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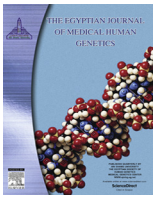

Original article

Left ventricle myocardial performance in Down Syndrome children with clinically and anatomically normal hearts: Relationship to oxidative stress

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ABSTRACT

Oxidative stress is implicated in many organs pathophysiologies in Down syndrome. Scarce data exist concerning left ventricular (LV) performance in DS children with normal hearts. Tissue Doppler derived myocardial performance index (TDI-Tei index) is a reliable method for ventricular performance evaluation. Myeloperoxidase (MPO) enzyme plays a crucial role in oxidants production and is a marker of cardiovascular risk.

Aim: To evaluate LV myocardial performance in DS children with normal hearts using TDI-Tei index and correlate it with plasma MPO as a marker of oxidative stress.

Patients and methods: This cross-sectional study included 120 DS children recruited from Children s Hospital, Ain Shams University. Out patients clinic and echocardiography unit (mean age, 8.35 ± 4.25 y ears) who were subjected to: history taking, clinical examination, laboratory investigations (Complete blood count, serum Alanine Transaminase, serum creatinine, Thyroid profile, 12 lead Electrocardiogram and conventional Doppler echocardiography). DS children with congenital or acquired heart diseases, dysrhythmias, anaemia, pulmonary hypertension, thyroid, renal disease, diabetes were excluded. The remaining 50 DS children with normal hearts (group I) were compared to 50 age. Sex matched healthy children as control (group II) Studied groups were subjected to: plasma MPO using ELISA technique and TDI LV-Tei index assessment using Vivid E9 Echocardiography machine (GE, Horton, Norway).

Results: LV TDI-Tei was significantly increased in group I compared to group II (0.46 ± 0.02 vs 0.32 ± 0.08, $p < 0.001$). Plasma MPO was increased in group I than group II (64.4831 ± 0.6 ng/ml vs 50.4 ± 30.2 nglml, $p < 0.001$). A significant positive correlation was found between plasma MPO and LV TDI-Tei ($r = 0.877$, $p = 0.001$) in group I.

Conclusion: Subclinical Left ventricle dysfunction evidenced by increased TDI Tei index was detected in DS children with normal hearts. This dysfunction correlated with plasma MPO level which mandates antioxidants treatment and tissue Doppler myocardial performance regular evaluation for early identification, monitoring and early intervention.

1. Introduction

Down Syndrome (DS) is the most common human aneuploidy [1]. Nearly 50% of DS patients have cardiac defects [2]Right ventricular function affection resulting from pulmonary hypertension due to upper airway obstruction and abnormal vasculature growth, is a known complication in DS patients [3]. Very scarce data exist about left ventricular (LV) performance in DS patients with clinically and anatomically normal hearts especially in the pediatric age group.

DS is a human disorder etiologically related to oxidative stress. This was found to be due to redox imbalance from overexpression of Cu, Zn-superoxide dismutase (SOD-1), encoded by trisomic chromosome 21 [4].

Oxidative stress in DS was also reported to result from genes located at chromosomes other than chromosome 21 and in transcriptional regulation of those genes. This is implicated in many of DS patients organs pathophysiologies [5].

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Myeloperoxidase (MPO) enzyme released by leukocytes plays a crucial role in inflammation and oxidative stress [6]. MPO plays a central role in oxidants production by neutrophils and uses superoxide and hydrogen peroxide to catalyse hypochlorous acid generation which is a strong oxidant produced at sites of inflammation with antibacterial effect [6].

Numerous studies showed significant elevations of the systemic MPO levels in many cardiovascular disease scenarios with acute coronary syndromes and heart failure being the most studied. The involvement of MPO in the pathogenesis of cardiovascular diseases is supported by evidence that elevated MPO concentrations are an independent risk factor for future cardiovascular events in healthy individuals [7].

Tissue Doppler derived myocardial performance index (TDI-MPI) also known as TDI-Tei index, is a simple, reproducible method for ventricular function assessment both systolic and diastolic [8]. TDI-Tei index records both systolic and diastolic velocity signals during the same cardiac cycle and has been reported to correlate well with other invasive and noninvasive measures [9,10].

The aim of the current study was to evaluate left ventricular myocardial performance in DS children with clinically and anatomically normal hearts using tissue Doppler derived myocardial performance index (TDI - Tei) and correlate it with plasma Myeloperoxidase as a marker of oxidants stress in those patients.

2. Patients and methods

The current cross-sectional study included 120 DS children recruited from Children s Hospital, Ain Shams University Out patients clinic and echocardiography unit (mean age, 8.35 ± 4.25 years) in the period from January 2014 till April 2016. DS children were subjected to: Thorough history taking, clinical general and cardiac examination, laboratory investigations [Complete blood Count (CBC), serum Alanine Transaminase (ALT), serum creatinine, Thyroid stimulating hormone (TSH), thyroid hormones (FT3 and T4)], 12 lead ECG as well as Two dimension (2D), Motio (M) mode, color, pulsed and continuous wave Doppler echocardiography using (Vivid E9, Vingmed, GE, Horten, Norway). Left ventricle (LV) end-diastolic and end-systolic dimensions (LVEDD, LVESD), posterior wall thickness (LVPWT), interventricular septal thickness (IVSd), and LV ejection fraction (EF%) were evaluated by M-mode The pulmonary artery systolic pressure was measured via tricuspid regurgitation jet using the Bernoulli equation [11].

DS children with congenital or acquired heart diseases, dysrhythmias, anaemia, pulmonary hypertension (mean pulmonary artery pressure more than 25 mmHg) thyroid, renal disease, diabetes were excluded from the study.

2.1. The remaining 50 DS children

with anatomically and clinically normal hearts (group I) were compared to 50 age and sex matched healthy children as control (group II).

Studied groups were subjected to: plasma Myeloperoxidase (MPO)level assessment by ELISA technique and TDI derived LV Tei index evaluation using echocardiographic machine equipped with 5-M HZ transducer and simultaneous electrocardiogram. Three consecutive cardiac cycles were measured and averaged. Heart rate was determined from ECG tracings obtained during echocardiographic studies [12].

2.2. Assessment of TDI derived LV Tei index

Tissue Doppler imaging waveforms of the mitral annulus were recorded and analyzed. Early diastolic waves ($E^{/}$), late diastolic waves ($A^{/}$), systolic waves ($S)^{/}$. The time interval from the end to the onset of the mitral annular velocity pattern during diastole (**A**) was measured from the TDI recordings. The duration of wave (**B**) was measured from the onset to the end of $S^{//}$ wave. LV- TDI Tei index was calculated as (A-B)/B, Fig. 1.

The isovolumic contraction time (ICT) was measured from the end of the $\mathbf{A}^{/}$ wave to the beginning of the $\mathbf{S}^{/}$ wave. The isovolumic relaxation time (IRT) was measured from the end of the $\mathbf{S}^{/}$ wave to the beginning of the $E^{//}$ wave. The average of septal and lateral mitral annular values were estimated for measured waves and intervals. Waves mean values were obtained by averaging five consecutive beats [13]. An informed written consent was obtained from all parents/caregivers before the start of clinical, laboratory and radiological studies. The study was accepted by the ethical committee of Ain Shams University. The work has been carried out in accordance with the Code of Ethics of World Medical association of Helsinki for experiments in humans.

Statistical analysis: were performed using SPSS version 15.0 (SPSS, Inc. Chicago IL) software. Data were presented as mean (standard deviation) values. Pearson's product-moment correlation coefficient analysis, the Chi-square analysis, unpaired Student's *t* test for comparison of mean values of groups. P value < 0.05 was statistically significant (see Fig. 2).

3. Results

The demographic and clinical characteristics of studied groups are shown in Table 1.

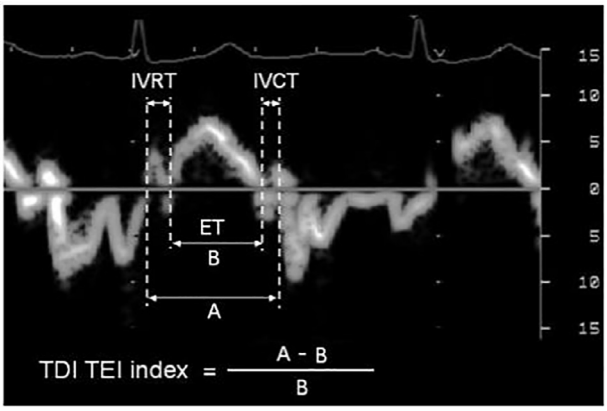

Fig. 1. TDI derived Tei index (A-B/B) [12]. IVRT: isovolumetric relaxation time, ICT: isovolumetric contraction time. ET: ejection time.

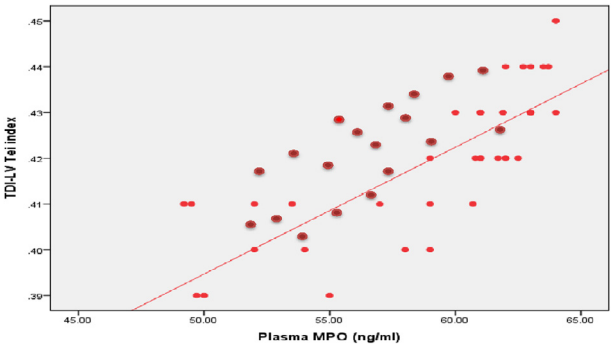

Fig. 2. Correlation between LV TDI-Tei index and plasma MPO in DS children.

Table 1
Comparison between studied groups as regards gender, age and ABP values.

		DS (n = 50)		Control (n = 50)		P value
		n	%	n	%	
Gender	Male	**22**	**44.0%**	**21**	42.0%	0.840[#]
	Female	**28**	**56.0%**	**29**	58.0%	NS
Age	50	mean ± SD	50	mean ± SD		0.75[$]
		8.35 ± 4.25		8.2 ± 3.6		NS
		DS (N = 50)		Control (N = 50)		P value
		Mean	±SD	Mean	±SD	
Systolic BP (mmHg)		102.66	±8.12	106.98	±6.58	0.72[$]
Diastolic		72.16	±7.64	75.54	±4.32	0.64[$]

BP: Blood Pressure.
[#] Student T test.
[$] Cbi square test.

No statistically significant difference was found between the DS children (group I) and control (group II) as regards age, gender, systolic and diastolic blood pressure values (p = 0.84, 0.75, 0.72, 0.64 respectively).

A statistically significant increase was found in heart rate mean values of DS children with normal hearts (group I) compared to controls (group II) (105.5 ± 5.5 VS 90 ± 7.5, P < 0.01) Table 1.

Conventional echocardiographic data are shown in Table 2.

DS children with normal hearts (group I) had normal LV systolic functions by conventional echocardiography (EF%68.2 ± 3.9 vs 67 ± 4.5 in group II, P = 0.46). DS children had higher ejection fractions than control but this increase did not reach statistical significance. Tissue Doppler mitral systolic **S**$^{/}$ waves which are more sensitive than crude systolic conventional echocardiographic measures (EF % and FS%) were found to be significantly increased in group I than group II (P < 0.001) (Tables 3 and 4).

Decreased diastolic function was detected in group I than group II[E$^{/}$/A$^{/}$ 1.24 ± 0. 23 VS 1.92 ± 0.4, P < 0.001) Table 4. Isovolumetric relaxation time (IVRT)was prolonged in group I compared to group II (61.25 VS 50.6, P P < 0.01) while no significant difference was found between studied groups as regards isovolumetric contraction time (ICT) (P 0.53)

Table 2
Comparison between studied groups as regards M mode data.

	DS (N = 50) Mean ± SD	Control (N = 50) Mean ± SD	P value
LAD (mm)	1.26 ± 0.2	1.24 ± 0.01	0.7
IVSd (mm)	0.71 ± 0.02	0.7 ± 0.02	0.730
LVPWT (mm)	0.75 ± 0.03	0.73 ± 0.01	0.73
LVEDD (mm)	4.23 ± 0.14	4.27 ± 0.17	0.194
LVESD (mm)	2.37 ± 0.24	2.36 ± 0.25	0.837
FS (%)	33.8 ± 1.77	33.02 ± 2.08	0.57
EF (%)	68.2 ± 3.91	67 ± 4.5	0.46

– Student T test. LAD: Left Atrial Diameter, LVSd: Left Ventricular Systolic Diameter, LVPWT: Left Ventricular Posterior Wall Thickness, LVEDD: Left ventricular End Diastolic Diameter, IVSd: Interventricular Septal Diameter, FS%: Fractional Shortening%, EF%: Ejection Fraction%.

Table 3
Comparison between studied groups as regards MPO levels.

	DS (N = 50) Mean ± SD	Controls (N = 50) Mean ± SD	P value
MPO (ng/ml)	64.48 ± 31.6	50.4 ± 30.2	<0.001[**]

MPO:myeloperoxidase.
[**] Highly significant.

Table 4
Comparison between studied groups as regards TDI data.

	DS (N = 50) Mean ± SD	Control (N = 50) Mean ± SD	P value
LV **S**$^{/}$ average septal and lateral (cm/s)	7.42 ± 0.29	6.6 ± 0.22	<0.001[**]
LV **E**$^{/}$ average septal and latera$^{/}$/(cm/s)	6.54 ± 0.21	8.16 ± 0.19	<0.001[**]
LV **E**$^{/}$/**A**$^{/}$ average septal and lateral	1.24 ± 0.23	1.92 ± 0.4	<0.001[**]

LV: left Ventricle s$^{/}$: Tissue Doppler systolic wave, E$^{/}$: Tissue Doppler early diastolic wave, A$^{/}$: Tissue Doppler late diastolic wave.
[**] Highly significant.

Table 5
Comparison between studied groups as regards LV-TDI Tei index.

	DS (N = 50) Mean ± SD	Control (N = 50) Mean ± SD	P value
LV-TDI Tei index	0.46 ± 0.02	0.32 ± 0.06	<0.001[**]

[**] Highly significant.

Table 6
Correlation between LV TDI-Tei index in DS children.

	TDI-LV Tei index	
	r	p-value
Plasma MPO (ng/ml)	0.877[**]	0.000[**]

r: correlation coefficient.
[**] Highly significant.

LV TDI-Tei was significantly increased in group I compared to group II (0.46 ± 0.02 vs 0.32 ± 0.08, p < 0.001) Table 5.

Plasma MPO was significantly increased in group I compared to group II (64.48 ± 31.6 ng/ml vs 50.4 ± 30.2 nglml, p < 0.001) Table 3.

A significant positive correlation was found between plasma MPO and LV TDI-Tei (r = 0.877, p = 0.001) in group I Table 6.

4. Discussion

Despite the numerous studies done on congenital heart disorders in DS children, there are very scarce data concerning cardiac functional status in DS children with structurally and clinically normal hearts [14]. No previous data exist on the possible effect of oxidant stress in those patients on their myocardial performance. The current study aimed to evaluate the left ventricle myocardial performance in DS children with structurally and

clinically normal hearts using a reliable Tissue Doppler derived measure. LVTDI -Tei index and correlate it with plasma MPO level as a marker of oxidative stress.

A statistically significant increase was found in DS Children (group I) heart rates compared to controls (group II) ($p < 0.01$) which came in accordance with Al-biltagi et al. [14] and Abtahi et al. [15] who attributed this to cardiac autonomic dysfunction in those patients [14,15].

Concerning conventional echocardiography data, fractional shortening % (FS%) and Ejection fraction % (EF%) were increased in group I than group II. Although this increase did not reach statistical significance yet the more sensitive mitral annular systolic wave $\mathbf{S}^{/}$ was significantly increased in gp I than gp II which agreed with Abtahi et al. [15] who attributed this increase to decreased cardiac afterload in DS patients and not to intrinsic myocardial abnormalities [15] However, this issue needs further studies.

Diastolic functions were found to be decreased in group I than group II [evidenced by the significant decrease in $E^{//}$ and $E^{/}/A^{/}$ of group I compared to group II]. Which agreed with Al-biltagi et al. [14] who attributed this to impaired cardiac muscle relaxation and isovolumetric relaxation phase (IVRT) prolongation which was also found in current studied group I [14].

Left ventricular tissue Doppler derived myocardial performance index (LV TDI –Tei index) was found to be significantly increased in DS children compared to controls which confirms subclinical left ventricular dysfunction in DS children with anatomically and clinically normal hearts and agreed with Abtahi et al. [15].

Plasma MPO levels were found to be significantly elevated in DS children with normal hearts (group I) than controls group II ($p < 0.001$) which denotes increased oxidants stress in DS children with normal hearts [4].

A significant positive correlation was found between plasma MPO levels and LVTDI-Tei in DS children with anatomically and clinically normal hearts (group I) ($p = 0.001$) which indicates that oxidant stress plays a role in the subclinical LV dysfunction detected in those patients.

Further studies are needed to assess the predictive value of TDI –Tei index for long term cardiovascular events in DS children with normal hearts, evaluate newer echocardiographic modalities role as Two Dimensional (2D) strain, Three Dimensional (3D) speckle tracking in detection of subclinical myocardial dysfunction in those children as well as the role of antioxidants treatment in reversing or improving such myocardial dysfunction. The role of other factors contributing to subclinical myocardial dysfunction in DS children with anatomically normal hearts remains to be elucidated.

5. Conclusion

Subclinical LV dysfunction evidenced by increased TDI Tei index was detected in DS children with anatomically and clinically normal hearts. This dysfunction is correlated with plasma Myeloperoxidase level which mandates antioxidants treatment and tissue Doppler myocardial performance evaluation for early identification, monitoring and early intervention

Conflict of interest

Authors declare no conflict of interests.

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