



# Assessment of Aortic Elasticity and the Doppler Tissue Echocardiography in Thalassemia Major Children

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J Child Sci 2020;10:e63–e73.

## Abstract

Cardiovascular diseases are the most common illness that needs special medical care in thalassemia particularly in children and adolescents. We aimed to compare aortic stiffness in thalassemia major and healthy children. The study included 65 asymptomatic thalassemia major 6 to 19-year-old children without known history of heart disease and 65 age- and sex-matched healthy controls. Arterial stiffness indices determined using two-dimensional (2D) and Doppler echocardiography. Data were analyzed by SPSS 20.0 with 0.05 as significant error. From the study, results showed that systolic ( $p = 0.009$ ) and diastolic ( $p < 0.001$ ) blood pressures were higher in controls. Left ventricular mass index (LVMI) was higher in patients ( $p < 0.001$ ). Aortic stiffness index ( $p < 0.001$ ), pulse pressure ( $p < 0.001$ ), and pressure strain elastic modulus ( $p < 0.001$ ) were higher in patients, while aortic strain ( $p < 0.002$ ) and aortic distensibility ( $p < 0.001$ ) were lower significantly. Aortic stiffness index was correlated with diastole aorta ( $p = 0.005$ ), systole aorta ( $p < 0.001$ ), and LVMI ( $p < 0.001$ ). Strain was correlated with diastole aorta ( $p < 0.001$ ). Pulse pressure was correlated with systolic blood pressure ( $p < 0.001$ ), diastolic blood pressure ( $p = 0.002$ ) significantly. Aortic distensibility was correlated with systolic blood pressure ( $p = 0.039$ ) and diastole aorta ( $p < 0.001$ ) significantly. The pressure strain elastic modulus was correlated only with diastole aorta ( $p = 0.029$ ). Concluded, aortic stiffness index, pulse pressure, and pressure strain elastic modulus were higher in thalassemia children, while aortic strain and aortic distensibility were lower. This increase may result in reduction of mechanical efficiency of the heart. Therefore, assessment of aortic elastic properties as nontraditional cardiovascular risk factors may contribute to the identification of cardiovascular risks in children with thalassemia

## Keywords

- ▶ aortic elasticity
- ▶ Doppler tissue echocardiography
- ▶ thalassemia
- ▶ children

## Introduction

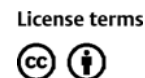
Cardiovascular disease (CVD) is a class of diseases that involve the heart or blood vessels which needs restorative consideration exceptionally in children. One of the most significant noninvasive strategies is assessing aortic elastic parameters to recognize future cardiovascular events.<sup>1</sup> The

parameters of aortic elastic regular are the after effect of incorporating cardiovascular hazard factors on the blood vessel divider over an extensive stretch of time. Estimating these parameters may open a window of opportunity to stop the event of cardiovascular infection.<sup>2</sup> The parameters are the consequence of regular maturing and natural aging that might be affected by numerous components of hereditary

received  
March 17, 2020  
accepted  
May 8, 2020

DOI <https://doi.org/10.1055/s-0040-1713595>.  
ISSN 2474-5871.

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inclination and cardiovascular hazard factors such as blood vessel hypertension, hypercholesterolemia, diabetes mellitus, smoking, and physical movement.<sup>3</sup> They are early signs of structural and functional changes of the vessel wall and an independent predictor of cardiovascular disorders that arise as a consequence of arteriosclerosis.<sup>2</sup> Many studies have been conducted about the aortic elastic changes due to various diseases.<sup>4-11</sup> Bayar et al<sup>4</sup> found changes in arterial stiffness parameters in patients with celiac diseases compared with the healthy when Ülger et al<sup>5</sup> did not find any changes in asthma patients. In this regard, Bektaş et al<sup>6</sup> found a significant change in asthmatic patients compared with posttreatment asthmatic patients. Prenner and Chirinos,<sup>7</sup> Zapolski et al,<sup>8</sup> and Sahin et al<sup>9</sup> found an increase of arterial stiffness parameters in diabetes mellitus, end stage renal and thalassemia major (TM) diseases compared with healthy in the order given. In addition, considering TM patients, Sherief et al<sup>10</sup> used the method of carotid artery intima media thickness and found a significant increase, while Cusmà Piccione et al<sup>11</sup> did not find. But the arterial stiffness was increased significantly. Physiopathology of vasculopathy in patients with TM cannot be explained by iron-related oxidative injury alone, as aortic elastic or similar disorder does not always accompany to hemochromatosis.<sup>9</sup> In patients with TM, structural changes in available mechanisms result in altered elasticity of vessels in subsequent period, thus, predispose to arterial dysfunction.<sup>12</sup> Recently, arterial elasticity parameters are assessed by relatively simple, noninvasive methods to assess vascular involvement in patient with TM especially. Increased aortic stiffness or decreased distensibility is applied as a marker for diffuse atherosclerotic involvement in vascular system.<sup>9</sup> Moreover, in some studies suggested, arterial stiffness can be used as a marker for early cardiovascular and vascular involvement in asymptomatic TM patients without significant iron load<sup>13</sup> and without any correlations with ferritin.<sup>14</sup> To date, no studies have yet been performed on aortic stiffness parameters on patients with TM in this region. Therefore, the present study aimed to assess the aortic strain; stiffness and elasticity in TM patients and compare with healthy children.

## Materials and Methods

### Study Design

This case-control study was performed on 130 participants aged 6 to 19 years consisted of 65 healthy children as controls and 65 thalassemia children as case group in pediatric cardiac center in collaboration with center for specific diseases at Ali Asghar Hospital of Zahedan in Sistan and Baluchistan provinces, Iran, from 2018 September to 2019 August. Thalassemia children collected from those thalassemia patients who were asymptomatic and those patients who had regular transfusions of hemoglobin higher than 10 g/dL and 48 to 72 hours after packed red blood cell transfusion were entered into the study. From selected patients, two had ejection fraction lower than 60% in which both were girls with 18 years that had 55 and 59%. Control children collected from those healthy children that referred to the clinics for routine check-up.

### Criteria

Exclusion criteria in both groups of participants were valvular heart disease, rhythm, and structural abnormality, active infection, systemic inflammatory diseases, and renal insufficiency.

### Echocardiography Measurements

Major proceedings on patients were checking medical history, physical examination, chest X-ray, and echocardiography which was performed by one pediatric cardiologist. Echocardiography was performed on participants by the same pediatric cardiologist using the My laboratory 60 with transducer 3, 8 (made in Italy). To achieve high precision in echocardiography findings, measurement was repeated for three cycles and the average was considered. Echocardiogram was performed on participants without them holding their breath.

Echocardiography findings by M-mode (a diagnostic ultrasound presentation of the temporal changes in echoes in which the depth of echo-producing interfaces is displayed with two axes of time and motion) were diastolic diameter of the aorta (Aod), systolic diameter of the aorta (Aos), left ventricular end diastolic dimension (LVDD), posterior wall dimension (PWD) in diastole, interventricular septal dimension in diastole (IVSD), interventricular septal dimension in systole (IVSS), relative wall thickness (RWT) that defined as twice PWT divided by the LV diastolic diameter, ejection fraction (EF), fractional shortening (FS), LV mass (LVM), and LVM index (LVMI) were measured using conventional echocardiography of the left side and estimated from three cardiac cycles. LVMI was calculated by the following formula:  $LVM (g) = 0.8 (1.04 [LVDD + PWD + IVSD]^3 - LVDD^3) + 0.6$ , and  $LVMI (g/m^2) = LVM/2.7 (g/m^2)$ . All the parameters in the above formula were measured in the M-mode view and in diastole and were utilized for LVM evaluation.<sup>15</sup> After routine echocardiographic investigation, ascending aorta were obtained from 3 cm above the aortic valve by the M-mode. Aortic diameters were calculated as the distance between the anterior and posterior wall inner edges of the aorta at systole and diastole. Aos was recorded when the aortic wall was fully open. Aod was recorded simultaneously when the QRS peak was seen on electrocardiographic (ECG) recordings. Measurements were taken during three consecutive pulses and the mean was calculated. The Doppler tissue echocardiography (DTE) is another method that was performed from the apical four-chamber view and a 3-mm pulsed Doppler sample volume was placed at the level of lateral mitral annulus. Myocardial velocity profiles of the lateral tricuspid annulus and lateral mitral annulus were obtained by placing the sample volume at the junction of the tricuspid annulus and the right ventricle (RV) free wall and at the junction of the mitral annulus and LV posterior wall, respectively. With this modality, the recorded values were the early (E') and late (A') diastolic mitral and tricuspid annular velocities, and the ratio of E'/A'. Left and right S': systolic myocardial velocity above the baseline in mitral and tricuspid. Left and right E': early diastolic myocardial relaxation velocity below the baseline in mitral and tricuspid. Left and right A': myocardial velocity associated with atrial contraction in mitral and tricuspid.<sup>16</sup>

### Blood Pressure Measurement

Blood pressure (BP) levels were measured from the brachial artery at the level of the heart with a sphygmomanometer after resting for at least 5 minutes in the supine position. Three measurements, at least 2-minute apart, were performed, and the average of the closest two readings was recorded. A pressure drop rate of approximately 2 mm Hg/s was applied, and Korotkoff's phases I and V were used for systolic and diastolic BP (SBP and DBP, respectively) levels, respectively. All BP measurements were made by a cardiologist. Pulse pressure (PP) was calculated as systolic minus diastolic BP.

### Aortic Elasticity Parameters

The systolic and diastolic ascending aortic diameters were recorded in M-mode under echocardiographic and electrocardiographic guidance approximately 3 cm above the aortic valve from parasternal long-axis views. The systolic aortic diameter was measured at the time of maximum anterior motion of the aorta, while the diastolic diameter was measured at the start of the QRS complex in electrocardiography (► Fig. 1). The following formulas were used to assess the aortic elasticity of the aorta.<sup>4</sup>

**Aortic strain (%)** = (aortic SD [systolic diameter] – aortic DD [diastolic diameter]) × 100/aortic DD

**Aortic stiffness  $\beta$  index** = natural logarithm (SBP [BP]/DBP)/([aortic SD – aortic DD]/aortic DD)

**Aortic distensibility ( $\text{cm}^2 \times \text{dyne}^{-1.10-6}$ )** =  $2 \times ([\text{aortic SD} - \text{aortic DD}] / \text{aortic DD}) / (\text{SBP} - \text{DBP})$

**Pressure strain elastic modulus** =  $(\text{SBP} - \text{DBP}) / ([\text{aortic SD} - \text{aortic DD}] / \text{aortic DD})$

### Anthropomorphic Measurements

The participants' height and weight were measured by an experienced expert using standard equipment. Then, body mass index (BMI) was calculated according to the 2,000 sex-specific BMI-for-age growth charts of the Centers for Disease Control and Prevention. Participants' height was measured in the standing position with a balance using a scaled ruler and weight was calculated using a RAhpouyan Salamat Azma (RASA) scale factor with an error of 100 g (made in Iran). Then BMI was calculated as weight (kg)/height ( $\text{m}^2$ ).

### Ethical Approval

Consent form was obtained from the participants or their guardians after the study approval. The study was approved as a project proposed to the Children and Adolescent Health Research Center by the Ethics Committee of Zahedan University of Medical Sciences, Zahedan, Iran (ID number: 6798).

### Statistical Analysis

Data were analyzed by using SPSS for Windows version 20.0 (SPSS Inc.; Chicago, Illinois, United States). Kolmogorov–Smirnov test was used to assess distribution of continuous variables where homogeneity was tested. Student's *t*-test was used to compare mean values of quantitative variables with normal distribution while Mann–Whitney *U*-test was used to compare quantitative variables with skewed distribution. In correlation analyses, Pearson's test was used for parametric variables while Spearman's test was used for nonparametric variables. *p*-Value of < 0.05 was considered as statistically significant.

### Results

The study aimed to assess the aortic stiffness parameters in TM children comparing with controls. A total of 130 participants were entered into the study with 65 in each group. Sex distribution was 42.3 and 57.7% in terms of females and males, respectively. In patients, 28 (43.1%) were females and this pattern was 27 (41.5%) for the controls. ► Table 1 showed the data distribution in participants and only patients. In the case of participants, Aod, Aos, LVDD, LVDS, EF, FS, and BMI were distributed normally ( $p > 0.05$ ). The remaining variables had free distribution. In the case of only patients, the results revealed that height, Aod, Aos, IVSD, LVDD, EF, FS, Left E', BMI, LVMI, Left E'/A', and right E'/A' were normal ( $p > 0.05$ ).

► Table 2 showed the quantities variables comparative in TM and controls based on nonparametric Mann–Whitney *U*-test. The tables showed that the participant in TM and controls were similar in age ( $p = 0.05$ ). Weight ( $p < 0.001$ ) and height ( $p = 0.001$ ) of the patients were lower than controls. Systolic ( $p = 0.009$ ) and diastolic ( $p < 0.001$ ) blood pressures were higher in controls compared with patients, while conventional echocardiography parameters, such as IVSD, PWD, IVSS, and



**Fig. 1** Measurements of systolic (S) and diastolic (D) diameters of the ascending aorta are shown on the M-mode tracing obtained at a level 3 cm above the aortic valve.

**Table 1** Normality test for quantities variables in participants and TM patients

Variables	All participants				TM patients			
	Mean	SD	KS	p	Mean	SD	KS	p
Age (y)	13.7	3.65	0.14	< 0.001	13.98	3.84	0.15	0.001
Weight (kg)	41.49	13.88	0.08	0.037	36.23	11.71	0.11	0.039
Height (cm)	145.22	16.91	0.08	0.04	139.98	16.54	0.11	0.052
SBP (mm Hg)	105.38	6.81	0.18	< 0.001	103.46	5.99	0.16	< 0.001
DBP (mm Hg)	68.07	6.97	0.17	< 0.001	63.52	5.34	0.21	< 0.001
Aod (cm)	2.00	0.28	0.06	0.2	1.97	0.3	0.08	0.2
Aos (cm)	2.42	0.3	0.05	0.2	2.35	0.31	0.07	0.2
IVSD (cm)	0.76	0.18	0.09	0.007	0.86	0.17	0.07	0.2
LVDD (cm)	4.01	0.51	0.05	0.2	4.26	0.44	0.08	0.2
PWD (cm)	0.39	0.07	0.1	0.002	0.42	0.07	0.18	< 0.001
IVSS (cm)	0.93	0.2	0.15	< 0.001	1.01	0.2	0.17	< 0.001
LVDS (cm)	2.23	0.38	0.07	0.094	2.42	0.36	0.14	0.005
PWS (cm)	0.39	0.07	0.11	0.001	0.42	0.07	0.18	< 0.001
EF (%)	0.76	0.06	0.07	0.2	0.74	0.06	0.1	0.08
FS (%)	0.43	0.06	0.07	0.2	0.41	0.05	0.08	0.2
Left S' (m/s)	0.09	0.01	0.19	< 0.001	0.08	0.01	0.18	< 0.001
Left A' (m/s)	0.16	0.03	0.1	0.005	0.17	0.03	0.1	0.184
Left E' (m/s)	0.07	0.02	0.18	< 0.001	0.06	0.02	0.18	< 0.001
Right S' (m/s)	0.10	0.07	0.33	< 0.001	0.12	0.1	0.41	< 0.001
Right A' (m/s)	0.15	0.02	0.12	< 0.001	0.15	0.03	0.13	0.013
Right E' (m/s)	0.08	0.02	0.17	< 0.001	0.08	0.02	0.15	0.001
AS'	5.28	0.39	0.13	< 0.001	5.47	0.43	0.12	0.022
Strain (%)	21.21	6.87	0.09	0.008	19.82	8.6	0.13	0.011
PP (mm Hg)	37.32	6.15	0.22	< 0.001	39.94	5.36	0.27	< 0.001
AD (cm <sup>2</sup> × dyne <sup>-1</sup> × 10 <sup>-6</sup> )	1.18	0.44	0.1	0.006	1.01	0.43	0.16	< 0.001
PSEM (kPa)	2.03	1.14	0.24	< 0.001	2.46	1.44	0.25	< 0.001
BMI (kg/m <sup>2</sup> )	19.02	2.8	0.05	0.2	17.93	2.66	0.08	0.2
RWT	0.19	0.03	0.09	0.007	0.2	0.03	0.14	0.003
LVMI (g/m <sup>2</sup> )	38.34	16.07	0.11	< 0.001	48.01	15.61	0.11	0.061
Left E'/A'	2.49	0.69	0.08	0.044	2.72	0.68	0.08	0.2
Right E'/A'	1.99	0.39	0.08	0.035	1.93	0.47	0.09	0.2

Abbreviations: A', late diastolic myocardial velocity; AD, aortic distensibility; Aod, aortic diameter in diastole; Aos, aortic diameter in Systole; ASI, aortic stiffness index; BMI, body mass index; DBP, diastolic blood pressure; E', early diastolic myocardial relaxation velocity; EF, ejection fraction; FS, fractional shortening; IVSD, interventricular septal dimension in Diastole; IVSS, interventricular septal dimension in systole; KS, Kolmogorov-Smirnov; LVDD, left ventricular end diastolic dimension; LVDS, left ventricular end systolic dimension; LVMI, left ventricular mass index; PP, pulse pressure; PSEM, pressure strain elastic modulus; PWD, posterior wall dimension in diastole; PWS, posterior wall dimension in systole; RWT, relative wall thickness; S', systolic myocardial velocity; SBP, systolic blood pressure; SD, standard deviation; TM, thalassemia major.

PWS were different significantly ( $p < 0.001$ ). Doppler tissue imaging findings, such as left S' ( $p = 0.012$ ), left E' ( $p < 0.001$ ), right S' ( $p < 0.001$ ), right E' ( $p = 0.018$ ), LVMI ( $p < 0.001$ ), left E'/A' ( $p < 0.001$ ), and right E'/A' ( $p = 0.038$ ) were different in patients compared with controls. Aortic stiffness parameters such as; ASI ( $p < 0.001$ ), PP ( $p < 0.001$ ), and PSEM ( $p < 0.001$ ) were higher in patients, while AS ( $p < 0.002$ ) and AD ( $p < 0.001$ ) were significantly low. **Fig. 2** showed the boxplot presentation for four aortic stiffness.

**Table 3** showed the quantities variables comparative in TM and controls children based on parametric independent *t*-test. From the table resulted that the variables of Aos ( $p = 0.009$ ), LVDD ( $p < 0.001$ ), LVDS ( $p < 0.001$ ), EF ( $p < 0.001$ ) FS ( $p < 0.001$ ), and BMI ( $p < 0.001$ ) were different in patients when compared with controls.

**Table 4** showed the correlation between aortic stiffness parameters and other studied variables in patients. From the table observed that ASI was correlated with age ( $p < 0.001$ ),

**Table 2** Quantities variables comparative in TM and controls based on nonparametric Mann–Whitney U-test

Variables	Groups	Mean	SD	Mean rank	Sum of ranks	MWU	p-Value
Age (y)	TM patients	13.98	3.84	68.19	4,432.50	1,937.50	0.413
	Controls	13.42	3.45	62.81	4,082.50		
Weight (kg)	TM patients	36.23	11.71	51.79	3,366.50	1,221.50	< 0.001
	Controls	46.75	13.96	79.21	5,148.50		
Height (cm)	TM patients	139.98	16.54	54.27	3,527.50	1,382.50	0.001
	Controls	150.46	15.71	76.73	4,987.50		
SBP (mm Hg)	TM patients	103.46	5.99	57.08	3,710.00	1,565.00	0.009
	Controls	107.31	7.08	73.92	4,805.00		
DBP (mm Hg)	TM patients	63.52	5.34	40.81	2,652.50	507.50	< 0.001
	Controls	72.62	5.24	90.19	5,862.50		
IVSD (cm)	TM patients	0.86	0.17	88.35	5,743.00	627.00	< 0.001
	Controls	0.65	0.11	42.65	2,772.00		
PWD (cm)	TM patients	0.42	0.07	82.63	5,371.00	999.00	< 0.001
	Controls	0.36	0.05	48.37	3,144.00		
IVSS (cm)	TM patients	1.01	0.2	81.75	5,314.00	1,056.00	< 0.001
	Controls	0.85	0.16	49.25	3,201.00		
PWS (cm)	TM patients	0.42	0.07	82.4	5,356.00	1,014.00	< 0.001
	Controls	0.36	0.05	48.6	3,159.00		
Left S' (m/s)	TM patients	0.08	0.01	57.44	3,733.50	1,588.50	0.012
	Controls	0.09	0.02	73.56	4,781.50		
Left E' (m/s)	TM patients	0.17	0.03	79.1	5,141.50	1,228.50	< 0.001
	Controls	0.15	0.02	51.9	3,373.50		
Left A' (m/s)	TM patients	0.06	0.02	60.16	3,910.50	1,765.50	0.099
	Controls	0.07	0.02	70.84	4,604.50		
Right S' (m/s)	TM patients	0.12	0.1	81.61	5,304.50	1,065.50	< 0.001
	Controls	0.09	0.01	49.39	3,210.50		
Right E' (m/s)	TM patients	0.15	0.03	57.8	3,757.00	1,612.00	0.018
	Controls	0.16	0.02	73.2	4,758.00		
Right A' (m/s)	TM patients	0.08	0.02	65.51	4,258.00	2,112.00	0.998
	Controls	0.08	0.01	65.49	4,257.00		
ASI	TM patients	5.47	0.43	84.26	5,477.00	893.00	< 0.001
	Controls	5.09	0.22	46.74	3,038.00		
Strain (%)	TM patients	19.82	8.6	55.03	3,577.00	1,432.00	0.002
	Controls	22.6	4.16	75.97	4,938.00		
PP (mm/Hg)	TM patients	39.94	5.36	81.61	5,304.50	1,065.50	< 0.001
	Controls	34.69	5.79	49.39	3,210.50		
AD (cm <sup>2</sup> × dyne <sup>-1</sup> × 10 <sup>-6</sup> )	TM patients	1.01	0.43	47.69	3,100.00	955.00	< 0.001
	Controls	1.35	0.39	83.31	5,415.00		
PSEM (kPa)	TM patients	2.46	1.44	83.31	5,415.00	955.00	< 0.001
	Controls	1.59	0.43	47.69	3,100.00		
RWT	TM patients	0.2	0.03	69.84	4,539.50	1,830.50	0.189
	Controls	0.19	0.03	61.16	3,975.50		

(Continued)



**Table 2** (Continued)

Variables	Groups	Mean	SD	Mean rank	Sum of ranks	MWU	p-Value
LVMI (g/m <sup>2</sup> )	TM patients	48.01	15.61	89.19	5,797.50	572.50	< 0.001
	Controls	28.66	9.29	41.81	2,717.50		
Left E'/A'	TM patients	2.72	0.68	78.43	5,098.00	1,272.00	< 0.001
	Controls	2.27	0.63	52.57	3,417.00		
Right E'/A'	TM patients	1.93	0.47	58.65	3,812.00	1,667.00	0.038
	Controls	2.04	0.3	72.35	4,703.00		

Abbreviations: A', late diastolic myocardial velocity; DBP, diastolic blood pressure; E', early diastolic myocardial relaxation velocity; IVSD, interventricular septal dimension in diastole; IVSS, interventricular septal dimension in systole; LVMI, left ventricular mass index; MWU, Mann-Whitney U test; PWD, posterior wall dimension in diastole; PWS, posterior wall dimension in systole; RWT, relative wall thickness; S', systolic myocardial velocity; SBP, systolic blood pressure; SD, standard deviation; TM, thalassemia major.

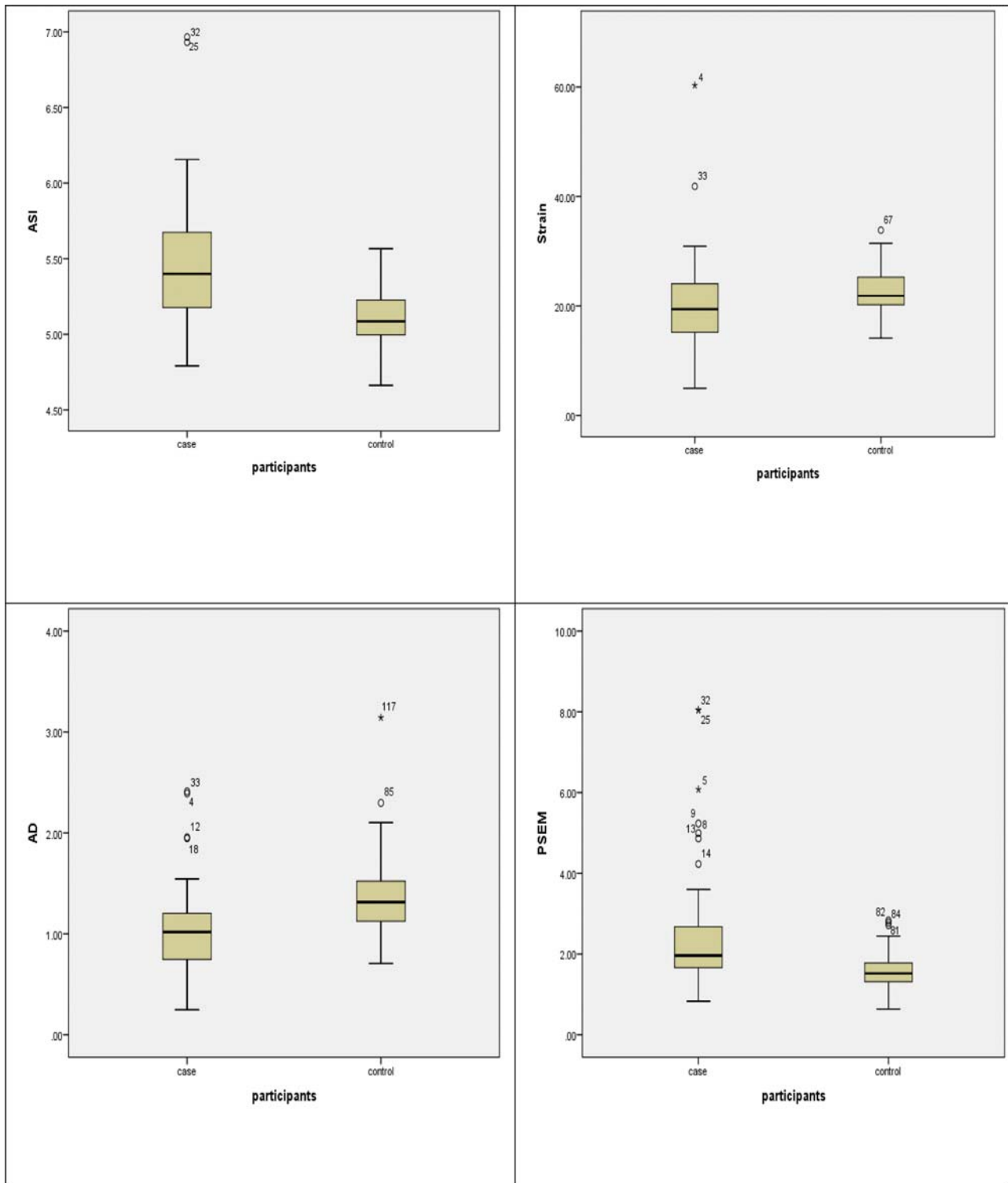
weight ( $p < 0.001$ ), height ( $p = 0.001$ ), Aod ( $p = 0.005$ ), Aoa ( $p < 0.001$ ), IVSD ( $p < 0.001$ ), LVDD ( $p = 0.008$ ), PWD ( $p = 0.010$ ), IVSS ( $p < 0.001$ ), PWS ( $p = 0.007$ ), BMI ( $p = 0.002$ ), and LVMI ( $p < 0.001$ ). Strain was correlated with Aod ( $p < 0.001$ ) and Left E'/A' ( $p = 0.028$ ) significantly. PP was correlated with SBP ( $p < 0.001$ ) and DBP ( $p = 0.002$ ) significantly. AD was correlated with SBP ( $p = 0.039$ ) and AD ( $p < 0.001$ ) significantly. The PSEM was correlated only with Aod ( $p = 0.029$ ).

The patients were grouped in different age groups, such as 17 years in age lower than 10 years, 19 years in age group of 10 to 15 years, and the remaining patients included in the last age group of 15 to 19 years. Therefore, **Table 5** showed aortic stiffness parameters comparison in age groups of TM patients, indicating that two indices of ASI and aortic strain were different in TM patients considering age. ASI was high ( $5.84 \pm 0.51$ ) in the age group of  $\leq 10$  years and then increased by age so that reached to ( $5.32 \pm 0.33$ ) for the age group of  $> 15$  years ( $F = 11.415$ ,  $p < 0.001$ ). Aortic strain levels had the highest level (24.26) in the age group of 11 to 15 years and had the lowest level (17.76) in the age group of  $> 15$  years. The TM patients had no different levels of PP, aortic distensibility and pressure strain elastic modulus in different age groups. The difference of aortic stiffness index observed in paired age groups of ( $\leq 10$  and 11 to 15) and ( $\leq 10$  and  $> 15$ ) years. For the Aorta strain the difference observed in paired age group of (11 to 15 and  $> 15$ ) years.

## Discussion

Despite the fact that the futurity and personal atonement of TM patients have particularly expanded as of late, the patients still experience the ill effects of numerous difficulties.<sup>17</sup> At present, the most widely recognized complexity and the primary driver of death in these patients are transfusion-related hemosiderosis-incited heart failure and fatal arrhythmia.<sup>18</sup> In these patients, iron deposition in the heart does not occur until the other organs are saturated and iron overload may result in systolic and diastolic dysfunction of the LV accumulation and of hepatic iron does not represent the deposition of the myocardial iron.<sup>19</sup> An improvement in parameters of aortic stiffness in the absence of cardiac iron

overload in patients with TM has been demonstrated.<sup>13</sup> Aortic stiffness increases SBP and LVM due to decreased buffering mechanism and rapid return of reflective pressure waves from periphery. Associated decrease in diastolic pressure predisposes to increased cardiovascular disorder by reducing coronary blood flow.<sup>20</sup> In the present study, the patients had lower SBP and DBP compared with controls and some of conventional and Doppler tissue findings were different. In the patients, aortic stiffness index, PP, and pressure strain elastic modulus were higher, while aortic strain and aortic distensibility were lower compared with controls. Aortic stiffness index was correlated with diastole and systole aorta and LVMI. Aorta strain was correlated with diastole aorta and Left E'/A'. PP was correlated with SBP and DBP. Aortic distensibility was correlated with SBP and diastole aorta. The pressure strain elastic modulus was correlated with only diastole aorta. Noori et al<sup>15,21,22</sup> found that left EF and FS were decreased in TM patients compared with healthy ones that was consistent with the present study. In some studies, LVMI found with an increased in TM patients compared with controls same our findings.<sup>16,22</sup> Noori et al<sup>16,21</sup> found that LVDD was lower in control when found higher in another study.<sup>15</sup> In our late study, we concluded that LVSD, PWD, FS, EF, right S', right A', and LVMI were different between TM patients and healthy children.<sup>16</sup> In another study, Noori et al<sup>23</sup> found Doppler tissue parameters such as left S', left A', and right A' were higher in controls compared with TM patients. When the parameters of left E', right S', and right E' were similar, comparable with the related findings of the present study. Similar to the patients of our study, Sahin et al<sup>9</sup> conducted a study on asymptomatic TM patients to determine the changes of aortic stiffness indices. They found higher SBP and DBP and lower PP in controls compared with TM patients. Regarding the stiffness indices, aortic strain, and aortic distensibility were lower and aortic stiffness index and elastic modulus were higher in TM patients. They also found that DBP was correlated with only aortic stiffness. Gedikli et al<sup>12</sup> found smaller body size, lower SBP and DBP, and higher Aoa and Aod in TM patients compared with controls. Aortic strain, distensibility, and stiffness index values also were higher in TM patients. In their study, aortic strain had a significant correlation with



**Fig. 2** Boxplot presentation for aortic stiffness parameters for thalassemia and controls. ASI, aortic stiffness index; PSEM, pressure strain elastic modulus.

age and body surface area (BSA), aortic distensibility was correlated with age, SBP. Tantawy et al<sup>24</sup> led a study on 60 TM patients. They resulted that aortic strain, aortic distensibility, aortic stiffness index, and elastic modulus were different in patients compared with controls. In their study, patients had significantly lower weight and height than controls. LVMI, aortic stiffness index were higher in TM children. Whereas aortic strain, aortic distensibility, EF, and FS were lower. In

addition, aortic stiffness was positively correlated to aortic distensibility. Cusmà Piccione et al<sup>11</sup> conducted a study to evaluate LV myocardial deformation and carotid arterial stiffness in patients with asymptomatic TM without significant myocardial iron overload. Their patients who were adult, went under ultrasonography using a color Doppler echocardiography with high resolution. The stiffness parameters were obtained from the right and left common carotid

**Table 3** Quantities variables comparative in TM and controls based on parametric Independent t-test

Variables	Groups	Mean	SD	T	p-Value
Aod (cm)	TM patients	1.97	0.3	-1.280	0.203
	Controls	2.04	0.26		
Aos (cm)	TM patients	2.35	0.31	-2.665	0.009
	Controls	2.49	0.27		
LVDD (cm)	TM patients	4.26	0.44	6.47	< 0.001
	Controls	3.76	0.44		
LVDS (cm)	TM patients	2.42	0.36	6.72	< 0.001
	Controls	2.04	0.29		
EF (%)	TM patients	0.74	0.06	-3.68	< 0.001
	Controls	0.77	0.05		
FS (%)	TM patients	0.41	0.05	-5.68	< 0.001
	Controls	0.46	0.05		
BMI (kg/m <sup>2</sup> )	TM patients	17.93	2.66	-4.80	< 0.001
	Controls	20.11	2.52		

Abbreviations: Aod, aortic diameter in diastole; Aos, aortic diameter in systole; BMI, body mass index; EF, ejection fraction; FS, fractional shortening; LVDD, left ventricular end diastolic dimension; LVDS, left ventricular end systolic dimension; SD, standard deviation; T, Student's t-test value; TM, thalassemia major.

**Table 4** Association of study variables with Stiffness indices in TM patients

Variables	Statistics	ASI	Strain	PP	AD	PSEM	Variables	ASI	Strain	PP	AD	PSEM
Age (y)	r	-0.465	-0.164	0.051	-0.134	-0.013	EF (%)	0.009	0.198	0.046	0.201	-0.051
	p	<0.001	0.193	0.687	0.287	0.918		0.941	0.114	0.715	0.109	0.687
Weight (kg)	r	-0.448	-0.186	0.028	-0.156	0.014	FS (%)	0.094	0.067	0.051	0.079	0.119
	p	<0.001	0.137	0.827	0.214	0.91		0.458	0.596	0.684	0.532	0.347
Height (cm)	r	-0.414	-0.239	0.073	-0.226	0.049	Left S' (m/s)	-0.114	0.053	-0.15	0.149	-0.041
	p	0.001	0.055	0.563	0.071	0.701		0.365	0.674	0.233	0.236	0.743
IVSD (cm)	r	-0.476	0.095	0.05	0.124	-0.102	Left E' (m/s)	-0.126	0.105	0.007	0.091	-0.104
	p	<0.001	0.453	0.695	0.326	0.419		0.316	0.406	0.956	0.47	0.409
LVDD (cm)	r	-0.325	0.031	0.215	-0.074	-0.013	Left A' (m/s)	-0.13	-0.147	-0.067	-0.103	0.049
	p	0.008	0.805	0.086	0.559	0.92		0.303	0.244	0.597	0.416	0.699
PWD (cm)	r	-0.317	-0.075	0.029	-0.044	0.042	Right S' (m/s)	-0.038	-0.017	0.019	-0.024	0.009
	p	0.01	0.554	0.817	0.729	0.737		0.762	0.896	0.883	0.853	0.946
IVSS (cm)	r	-0.461	-0.031	0.023	0.015	-0.008	Right E' (m/s)	-0.088	0.025	-0.038	0.075	0.034
	p	<0.001	0.804	0.856	0.906	0.947		0.486	0.846	0.766	0.552	0.789
LVDS (cm)	r	-0.194	-0.128	0.095	-0.189	0.045	Right A' (m/s)	-0.102	-0.009	-0.071	0.044	0.158
	p	0.121	0.311	0.452	0.132	0.723		0.418	0.945	0.572	0.73	0.209
PWS (cm)	r	-0.33	-0.069	0.039	-0.042	0.038	BMI (kg/m <sup>2</sup> )	-0.377	-0.027	-0.001	0.006	-0.02
	p	0.007	0.584	0.757	0.74	0.765		0.002	0.831	0.992	0.96	0.875
Left E'/A'	r	0.019	0.273	0.068	0.214	-0.192	LVMI (g/m <sup>2</sup> )	-0.458	0.044	0.111	0.019	-0.073
	p	0.883	0.028	0.588	0.086	0.125		<0.001	0.725	0.379	0.883	0.565
Right E'/A'	r	0.09	0.004	0.024	-0.007	-0.102	RWT	-0.146	-0.119	-0.118	-0.003	0.069
	p	0.476	0.975	0.851	0.954	0.421		0.245	0.347	0.351	0.979	0.586

Abbreviations: A', late diastolic myocardial velocity; AD, aortic distensibility; ASI, aortic stiffness index; BMI, body mass index; E', early diastolic myocardial relaxation velocity; EF, ejection fraction; FS, fractional shortening; IVSD, interventricular septal dimension in diastole; IVSS, interventricular septal dimension in systole; LVDD, left ventricular end diastolic dimension; LVDS, left ventricular end systolic dimension; LVMI, left ventricular mass index; PP, pulse pressure; PSEM, pressure strain elastic modulus; PWD, posterior wall dimension in diastole; PWS, posterior wall dimension in systole; RWT, relative wall thickness; S', systolic myocardial velocity; TM, thalassemia major.



**Table 5** Aortic stiffness parameters comparison in age groups of TM patients

Aortic stiffness parameters	Age groups (y)	Number	Mean	SD	F-Value	p-Value
ASI	≤10	17	5.840	0.508	11.415	<0.001
	11–15	19	5.364	0.305		
	>15	29	5.318	0.326		
	Total	65	5.469	0.433		
Strain (%)	≤10	17	18.355	7.341	3.946	0.024
	11–15	19	24.262	11.722		
	>15	29	17.762	5.544		
	Total	65	19.817	8.597		
PP (mm Hg)	≤10	17	37.941	4.351	1.899	0.158
	11–15	19	41.316	4.956		
	>15	29	40.207	5.930		
	Total	65	39.938	5.356		
AD (cm <sup>2</sup> × dyne <sup>-1</sup> × 10 <sup>-6</sup> )	≤10	17	0.976	0.376	1.974	0.148
	11–15	19	1.163	0.508		
	>15	29	0.920	0.381		
	Total	65	1.006	0.427		
PSEM (kPa)	≤10	17	2.785	2.182	1.379	0.26
	11–15	19	2.026	0.920		
	>15	29	2.553	1.118		
	Total	65	2.460	1.436		

Abbreviations: AD, aortic distensibility; ASI, aortic stiffness index; PP, pulse pressure; PSEM, pressure strain elastic modulus; SD, standard deviation; TM, thalassemia major.

arteries approximately 1 cm proximal to the bulb region. They found no differences between the patients and healthy population regarding the LV volume, EF, myocardial mass, diastolic indices, and all the echocardiography findings but observed higher elastic modulus and stiffness index in patients.

A strong link between arterial stiffness and age approved in both healthy and diseased populations such that aortic stiffness decreases sharply with age in the first decade of life, reaching a minimum at 10 years of age, and thereafter increasing with age in both genders.<sup>25</sup> The underlying basis for these age-dependent changes is still incompletely understood. Pathologically, fracture and fragmentation of the elastin fibers after repetitive stress cycles with consequent dilation and stiffening have been observed.<sup>26</sup>

Central arteries stiffen progressively with age, whereas stiffness of muscular arteries changes little with age.<sup>25</sup> Although large artery stiffness increases with age independently of the presence of cardiovascular risk factors or other associated conditions, the extent of this increase may depend on several environmental or genetic factors.<sup>27</sup> The impact of age on parameters of arterial stiffness among TM patients has been poorly studied. But Cho et al<sup>28</sup> has conducted a study to find the effects of age on arterial stiffness in adulthood patients with newly diagnosed untreated hypertension. They found that age was well-known major determinants of arterial stiffness. They

found augmentation index or augmentation pressure was significantly higher in the old hypertension group.

In similar, we did analysis to find the correlation between age and aortic stiffness indices in our TM patients. We found that aortic stiffness indices increases with age. Therefore, large artery stiffening can be considered as a marker of arterial age and should be considered as a major risk factor for cardiovascular events. The results of the present study suggested that parameters of arterial stiffness were more significantly affected by age rather than the level of BP.

TM is frequently associated with progressive LV systolic and diastolic dysfunction, leading to congestive heart failure. Aortic elastic properties are important determinants of left ventricular systolic and diastolic function. Clinical studies have also linked increased aortic stiffness to overt diastolic heart failure.<sup>12</sup> By virtue of its elastic properties, the aorta influences LV diastolic function and whereby coronary blood flow. Impaired function of aorta may contribute to LV dysfunction in patients with TM. Also deteriorated aortic function may be associated with increased risk of coronary events. Because of extremely low level of lipid levels, thromboembolic events are rare in patients with TM.<sup>29</sup> Taking into account low rate of atherogenic events, elastic properties of aorta should be thought of as a risk factor leading to left ventricular dysfunction in patients with TM. However, long-term followed studies considering relation between

aortic elastic properties and cardiovascular morbidity are needed.<sup>12</sup> From the study and literatures, provided that the first evidence that function of the arterial system in patients with TM is putting at risk by endothelial dysfunction and increased stiffness that may result in reduction of mechanical efficiency of the heart.

### Study Limitation

One limitation was the use of brachial artery measurements for blood pressure values obtained to evaluate aortic elasticity, although the fact that blood pressure values obtained by using same technique in both TM and control groups did not affect the results and did not change the results. In addition, the study was a single-center study that was a reason for small number of patients.

### Conclusion

From the study we concluded that aortic stiffness index, PP, and pressure strain elastic modulus were higher in TM patients when, aortic strain, aortic distensibility were lower. In TM patients, aortic stiffness index was correlated with LVMI. Strain was correlated with aorta in diastole. PP was correlated with SBP and DBP. Aortic distensibility was correlated with SBP and aorta in diastole. The pressure strain elastic modulus was correlated with aorta in diastole. Therefore, assessment of aortic elastic properties as nontraditional cardiovascular risk factors may contribute to the identification of cardiovascular risks in patients with thalassemia.

### Authors' Contributions

N.M.M. contributed in conception, supervision, data collection, literature review, and critical review. A.T. participated in analysis and interpretation, writing manuscript, literature review, and critical review.

### Conflict of Interest

None declared.

### Acknowledgments

The authors would like to thank all the patients and their parents for warm and tolerate participation.

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