

Original Article

Evaluation of Cardiac Functions among Children with Down Syndrome: When to screen?

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Abstract:

Background: The chromosomal trisomy 21 known as Down syndrome (DS), is frequently associated with congenital structural heart disease, and functional abnormalities.

Aim of the work: to evaluate systolic and diastolic cardiac function in children with DS and structurally normal hearts.

Subjects and Methods: This cross-sectional case- control study included 80 children with Down syndrome confirmed by karyotyping, with structurally normal hearts, and were regularly monitored at Cairo University Specialized Children's Hospital's Pediatric Genetics Clinic and 80 healthy age and sex matched children as a control group. They all underwent tissue Doppler imaging (TDI), two-dimensional, and M-mode echocardiography.

Results: The mean age of the studied DS patients was 2.5 ± 1.54 , 47(58.8%) were males, and 74(92.5%) had non-disjunction genetic types. Compared to controls, DS patients exhibited significantly lower systolic and diastolic blood pressures and higher heart and respiratory rates ($p < 0.001$). Conventional indices (EF% and FS%) were paradoxically elevated in DS ($p < 0.001$), whereas longitudinal function markers were markedly reduced: tricuspid annular plane systolic excursion (TAPSE) (16.0 ± 2.59 vs 18.52 ± 3.30 , $p < 0.001$), mitral annular plane systolic excursion (MAPSE) (12.4 ± 2.15 vs 15.04 ± 2.94 , $p < 0.001$), and TDI-derived LV and RV S' velocities ($p < 0.05$). Decreased LV E'/A' ratios and myocardial performance index (MPI) confirmed global dysfunction ($p < 0.001$). In absence of associated comorbidities, heart rate (cut off above 94 beats/minute) and systolic blood pressure (SBP) percentiles (cutoff $\leq$ 55th percentile) each predicted reliably LV systolic dysfunction, showing sensitivities of 84% and 81%, and specificity of 71% each. No significant effect of age, sex, BMI z-score, or genetic subtype on ventricular function was observed ($p = 0.78$, $p = 0.34$, $p = 0.33$, and $p = 0.99$ respectively).

Conclusion: Children with DS exhibit subclinical impairment of both left and right ventricular function despite structurally normal hearts. HR above 94/minute and lower SBP percentile less than 55th percentile for age predict LV systolic dysfunction and may serve as a simple practical bedside screening tool.

Keywords: Cardiac dysfunction; children; Down syndrome; echocardiography; structurally normal heart; tissue Doppler imaging

Abbreviations: A': Late diastolic annular myocardial velocity; CHD: congenital heart disease; DS: Down syndrome; E': early diastolic annular myocardial velocity; HR: heart rate; LV: left ventricle; MAPSE: mitral annular plane systolic excursion; MPI: myocardial performance index; PAP: pulmonary artery pressure; RR: respiratory rate; RV: right ventricle; S': systolic annular myocardial velocity; TAPSE: tricuspid annular plane systolic excursion; TDI: tissue Doppler imaging

Introduction

One of the most prevalent chromosomal anomalies in humans, Down syndrome (DS) is characterized by a wide range of phenotypic variations, including cardiac and systemic abnormalities (1). Given the high prevalence of congenital heart disease (40–60%), cardiac evaluation is essential for all children with DS (2). Subclinical alterations in biventricular functions have been reported in DS patients without structural lesions in several observational studies employing conventional echocardiography, tissue Doppler imaging (TDI), and more sensitive techniques like two-dimensional speckle-tracking (3, 4). Children with DS may have a variety of functional cardiac abnormalities, including those caused by intrinsic myocardial abnormalities, autonomic dysregulation, or concomitant conditions such as metabolic syndrome, sleep apnea, and thyroid dysfunction (5). To guide prompt therapies and maximize quality of life in this population, early diagnosis of subclinical cardiac function impairment is crucial (6).



In children with DS with structurally normal hearts and no associated comorbidities, routine or serial functional echocardiographic evaluation may not be feasible in developing countries with limited healthcare resources. There is a need to explore when to investigate for subclinical cardiac dysfunction among children with DS, its correlation with demographic, anthropometric, and clinical parameters, identifying potential risk factors that may justify closer cardiology follow-up and echocardiographic surveillance. Hence, we aimed to evaluate systolic and diastolic cardiac function in healthy DS children with structurally normal hearts.

Subjects and Methods

This cross-sectional case-control study was conducted at the Pediatric Cardiology Outpatient Clinic of Children Hospital, and at Paediatric Genetic Clinic, Cairo University Hospitals, Faculty of Medicine, Cairo University. The study was approved by the Committee of Higher Education and Research and of Faculty of Medicine, Cairo University, Egypt. The parents of all subjects consented verbally prior to the study entry.

Participants

The study included 80 children with Down syndrome confirmed by karyotyping and structurally normal hearts, aged 6 months -8 years, who attended the Pediatric Genetic Clinic at Cairo University Specialized Children's Hospital. Those having significant respiratory, systemic, or chronic airway disorders were not included. A control group of 80 healthy children was also included.

Methods

Both healthy controls and children with Down syndrome underwent medical history taking, including maternal age, prenatal history, and any cardiac or respiratory issues was gathered and thorough clinical examination. Additionally, demographic information such as height, weight, sex, and age were recorded. Blood pressure, heart rate, respiratory rate, and oxygen saturation were measured.

Both groups underwent echocardiography was performed using a GE Vingmed (Norway), and transducers were used based on the patient's size. One investigator evaluated the digitally recorded images using offline software. They underwent M-mode echocardiography. Traditional M-mode data were used at the ends of the mitral valve leaflets on the parasternal long axis to determine the ejection fraction (EF) and fraction shortening (FS). Tricuspid annular plane systolic excursion (TAPSE) and mitral annular plane systolic excursion (MAPSE) measurements in the apical four chambers were also performed using M-mode to evaluate longitudinal systolic function. They underwent tissue Doppler imaging (TDI) as well. The basal segments of the left ventricle (LV) lateral wall, RV free wall, and interventricular septum were used to quantify the systolic annular myocardial velocity (S'), early (E') and late diastolic (A') myocardial velocities, and the E'/A' ratio. Three cardiac cycles were necessary for every measurement and averaged to lessen the impact of respiration.

Using Tissue Doppler Imaging (TDI) at the lateral mitral annulus in the apical four-chamber view, left ventricular myocardial performance index (MPI) was obtained. The TDI velocity profile was used to find the isovolumic contraction time (IVCT); the time between the end of the A' wave and the start of the S' wave, the ejection time (ET); the time of the S' wave, and the isovolumic relaxation time (IVRT; the time between the end of the S' wave and the start of the E' wave. MPI was calculated as $(IVCT+IVRT)/ET$ (7).

Statistical Analysis

The data was analyzed using Statistical Package for Social Sciences (SPSS) by IBM version 23 (IBM Corp., Armonk, NY, USA). The continuous numerical variables' mean and standard deviation (SD) were shown. The unpaired t-test was employed to compare differences between groups. The categorical variables were presented as percentages, numbers, and ratios, and the differences between them were compared using Fisher's exact test. SPSS software was used to create charts and graphs. Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic performance of the studied variables in predicting the target outcome, with the area under the curve (AUC) and optimal cutoff values determined by the Youden index. Logistic regression analysis was performed to identify independent predictors, reporting odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was defined as p values below 0.05.

Results

The enrolled 80 patients with DS with structurally normal hearts comprised 43 (41.2%) females and 47 (58.8%) males. None had a family history of Down Syndrome, neither a history of chest nor cardiac complaints. DS cases had substantially older mothers than controls ($p < 0.001$). There was no statistically significant difference between the patients and controls regarding sex, age, weight (z score for age), BMI, and O₂ saturation. Down syndrome patients had significantly lower height for age z scores than controls ($p < 0.001$). The heart rate and respiratory rate of those with Down syndrome were higher than those of controls ($p < 0.001$). Additionally, compared to controls, blood pressure readings were considerably lower in DS ($p < 0.001$). (Table 1). Karyotyping, provided evidence that all had trisomy 21, of them 6 (7.5%) had translocation, and 74 (92.5%) had non-disjunction chromosome 21. (Figure 1). The LV systolic function by the traditional m-mode, DS cases had higher FS% and EF% than controls (42.6 ± 5.35 vs 36.31 ± 2.38) and (75.4 ± 5.39 vs 67.95 ± 3.55) respectively ($p < 0.001$ and $p < 0.001$). (Figure 2). Also, the MAPSE and TAPSE measurements of both LV and RV longitudinal systolic function revealed significantly lower values among the DS cases compared to the control group (12.4 ± 2.15 vs. 15.04 ± 2.94 and 16.0 ± 2.59 vs. 18.52 ± 3.30 respectively), ($p < 0.001$ and $p < 0.001$). (Figure 3). Systolic annular myocardial velocity S', early diastolic E', and E'/A' ratio were all significantly lower among those with Down syndrome, according to tissue Doppler imaging of the LV lateral wall ($p < 0.001$) with increased MPI, denoting global LV dysfunction ($p < 0.001$). DS cases had significantly lower systolic annular velocity S', early diastolic E' wave velocity, and E'/A' ratio when compared to the control group ($p < 0.001$) in relation to RV anterior wall and septal myocardial velocities. (Table 2). Of those with Down syndrome 48 (60%) had a MAPSE value < 14 mm, while 32 (40%) had a TAPSE value < 16 mm, indicating LV longitudinal systolic dysfunction compared to RV dysfunction. Regarding TDI-derived velocities, LV S' was < 8 cm/sec in 53 (66%) of those with Down syndrome, and RV S' was < 10 cm/sec in 39 (48%) patients.

Table 1. Demographic and clinical data of children with Down syndrome and healthy cohort

	Down Syndrome Cases (n=80)		Healthy Controls (n=80)		P value
	Males				
Sex	47	58.8%	49	61.2%	0.747
	Females	33	41.2%	31	
	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range	
Age (years)	2.5 $\pm$ 1.54	0.5-8	2.30 $\pm$ 1.72	0.5-7	0.206
Weight (Z score for age)	-1.21 $\pm$ 1.41	-3.6-2.03	-0.96 $\pm$ 1.53	-5.07-2.15	0.28
Height (Z score for age)	-2.43 $\pm$ 1.61	-7.34-3.67	-1.10 $\pm$ 2.46	-5.48-3.46	< 0.001
BMI	15.5 $\pm$ 3.86	10-33	16.2 $\pm$ 3.74	10-30	0.256
BMI (z score for age)	-1.27 $\pm$ 3.17	-8.12-3.78	-1.01 $\pm$ 3.59	-8.32-4.13	
HR(b/min)	107 $\pm$ 15.60	85-160	94.9 $\pm$ 11.41	80-130	< 0.001
SBP (mmHg)	77.1 $\pm$ 8.43	65-100	88.7 $\pm$ 11.19	70-110	< 0.001
SBP -Percentiles	49.20 $\pm$ 22.91	7.12-93	55.62 $\pm$ 28.5	3.12-95	
DBP (mmHg)	50.0 $\pm$ 9.37	35-65	59.4 $\pm$ 9.65	40-80	< 0.001
DBP - Percentiles	45.82 $\pm$ 23.62	14.3-99.7	53.62 $\pm$ 28.02	5-98.7	
RR	32.5 $\pm$ 3.99	22-40	24.6 $\pm$ 3.45	20-35	< 0.001
O ₂ Saturation (%)	96.56 $\pm$ 2.16	92-99	97.01 $\pm$ 2.01	93-99	0.174
Maternal Age(years)	32.8 $\pm$ 5.71	21-46	26.4 $\pm$ 4.71	19-37	< 0.001

Heart Rate, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, RR: Respiratory Rate

Univariate logistic regression was done to explore demographic and clinical parameters that may be associated with increased risk of systolic dysfunction. Heart rate (HR) and systolic blood pressure (SBP) percentile were found to be significant predictors of LV systolic dysfunction (defined as MAPSE < 14 mm or LV S' < 8 cm/s.). High HR was independently associated with increased odds of LV dysfunction (OR = 1.12, $p = 0.012$, AUC = 0.84), while higher SBP percentile showed a protective effect (OR = 0.95, $p = 0.014$, AUC = 0.78). Diastolic blood pressure percentile (DBP%) and estimated systolic pulmonary artery pressure (ESPAP) were not significant predictors ($p = 0.182$ and $p = 0.777$ respectively), with lower discriminative ability (AUC = 0.63 and 0.51, respectively). (Figure 4). Diastolic dysfunction was less frequent, as LV E' was < 10 cm/sec in only 7(8%) patients and RV E' was < 12 cm/sec in 8 (10%) patients. For MPI, all those with Down syndrome demonstrated values > 0.5 , consistent with global cardiac dysfunction, with non-significant correlation to the age ($r = -0.10$, $p = 0.376$). Furthermore, 42(52.5 %) of Down

syndrome patients had systolic pulmonary artery pressure ≥ 30 mmHg with significantly higher mean value in comparison to controls (28.90 ± 5.21 versus 20.6 ± 3.41 , p value < 0.001). (Figure 5).

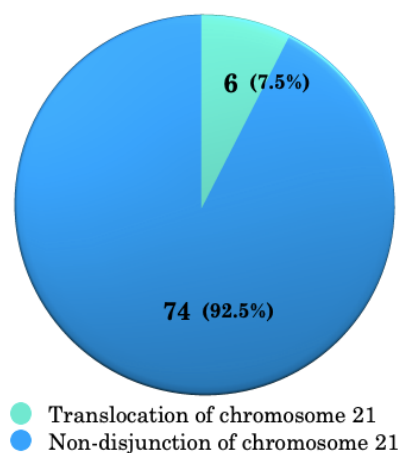


Figure 1. Karyotyping of the study group with Down Syndrome (n=80)

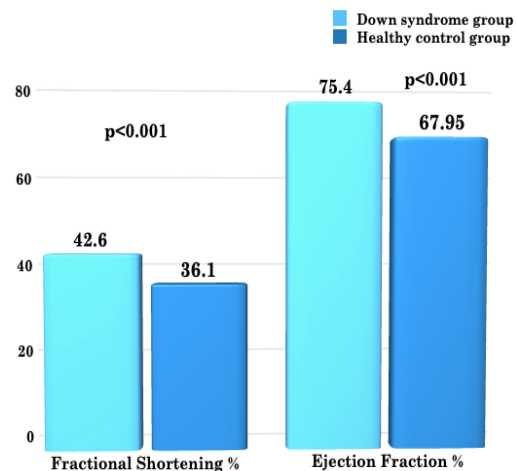


Figure 2. Ejection Fraction (EF%) and Fraction Shortening (FS%) in those with Down Syndrome and healthy control group

Table 2. Tissue Doppler Velocities in Down Syndrome cases and healthy Controls

	Down syndrome (n=80)		Healthy Controls (n=80)		P value
	Mean ±SD	Range	Mean ±SD	Range	
Left Ventricle (LV)					
LV S'(m/s)	7.64±1.96	4.5-13	7.88±1.17	6-11	0.028
LV E'(m/s)	12.68±2.42	7.4-18.2	14.51±3.02	9-19.7	< 0.001
LV A'(m/s)	8.82±2.36	4.3-16.7	7.55±1.35	5-11.6	< 0.001
E'/A'	1.51±0.42	0.77-2.7	1.95±0.47	1.2-3.45	< 0.001
E/E'	7.83±0.16	3.8-13.6	8.07±1.66	1.77-12.8	0.206
MPI	0.69±0.12	0.5-1.18	0.33±0.03	0.24-0.4	< 0.001
Right Ventricle (RV)					
RV S'(m/s)	10.3±2.85	5.5-22	11.5±2.66	7.9-19	0.005
RV E'(m/s)	14.5±3.16	7.7-24.7	16.3±2.04	13.3-20.3	< 0.001
RV A'(m/s)	10.66±3.30	4.7-19	10.1±1.80	7.4-14	0.691
E'/A'	1.44±0.40	0.67-2.7	1.65±0.28	1.14-2.3	< 0.001
Interventricular Septum (IVS)					
Sep. S'(m/s)	6.77±1.07	4.2-9.3	7.35±1.05	5.7-10	0.001
Sep. E'(m/s)	11.56±1.87	8.1-17.2	12.5±2.54	7.8-17.7	0.011
Sep. A'(m/s)	7.47±1.61	5.1-12	6.91±1.07	5-9.2	0.046
E'/A'	1.58±0.38	0.75-2.8	1.82±0.35	1.22-2.6	< 0.001
Cardiac dysfunction	Number	%	Number	%	
Low MAPSE(<14mm)	48	60	9	11	< 0.001
Low TAPSE(<16mm)	32	40	8	10	< 0.001
Low LV S' (< 8 m/s)	53	53	6	6	< 0.001
Low RV S' (<10 m/s)	39	39	8	8	0.006
Low LV E' (<10 m/s)	7	8	0	0	< 0.001
Low RV E' (<12 m/s)	8	7	2.4	3	0.12
High MPI (>0.5)	80	100	0	0	< 0.001

A': late diastolic myocardial velocity; E': early diastolic myocardial velocity; m/s: meter per second; MPI: Myocardial performance Index; S': systolic annular myocardial velocity

Using Youden's index from univariate ROC analyses, high HR (cut off above 94 beats/minute) showed sensitivity 84% and specificity 71% while SBP cutoff ≤ 55 th percentile had sensitivity 81% and specificity 71% in predicting LV systolic dysfunction (MAPSE <14 mm, or LV S' <10 m/s, Number of events 58). Univariate logistic regression showed that BMI z-score (OR 1.12, $p=0.33$), age (OR 0.93, $p=0.78$), sex (OR 0.47, $p=0.34$), and genetic subtype ($p=0.99$) were not significant predictors of LV systolic dysfunction. Both BMI z-score and age demonstrated weak, non-

significant associations ($AUC < 0.65$), as the study included children with variable age groups, heart rate was correlated to age (8), patients were identified either high, normal and low HR for age (25, 32 and 23 patients respectively). It was noted that in patients with tachycardia 100% had LV dysfunction, while among patients with normal and low HR for age, 62.5% and 56.5% had LV systolic dysfunction respectively ($p < 0.001$). (Figure 6).

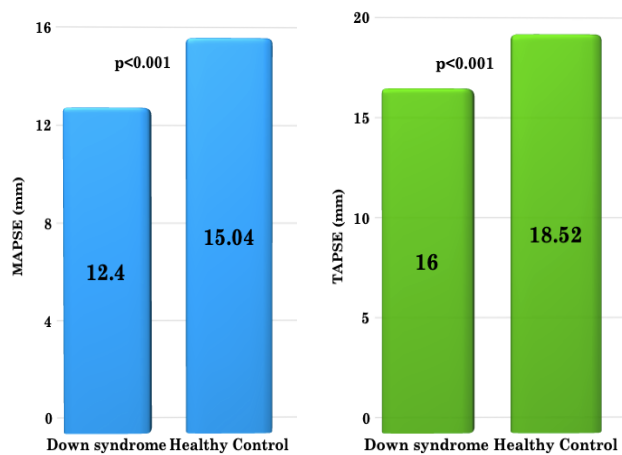


Figure 3. Mitral Annular Plane Systolic Excursion (MAPSE) and Tricuspid Annular Plane Systolic Excursion (TAPSE) in both studied groups

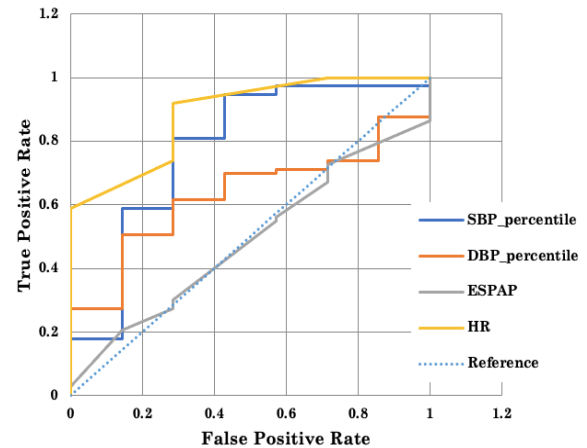


Figure 4. Receiver operating characteristic (ROC) curves for predictors of LV systolic dysfunction (MAPSE < 14 mm or LV S' < 8 cm/s)

None of the studied variables showed significant discriminative predictor ability of RV systolic dysfunction (defined as TAPSE < 16 mm or RV S' < 10 cm/s). Among hemodynamic parameters, heart rate demonstrated the highest individual predictive performance ($AUC = 0.60$, $p = 0.16$), while SBP and DBP percentiles as well as ESPAP had lower accuracy ($AUC = 0.44$ – 0.46). The combined model incorporating all four hemodynamic predictors yielded limited diagnostic performance. Similarly, demographic and genetic factors including BMI z-score, age, sex, and genetic type were not significantly associated with RV dysfunction (all $p > 0.05$).

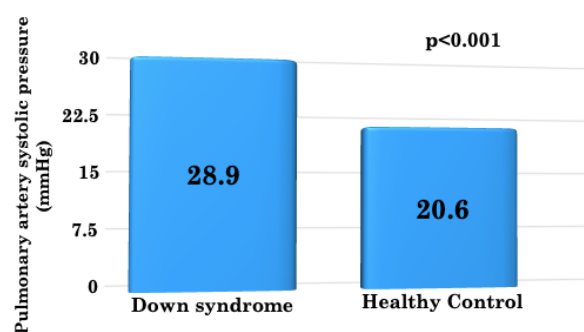


Figure 5. Pulmonary artery pressure among control group and those with Down syndrome

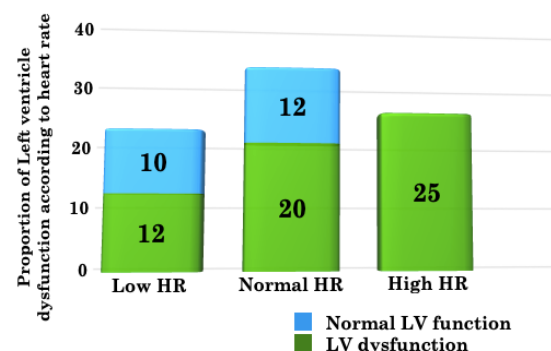


Figure 6. Left ventricle dysfunction according to heart rate (HR) in children with Down syndrome

Discussion

In this cross-sectional cohort, children with DS demonstrated significantly lower blood pressure and higher heart and respiratory rates compared with healthy controls ($p < 0.001$). These autonomic and hemodynamic alterations may reflect subtle underlying myocardial or vascular abnormalities, suggesting a tendency toward cardiovascular dysregulation even in the absence of overt structural heart disease. Our findings confirm the previously reported findings that suggest impaired autonomic control and altered vascular tone in DS populations (4, 9). Conventional echocardiographic assessment in the present study revealed evidence of left ventricular hyperkinesia, as indicated by significantly higher EF and FS compared with controls

($p < 0.001$). This apparent hypercontractility may be related to reduced afterload or intrinsic myocardial remodeling commonly described in Down syndrome which were consistent with findings reported earlier among those with DS, supporting the hypothesis that altered myocardial and vascular mechanics underly these functional changes (4, 10).

In the current study, children with DS exhibited a marked reduction in longitudinal systolic function of both ventricles, as evidenced by significantly lower MAPSE and TAPSE values compared with the control group ($p < 0.001$). These findings suggest subtle impairment of myocardial contractility that may not be apparent through conventional indices such as EF or FS. Unlike radial measures, longitudinal systolic M-mode parameters are less influenced by preload and afterload conditions and more accurately reflect the intrinsic performance of subendocardial longitudinal fibers, which are particularly sensitive to early myocardial dysfunction (11). This highlights their clinical relevance in detecting subclinical ventricular impairment in DS. Yet it seems that the change in TAPSE is not a consistent finding in DS. Others reported preserved TAPSE but significantly lower MAPSE values in DS patients with structurally normal hearts (12). This inconsistency suggests that there are other co-factors that are responsible for this subtle longitudinal systolic dysfunction of ventricles among children with DS. These factors maybe indeed preventable, and need future studies to define them.

TDI has emerged as a reliable, non-invasive, and cost-effective modality for assessing both regional and global myocardial function (13). In the present study, DS patients demonstrated significantly lower systolic annular velocities (S') at the LV lateral wall, RV free wall, and interventricular septum compared with healthy controls, indicating early impairment of longitudinal systolic function. The reduction in S' velocities suggest subtle myocardial contractile abnormalities that may precede overt systolic dysfunction detectable by conventional measures such as ejection fraction or fractional shortening. In addition, the significantly lower E'/A' ratios at the LV, RV, and septal annuli observed in Down syndrome patients reflect diastolic relaxation abnormalities, consistent with early ventricular compliance disturbances. The concomitant increase in left ventricular myocardial performance index (MPI) further supports the presence of global myocardial dysfunction, encompassing both systolic and diastolic components.

Collectively, these findings highlight the value of TDI-derived parameters in detecting subclinical myocardial involvement in DS, even in the absence of structural heart disease (3, 4). Similar findings were seen in earlier research employing TDI (3, 14). Even in the absence of structural cardiac anomalies, children with Down syndrome are predisposed to developing pulmonary hypertension. This predisposition has been attributed to factors such as alveolar hypoventilation, recurrent respiratory infections, and intrinsic abnormalities of the pulmonary vasculature (15). In the present study, despite excluding patients with chronic respiratory or airway disease, pulmonary artery pressure (PAP) was significantly higher in the DS group compared with controls (28.9 ± 5.21 mmHg vs. 20.6 ± 3.41 mmHg, $p < 0.001$). These findings reinforce previous evidence suggesting that pulmonary vascular dysfunction may occur independently of structural or overt pulmonary pathology and underscore the importance of early screening and longitudinal monitoring for pulmonary hypertension in DS patients to enable timely intervention and prevent progression to clinically significant cardiopulmonary compromise (15).

The present study provided evidence that HR and SBP percentile are reliable, non-invasive clinical indicators of LV systolic dysfunction (MAPSE < 14 mm or LV $S' < 8$ m/s) in absence of systemic, thyroid or metabolic disease in the studied cohort. High HR (above 94 beats/minute) showed sensitivity 84% and specificity 71% while SBP percentile ≤ 55 th had sensitivity 81% and specificity 71% in predicting LV systolic dysfunction. The strong positive association between tachycardia and LV impairment confirms the correlation between HR and cardiac function in pediatric population as a compensatory mechanism to maintain cardiac output. Both HR and SBP maybe used as crude indicators for initiation of the regular cardiac assessment and possible intervention in children with DS.

Conversely, lower SBP percentiles reflect reduced cardiac output and forward flow, consistent with systolic dysfunction. The lack of association between DBP percentile or ESPAP and LV dysfunction suggests that these parameters may be less sensitive to early systolic changes. Overall, these results support incorporating HR and SBP percentiles into bedside screening protocols for early cardiology referral and detection of LV dysfunction in those children. There is a need to define HR percentiles for DS according to age and not rely upon the normal population HR charts. Neither demographic nor anthropometric factors as age, BMI z-score, sex, or genetic subtype significantly influenced LV systolic function in this cohort. These findings suggest that myocardial impairment in DS is largely driven by intrinsic cardiac or hemodynamic factors rather than by constitutional characteristics, aligning with previous reports describing the

multifactorial nature of cardiac dysfunction in this population (5). The studied clinical, anthropometric, and hemodynamic variables showed limited value to predict RV systolic dysfunction in our studied DS cohort (TAPSE <16 mm or RV S' <12 m/s). This may be explained by the complex and multifactorial determinants of RV performance, which are influenced by ventricular interdependence, and intrinsic myocardial contractility rather than demographic or static hemodynamic measures. The available histopathological and molecular data imply that, compared with healthy populations, individuals with DS may have microscopic myocardial abnormalities (papillary muscle calcification, lymphocytic infiltrates and potential low-grade fibrosis) that may contribute to the complex and multifactorial determinants of RV performance in this cohort (16).

The presence of subtle cardiac dysfunction in DS populations, even in absence of cardiac defects emphasizes the need for lifelong cardiac follow up, promotion of a healthy lifestyle, optimal management of comorbidities through a multidisciplinary approach, and careful consideration regarding participation in competitive sports.

The study limitations include being a single-center study without longitudinal follow-up. Future multicenter studies with serial follow-up are warranted to clarify the predictors of progression of cardiac involvement in children with Down syndrome, identify potential contributing factors, and explore correlations with thyroid dysfunction and dyslipidemia.

Conclusion

Children with Down syndrome demonstrate early subclinical ventricular dysfunction, despite preserved conventional function indices and normal cardiac anatomy. These findings emphasize the importance of incorporating tissue Doppler echocardiography in initial cardiac function assessment and follow up of these patients. Heart rate and systolic blood pressure percentile emerged as simple, sensitive non-invasive possible markers for predicting LV dysfunction that may be used as screening tools in routine pediatric health care evaluation.

Author Contributions

The authors contributed as follows: SB: manuscript preparation, IE: manuscript review, AG: cases and data collection, RI: data review. All authors approved the final manuscript.

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Authors declare that there was no extramural funding of the study.

CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. All information is accessible from the corresponding author upon request.

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