group ($P<0.01$, $P<0.001$, respectively). Left

Table 1. Characteristics and echocardiographic parameters of left ventricular morphology in children with DS and controls.

Variables	DS group (n=115)	Control group (n=55)	P value*
Gender (female/male)	56/59	27/28	0.82
Age (y)	10.2±2.7	10.4±2.8	0.78
Body mass index (kg/m^2)	20.4±2.2	20.2±2.4	0.81
Systemic systolic blood pressure (mmHg)	100.5±8.6	102.4±9.2	0.79
Systemic diastolic blood pressure (mmHg)	59.4±4.8	60.5±5.3	0.83
Systolic pulmonary artery pressure (mmHg)	27.3±5.9	27.2±6.2	0.87
LVMI (g/m^2)	62.7±10.4	55.6±9.8	**<0.01**
Left atrial volume index (mL/m^2)	22.4±4.2	22.3±4.4	0.86
BNP (pg/mL)	19.4±0.42	19.1±0.40	0.77

Data are expressed as mean±standard deviation. *P* values less than 0.05 in bold type. DS: Down syndrome; BNP: B-type natriuretic peptide; LVMI: left ventricular mass index. *: Groups were compared by the Chi-square test and unpaired *t* test.

Table 2. Comparison of left ventricle echocardiographic findings from children with DS and unaffected controls aged 6-13 years

Variables	DS group	Control group	*P* value*
Left ventricle ejection fraction	70.41±9.5	65.2±8.8	**0.03**
Mitral valve E/A	1.41±0.26	1.62±0.31	**0.04**
Ea (average of septal, lateral), cm/s	13.32±2.21	16.23±3.31	**<0.001**
Mitral annulus Ea/Aa (average of septal, lateral)	1.42±0.25	1.95±0.44	**<0.001**
Left ventricle E/Ea (average of septal, lateral)	6.31±0.43	6.50±0.51	0.66
Mitral anulus Sa (average of septal, lateral), cm/s	9.81±1.8	8.11±1.7	**<0.01**
Isovolumic contraction time of mitral annulus, ms	37.23±6.7	38.52±7.1	0.56
Isovolumic relaxation time of mitral annulus, ms	63.42±8.3	53.61±7.1	**<0.001**
Ejection time of mitral annulus, ms	228.63±35.8	236.12±36.4	0.33
Deceleration time, ms	125.32±18.3	112.61±16.7	**<0.01**
Myocardial performance index of left ventricle	0.44±0.09	0.39±0.08	**<0.01**
Mitral annular plane systolic excursion, cm	1.75±0.22	1.56±0.33	**<0.01**

Data are expressed as mean±standard deviation. *P* values less than 0.05 in bold type. ms: millisecond; DS: Down syndrome; E/A: early to late diastolic pulse wave Doppler peak velocity ratio; Ea/Aa: early to late diastolic tissue Doppler peak velocity ratio; Sa: peak systolic tissue Doppler velocity. *: Groups were compared by unpaired *t* test.

Table 3. Comparison of right ventricle echocardiographic findings from children with DS and unaffected controls aged 6-13 years

Variables	DS group	Control group	*P* value*
Tricuspid valve E/A	1.53±0.28	1.68±0.32	**0.04**
Tricuspid annulus Ea/Aa	1.21±0.18	1.55±0.24	**<0.001**
Tricuspid anulus (Ea), cm/s	12.35±2.29	15.99±3.27	**<0.001**
Tricuspid anulus systolic velocity (Sa), cm/s	9.62±1.8	9.3±1.9	0.09
Tricuspid annular plane systolic excursion, cm	2.01±0.35	1.98±0.28	0.54
Isovolumic contraction time of tricuspid annulus, ms	35.2±6.8	36.41±7.1	0.22
Isovolumic relaxation time of tricuspid annulus, ms	68.2±11.3	51.52±10.1	**<0.001**
Ejection time of tricuspid annulus, ms	295.4±22.3	283.52±20.9	0.21
Myocardial performance index of right ventricle	0.35±0.6	0.31±0.5	**<0.01**

ms: millisecond; DS: Down syndrome; E/A: early to late diastolic pulse wave Doppler peak velocity ratio; Ea/Aa: early to late diastolic tissue Doppler peak velocity ratio; Sa: peak systolic tissue Doppler velocity. *: Groups were compared by unpaired *t* test; data are expressed as mean±standard deviation, and *P* values less than 0.05 in bold type.

ventricular MPI was higher in the DS group than in the control group ($P<0.01$). Positive correlation was found between LVMI and left ventricular MPI ($P<0.01$, $r=0.4$). MAPSE was found to be correlated with LV ejection fraction ($P=0.02$, $r=0.52$).

Right ventricular echocardiographic data of the DS group and the control group are shown in Table 3. Tricuspid annulus Ea velocity was significantly lower in the DS group ($P<0.001$). The systolic wave velocity (Sa) of tricuspid valve annulus and TAPSE were similar in both groups ($P>0.05$). Both E/A and Ea/Aa of the tricuspid valve annulus were lower ($P<0.05$ and $P<0.001$, respectively) in the DS group than in the control group. Right ventricular MPI was higher in the DS group than in the control group ($P<0.01$). Positive correlation was found between pulmonary artery pressure and right ventricular MPI ($P=0.02$, $r=0.58$). Pulmonary venous Doppler S/D ratio was found to be reduced in the DS group ($P<0.001$) (Table 4).

Longitudinal analysis of the left ventricular (LV) myocardium was calculated by STE in the DS group at the apical four chamber view. All the S and SR tracings were acceptable for the analysis. There were significant differences between the control group and the DS group in two-dimensional strain longitudinal myocardial deformation properties of LV in the basal, mid and apical segments ($P<0.05$). Peak systolic strain and SR, indices of systolic function, were similar in all 3 segments in the DS group. Significant differences were observed with early and late diastolic SR, early/late SR ratios (SRE/A) using strain imaging of diastolic

Table 4. Comparison of systolic (S-wave) and diastolic (D-wave) velocities of pulmonary venous flow findings from children with DS and unaffected controls aged 6-13 years

Variables	DS group	Control group	*P* value*
PV S wave, m/s	0.71±0.03	0.72±0.03	0.67
PV D wave, m/s	0.70±0.03	0.56±0.02	**<0.001**
PV AR wave, m/s	0.29±0.02	0.30±0.02	0.32
PV S/D ratio	1.01±0.04	1.28±0.05	**<0.001**

Data are expressed as mean±standard deviation. *P* values less than 0.05 in bold type. DS: Dowm syndrome; PV: pulmonary vein; S: systolic wave peak velocity; D: diastolic wave peak velocity; AR: atrial reversal wave peak velocity. *: Groups were compared by unpaired *t* test.

Table 5. Comparison of systolic and diastolic strain rate (s^{-1}) and strain (%) values for regional left ventricular longitudinal at the septum in children with DS and unaffected controls aged 6-13 years

Longitudinal function (A4C)		DS group (*n*=115)	Control group (*n*=55)	*P* value*
Strain (sep)	Basal (%)	-18.4±4.6	-18.4±4.2	0.88
	Mid	-19.5±5.5	-20.2±3.6	0.66
	Apical	-21.7±5.4	-22.3±2.9	0.55
SRsys (sep)	Basal (s^{-1})	-1.4±0.23	-1.3±0.3	0.21
	Mid	-1.3±0.22	-1.2±0.3	0.19
	Apical	-1.1±0.20	-1.2±0.4	>0.05
SR_E (sep)	Basal (s^{-1})	1.6±0.3	1.7±0.5	**0.03**
	Mid	1.3±0.37	1.5±0.3	**0.02**
	Apical	1.1±0.7	1.3±0.7	**<0.01**
SR_A (sep)	Basal (s^{-1})	1.2±0.22	0.8±0.30	**<0.01**
	Mid	1.1±0.11	0.7±0.26	**<0.01**
	Apical	0.8±0.6	0.6±0.3	0.08
$SR_{E/A}$ (sep)	Basal	1.4±0.56	2.1±0.69	**<0.01**
	Mid	1.3±0.82	1.9±1.22	**<0.01**
	Apical	1.3±1.1	2.0±1.53	**<0.01**

Data are expressed as mean±standard deviation. *: *P* values less than 0.05 in bold type. Groups were compared by unpaired *t* test. DS: Down syndrome; sep: septum; SR: strain rate; SR_{sys}: peak systolic SR (s^{-1}); SR_E: peak early diastolic SR; SR_A: late diastolic SR; mid: middle; A4C: apical four chamber.

Table 6. Comparison of systolic and diastolic strain rate (s^{-1}) and strain (%) values for regional left ventricular longitudinal function at the lateral wall in children with and unaffected controls aged 6-13 years

Longitudinal function (A4C)		DS group (*n*=115)	Control group (*n*=55)	*P* value*
Strain (lat)	Basal (%)	-24.3±3.1	-25.7±3.98	0.13
	Mid	-24.5±2.5	-23.0±4.1	0.09
	Apical	-24.1±2.3	-23.9±5.34	0.77
SRsys (lat)	Basal (s^{-1})	-1.59±0.32	-1.6±0.41	0.81
	Mid	-1.37±0.23	-1.4±0.54	0.66
	Apical	-1.34±0.20	-1.33±0.36	0.86
SR_E (lat)	Basal (s^{-1})	1.53±0.46	1.9±0.74	**0.01**
	Mid	1.44±0.65	1.66±0.50	**0.042**
	Apical	1.25±0.54	1.47±0.66	**0.01**
SR_A (lat)	Basal (s^{-1})	1.22±0.28	0.82±0.4	**<0.01**
	Mid	1.14±0.30	0.73±0.34	**<0.01**
	Apical	0.93±0.24	0.57±0.30	**<0.01**
$SR_{E/A}$ (lat)	Basal	1.29±0.58	2.40±1.68	**<0.01**
	Mid	1.24±0.48	2.26±1.40	**<0.01**
	Apical	1.39±0.41	2.21±1.92	**<0.01**

Groups were compared by unpaired *t* test. Values were expressed as mean±standard deviation. *: *P* values less than 0.05 in bold type. DS: Down syndrome; lat: lateral wall; mid: middle; A4C: apical four chamber.

function when comparing different segments of different walls in the DS group (Tables 5 and 6).

Discussion

Heart defects are the most common birth defects in children with DS. Cardiac dysfunction may affect the patient's exercise capacity, but hypotonia may also cause decreased exercise capacity. Patients with DS can't clearly express their physical functional capacity. Cardiac response after light exercise testing was found to be decreased in adults with DS.[20]

We detected diastolic dysfunction with conventional pulse waved Doppler and tissue Doppler in children even in the absence of anatomic heart disease in patients with DS. These findings may be associated with prolonged isovolumic relaxation time due to impaired cardiac relaxation.[21] In addition, increased deceleration time was detected in patients with DS in our study. Generalized hypotonia experienced by many children with DS is another variable that can also affect the heart muscle in this population.

Increased cardiac mass may also reduce the cardiac compliance and lead to diastolic dysfunction. In a study, there were 15 patients with DS who did not have congenital heart disease and 15 age- and sex-matched controls by counting the number of cardiac muscle cells in specified areas of microscopic sections (method of Black-Schaffer and Turner). The mean ratio of muscle cells per unit area for the DS patients versus the controls was 84.9%, with a mean cross-sectional area of fibers in DS patients was 117.8% of control value and a calculated mean volume of cells in DS patients was 127.7% of control value. Calculated rate of total cardiac muscle cell number in hearts of patients with DS was 62.5% of that in the controls.[7]

The MAPSE and TAPSE values are correlated with the LV and right ventricle (RV) ejection fraction as well as with the prognosis of patients with heart failure. These are sensitive markers for impaired longitudinal function which can be the earliest marker of myocardial dysfunction in cardiomyopathies with preserved ejection fraction. We found an increased mean MAPSE value and a mitral Sa velocity in accordance with increased LV ejection fraction in children with DS. Previous studies[21-25] have shown that DS patients without congenital heart disease have LV hyperkinesia, which does not seem to reflect intrinsic abnormalities of myocardial properties but a reduced afterload.

The MPI is a Doppler-derived time interval index that combines both systolic and diastolic cardiac performance.[26,27] A number of studies have documented that the MPI is independent of arterial pressure, heart rate, ventricular geometry, atrioventricular valve regurgitation afterload and preload.[28-31] The mean normal range of the MPI is 0.39±0.5 for the LV, whereas it is 0.28±0.4 for the RV. In adults, values of the LV index <0.40 and those of the RV <0.30 are considered normal. Higher index values correspond to more pathological states with overall cardiac dysfunction.[32] We found increased MPI in both LV and RV in patients with DS ($P<0.01$). This change was largely due to prolongation of isovolumic relaxation time in children with DS. The prolongation of isovolumic relaxation

time is inversely related to myocardial contractility.[21]

Echocardiographic studies have shown that LV filling pressures are correlated with the ratio of the mitral inflow E wave to the tissue Doppler Ea wave (E/Ea). This relation is based on Ea velocities that "correct" E-wave velocities for the impact of relaxation. The E/Ea ratio can be used to estimate LV filling pressures as follows: E/lateral Ea>10 or E/septal Ea>15 is correlated with an elevated LV end-diastolic pressure, and E/Ea<8 is correlated with a normal LV end-diastolic pressure.[33,34] E/Ea ratios were within normal limits and similar in both groups in our study.

In patients with impaired LV relaxation, the mitral inflow E and Ea velocity is decreased depending on impaired LV relaxation. Pulmonary venous flow pattern provides additional information in the evaluation of diastolic dysfunction. Because of the complimentary mechanisms, the mitral inflow A velocity is increased and as a result S/D ratio is reduced.[35] We also found reduced S/D ratio in children with DS as an indicator of diastolic dysfunction.

The STE-derived strain parameter is a relatively new parameter that is used to assess systolic and diastolic myocardial function.[14] In the present study, the DS children compared with the controls had a lower STE-derived LV diastolic strain parameter. Moreover, an increase in LV mass and abnormal regional myocardial dysfunction was observed in patients with DS.

This study had limitations that need to be considered. It was a relatively small cross-sectional study. This study included the dependence of the method on the angle and difficulty of providing a good echocardiographic window due to the difficulty in obtaining normal respiration.

In conclusion, these findings showed that biventricular dysfunction was present in patients with DS when conventional, tissue Doppler and two-dimensional longitudinal speckle-tracking strain echocardiography were used to investigate ventricular function. These findings suggest that patients with DS are at higher risk for these structural and functional cardiac disorders and that echocardiographic evaluation is a valuable non-invasive test for early identification to support appropriate care for this vulnerable population. Even in the absence of anatomic heart disease, cardiac functions may be affected in children with DS.

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Contributors: BS, YIK and CS collected data, and wrote some parts of the draft. KAE and EI analyzed the data, contributed to the design and interpretation of the study. DES and BS analyzed data and wrote main parts of the first draft of this paper. BS and CIK wrote further parts of the draft and revised it. All authors contributed to the intellectual content and approved the final version.

References

1 Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002;39:1890-1900.
2 Hoffman JI, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. Am Heart J 2004;147:425-439.
3 Hamertone JL, Briggs SM, Giannelli F, Carter CO. Chromosome studies in detection of parents with high risk of second child with Down's syndrome. Lancet 1961;2:788-791.
4 Hoe TS, Chan KC, Boy NY. Cardiovascular malformations in Malasian neonates with Down's syndrome. Singapore Med J 1990;31:474-476.
5 Elmagrpy Z, Rayani A, Shah A, Habas E, Aburawi EH. Down syndrome and congenital heart disease: why the regional difference as observed in the Libyan experience? Cardiovasc J Afr 2011;22:306-309.
6 Recalde AL, Landing BH, Lipsey AI. Increased cardiac muscle fiber size and reduced cell number in Down syndrome: heart muscle cell number in Down syndrome. Pediatr Pathol 1986;6:47-53.
7 Landing BH, Shankle WR. Reduced number of skeletal muscle fiber nuclei in Down syndrome: speculation on a "shut off" role of chromosome 21 in control of DNA and nuclear replication rates, possibly via determination of cell surface area per nucleus. Birth Defects Orig Artic Ser 1982;18:81-87.
8 Cua CL, Blankenship A, North J, Hayes J, Nelin LD. Increased incidence of idiopathic persistent pulmonary hypertension in Down syndrome neonates. Pediatr Cardiol 2007;28:250-254.
9 Chi TPL, Krovetz J. The pulmonary vascular bed in children with Down syndrome. J Pediatr 1975;86:533-538.
10 Jacobs IN, Gray RF, Todd NW. Upper airway obstruction in children with Down syndrome. Arch Otolaryngol Head Neck Surgery 1996;122:945-950.
11 Shah PS, Hellmann J, Adatia I. Clinical characteristics and follow up of Down syndrome infants without congenital heart disease who presented with persistent pulmonary hypertension of newborn. J Perinatal Med 2004;32:168-170.
12 Levine OR, Simpser M. Alveolar hypoventilation and cor pulmonale associated with chronic airway obstruction in infants with Down syndrome. Clin Peadiatr 1982;21:25-29.
13 Levanon A, Tarasiuk A, Tal A. Sleep characteristics in children with Down syndrome. J Pediatr 1999;134:755-760.
14 Barbosa MM, Beleigoli AM, de Fatima Diniz M, Freire CV, Ribeiro AL, Nunes MC. Strain imaging in morbid obesity: insights into subclinical ventricular dysfunction. Clin Cardiol 2011;34:288-293.
15 Imamura T, Kinugawa K, Shiga T, Endo M, Kato N, Inaba T, et al. An elevated ratio of early to late diastolic filling velocity recovers after heart transplantation in a time-dependent manner. J Cardiol 2012;60:295-300.
16 Chen X, Zhang N, Cai Y, Shi J. Evaluation of left ventricular diastolic function using tissue Doppler echocardiography and conventional Doppler echocardiography in patients with subclinical hypothyroidism aged <60 years: A meta-analysis. J Cardiol 2013;61:8-15.
17 Karaye KM, Habib AG, Mohammed S, Rabiu M, Shehu MN.

Assessment of right ventricular systolic function using tricuspid annular-plane systolic excursion in Nigerians with systemic hypertension. Cardiovasc J Afr 2010;21:186-190.
18 Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-1463.
19 Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. J Am Coll Cardiol 1997;30:474-480.
20 Vis JC, De Bruin-Bon HA, Bouma BJ, Huisman SA, Imschoot L, van den Brink K, et al. Adults with Down syndrome have reduced cardiac response after light exercise testing. Neth Heart J 2012;20:264-269.
21 Al-Biltagi M, Serag AR, Hefidah MM, Mabrouk MM. Evaluation of cardiac functions with Doppler echocardiography in children with Down syndrome and anatomically normal heart. Cardiol Young 2013;23:174-180.
22 Bussadori C, Moreo A, Di Donato M, De Chiara B, Negura D, Dall'Aglio E. A new 2D-based method for myocardial velocity strain and strain rate quantification in a normal adult and paediatric population: assessment of reference values. Cardiovasc Ultrasound 2009;13:7-8.
23 Sutherland GR, Di Salvo G, Claus P, D'hooge J, Bijnens B. Strain and strain rate imaging: a new clinical approach to quantifying regional myocardial function. J Am Soc Echocardiogr 2004;17:788-802.
24 Iellamo F, Galante A, Legramante JM, Lippi ME, Condoluci C, Albertini G, et al. Altered autonomic cardiac regulation in individuals with Down syndrome. Am J Physiol Heart Circ Physiol 2005;289:2387-2391.
25 Russo MG, Pacileo G, Marino B, Pisacane C, Calabrò P, Ammirati A, et al. Echocardiographic evaluation of left ventricular systolic function in the Down syndrome. Am J Cardiol 1998;81:1215-1217.
26 Tei C, Ling LH, Hodge DO, Bailey KR, Oh JK, Rodeheffer RJ. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function--a study in normals and dilated cardiomyopathy. J Cardiol 1995;26:357-366.
27 Tei C. New non-invasive index of combined systolic and diastolic ventricular function. J Cardiol 1995;26:135-136.
28 Tei C, Dujardin KS, Hodge DO, Kyle RA, Tajik AJ, Seward JB. Doppler index combining systolic and diastolic myocardial performance: clinical value in cardiac amyloidosis. J Am Coll Cardiol 1996;28:658-664.
29 Tei C, Dujardin KS, Hodge DO, Bailey KR, McGoon MD, Tajik AJ, et al. Doppler echocardiographic index for assessment of global right ventricular function. J Am Soc Echocardiogr 1996;9:838-847.
30 Tei C, Nishimura R, Seward JB, Tajik AJ. Noninvasive Doppler derived myocardial performance index: correlation with simultaneous measurements of cardiac catheterization measurements. J Am Soc Echocardiogr 1997;10:169-178.
31 LaCorte JC, Cabreriza SE, Rabkin DG, Printz BF, Coku L, Weinberg A, et al. Correlation of the Tei index with invasive measurements ofventricular function in a porcine model. J Am Soc Echocardiogr 2003;16:442-447.
32 Karatzis EN, Giannakopoulou AT, Papadakis JE, Karazachos AV, Nearchou NS. Myocardial performance index (Tei index): evaluating its application to myocardial infarction. Hellenic J Cardiol 2009;50:60-65.
33 Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788-1794.
34 Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527-1533.
35 Masuyama T, Lee JM, Yamamoto K, Tanouchi J, Hori M, Kamada T. Analysis of pulmonary venous flow velocity patterns in hypertensive hearts: its complementary value in the interpretation of mitral flow velocity patterns. Am Heart J 1992;124:983-994.

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