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TO STUDY RIGHT VENTRICLE (RV) AND LEFT VENTRICLE (LV) DYSFUNCTION IN TRANSFUSION DEPENDENT BETA THALASSEMIA CHILDREN AT TERTIARY CARE HOSPITAL IN NORTH WEST RAJASTHAN

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Abstract

Background- Regular blood transfusions used for long term survival in ß-thalassemia major patients cause a secondary state of tissue iron overload. Myocardial iron deposition can result in cardiomyopathy, and heart failure remains the leading cause of death. This study was planned to see the Right Ventricle (RV) and Left Ventricle(LV)dysfunction in beta thalassemia transfused patients.

Method- Patients of ß thalassemia major above 2 years of age received regular blood transfusions at least for 1 year duration, attending OPD in the Department of Pediatrics, S P Medical College, Bikaner were included.Echo was correlated with serum ferritin Level(SFL).

Results- Tissue Doppler imaging(TDI) parameters of 50 patients at mitral annulus e.g. Em septal, Em Lateral, Am septal, Am lateral, Sm Septal and Sm Lateral were abnormal(<2SD and >2SD)in 70% & 0%, 50% & 4%, 10% & 46%, 34% & 24%, 40% & 22% and 60% & 10% patients respectively.TDI parameters at tricuspid valvee.g. Et, At and St were abnormal(<2SD)in 98%, 96% and 98% patients respectively. The differences in mean values of Et, At and St, when compared in the SFL groups <2500,2500-5000 and>5000, was non significant($p>0.05$).

Conclusion- TDI is superior to conventional echocardiography in giving an early evidence of diastolic myocardial dysfunction in asymtopmatic and normal LV function patients.TDI can be applied as an integrated part of assessment of children & adolescents with ß-thalassemia. Septal Sm, Em & lateral Em, Sm, Am and RV Et, At, St were reduced early in majority of patients. Our study showed early involvement of septum and RV in thalassemic patients.

Key Words: ß-thalassemia major ;Right Ventricle (RV) and Left Ventricle (LV) dysfunction; Echocardiogram ;Tissue Doppler Imaging

Introduction

Every year, there are at least 60,000 individuals born with ß-thalassemia major (TM) globally[1]. Regular blood transfusions used for long term survival cause a secondary state of tissue iron overload. Myocardial iron deposition can result in cardiomyopathy, and heart failure remains the leading cause of death[2-4] .

Despite the good effects on iron toxicity of iron chelator, deferoxamine, long-term cardiac mortality has been very disappointing[3,5]. Inadequate compliance or genetic factors related to metal transporters are related with ongoing deaths from cardiac iron overloading but still not fully clear [6-8]. There is strong evidence that long-term deferoxamine chelation does not effectively prevent myocardial siderosis in majority of patients[9,10].Deferiprone, the first approved oral chelator, is an effective monotherapy at 100 mg/kg/day dose in treating mild to moderately severe myocardial iron loading (myocardial T2* 8–20 ms), significantly improving both myocardial iron and ejection fraction[11], and the combination of deferiprone at 75 mg/kg/day with deferoxamine is likewise effective[12]. Greater total iron clearance is seen with combined treatment[13-15] suggesting its usefulness for severe myocardial siderosis (T2* < 10 ms).

Although T2- MRI remains the gold standard for early diagnosis of cardiac hemochromatosis, still the echocardiography can be used as screening method[16]. Cardiac iron overload cardiomyopathy is considered as the most serious condition and is the leading cause of morbidity

and mortality (63.6%-71%)[17].The reported incidence of iron overload cardiomyopathy is from 11.4% to 15.1% in thalassemia major[17]. Iron deposition in myocardium mainly results in decreased left ventricular function[17]. Usually left sided heart failure is clinically more common than right sided heart failure but it has been shown that right ventricular dysfunction develops earlier in asymptomatic patients[17.]

As evident from above, cardiac dysfunction in multi transfused thalassemic children is a frequent occurrence. Currently, little information is available in literature on cardiac assessment of thalassemic children in India. In north-west part of Rajasthan, very few studies done on this aspect of thalassemia, hence present study is planned to assess the clinical and physiological status of heart by conventional echo-cardiography and Tissue Doppler Imaging (TDI).

Methods

This hospital based cross sectional study of 50 cases was conducted in Haldiram Moolchand Cardiac Center (HRMC), PBM HOSPITAL, S P Medical College, Bikaner Rajasthan over a period of 1 year during 2016-2017 . Patients of ß- thalassemia major above 2 years of age receiving regular blood transfusions at least for 1 year duration with exclusion of patients of ß-thalassemia with Congenital Heart Disease , Ex-thalassemic patients undergone bone marrow transplant ,thalassemia intermedia ,patients on cardio toxic drugs . All subjects' serum ferritin level was checked. All patients underwent transthoracic 2D echocardiography with doppler study for evaluation of ventricular dysfunction in transfusion dependant ß-thalassemia children and their correlation was seen Statistics

Required information from eligible patients were collected in a pre-structured pre-tested Proforma. For data analysis statistical software SPSS was used and data were analyzed with the help of frequencies, figures, proportions, measures of central tendency, appropriate statistical test.

Results

Maximum 27 cases were from age group 3-8 years, 14 in age group 9-12 years and 9 patients were in age group >12 years. Majority of patients were males 31(62%) while only 19(38%) were females. Table no 1 & 2 shows that 16(59.3%) out of 27 patient in serum ferritin Level (SFL) group <2500 ng/ml, had abnormal inter-ventricular septum in Diastole (IVSd) , in SFL group 2500-5000 ng/ml, 17(94.4%) out of 18 patients had abnormal IVSd while in SFL group >5000 ng/ml, all 5(100%) patients had abnormal IVSd (statistically significant as ferritin level increases; p value 0.001). In SFL group <2500 ng/ml, 6(22.2%) out of 27 patient had abnormal inter-ventricular septum in systole (IVSs), in SFL group 2500-5000 ng/ml, 11(61.1%) out of 18 patients had abnormal IVSs while in SFL group >5000 ng/ml, 3(60%) out of 5 patients had abnormal IVSs (statistically significant as ferritin level increases; p value 0.031). In SFL group <2500 ng/ml, 6(22.2%) out of 27 patients had abnormal Left ventricular posterior wall in diastole (LVPWd), in SFL group 2500-5000, 7(38.9%) out of 18 patients had abnormal LVPWd while in SFL group >5000, 4(80%) out of 5 patients had abnormal LVPWd (statistically significant as ferritin level increases; p value <0.001). In SFL group <2500, 6(22.2%) out of 27 patients had abnormal Left ventricular posterior wall in systole LVPWs, in SFL group 2500-5000, 7(38.9%) out of 18 patients had abnormal LVPWs while in SFL group >5000, 1(20%) out of 5 patients had abnormal LVPWs (statistically insignificant as ferritin level increases; p value 0.095). Mean values are well shown in the figure no 1.

Table no 3 and 4 shows that SFL group 2500-5000, who had abnormal values of E, A, E/A and IVRT, the percentage of patients were increased in comparison to below 2500 ng/ml SFL group. In SFL group <2500, 17(63.0%) patients had abnormal value of DT, in SFL group 2500-5000, 50%patients had abnormal value of DT while in SFL group >5000, all 5(100%) patients had abnormal value of DT. Mean values of E(Early peaking mitral velocity) (cm/sec) in SFL group <2500 was 105.61±14.57, in SFL group 2500-5000 was 116.86±20.53 and in SFL group >5000, it was 120.66±17.23 and the difference was found statistically insignificant (p>0.05).Mean values of A(Late peaking mitral velocity) (cm/sec) in SFL group <2500 was 62.06±11.08, in SFL group 2500-5000 was 66.23±13.12 and in SFL group >5000, it was 64.64±6.22 and the difference was found statistically insignificant (p>0.05).Mean values of E/A in SFL group <2500 was 1.74±0.31, in SFL group 2500-5000 was 1.80±0.31 and in SFL group >5000, it was 1.87±0.26 and the difference was found statistically insignificant (p>0.05).Mean values of DT (m)(Deaccerlation Time) in SFL group <2500 was 117.56±22.64, in SFL group 2500-5000 was 125.39±26.30 and in SFL group >5000, it was 119.60±22.26 and the difference was found statistically insignificant (p>0.05).Mean values of IVRT (ms)(Inter Ventricular Relaxation Time) in SFL group <2500 was 83.92±15.71, in SFL group 2500-5000 was 88.72±19.30 and in SFL group >5000, it was 99.40±9.15 and the difference was found statistically insignificant (p>0.05).

Table 5 & 6 shows that according to Tissue Doppler Velocities parameters, in SFL group <2500 to SFL group >5000, abnormal Em septal value was increased from 63% to 80%. In SFL group <2500 to SFL group >5000 abnormal Em lateral value was increased 37% to 80% & abnormal Am Septal was increased from 7.4% to 20% in SFL group <2500 to SFL group >5000. Abnormal Am Lateral, In SFL group <2500 to SFL group >5000, was increased from 33.33% to 40.00%. According to Sm Septal, In SFL group <2500 (n=27), 10(37%) patients had lower values than normal range while 7(25.9%) patient had higher values than normal range of Sm Septal. In SFL group 2500-5000 (n=18), 8(44.4%) patients had lower values than normal range while 2(11.1%) patient had higher values than normal range of Sm Septal. In SFL group >5000 (n=5), 2(40%) patient had lower values than normal range and 2(40%)

patient had higher values than normal range of Sm Septal. In SFL group <2500 to >5000 increase in value of abnormal Sm lateral was observed from 51.9% to 80%. Mean values are shown in figure 2. Mean values of Em septal(Early Peaking Mitral Velocity at Septum) in SFL group <2500 was 11.71±1.79, in SFL group 2500-5000 was 11.82±1.49 and in SFL group >5000, it was 11.65±1.67 and the difference was found statistically insignificant (p>0.05). Mean values of Em lateral(Early Peaking Mitral Velocity at Lateral) in SFL group <2500 was 16.10±2.77, in SFL group 2500-5000 was 15.99±2.79 and in SFL group >5000, it was 14.94±2.59 and the difference was found statistically insignificant (p>0.05). Mean values of Am septal(Late Peaking Septal Velocity at Septum) in SFL group <2500 was 6.87±1.60, in SFL group 2500-5000 was 6.31±0.76 and in SFL group >5000, it was 6.83±0.87 and the difference was found statistically insignificant (p>0.05). Mean values of Am lateral (Late Peaking Mitral Velocity at Lateral annulus)in SFL group <2500 was 6.63±1.51, in SFL group 2500-5000 was 6.34±1.38 and in SFL group >5000, it was 5.83±1.67 and the difference was found statistically insignificant (p>0.05).Mean values of Sm septal (Peak Systolic Velocity Septal)in SFL group <2500 was 7.67±0.96, in SFL group 2500-5000 was 7.51±0.87 and in SFL group >5000, it was 8.43±1.47 and the difference was found statistically insignificant (p>0.05).Mean values of Sm lateral (Peak Systolic Velocity Lateral)in SFL group <2500 was 8.68±1.67, in SFL group 2500-5000 was 8.32±1.47 and in SFL group >5000, it was 9.70±2.39 and the difference was found statistically insignificant (p>0.05). Table no & 7 and 8 shows that in SFL group <2500, 27(100%) patients had abnormal value of Et , in SFL group 2500-5000, 94.4% patients had abnormal value while in SFL group >5000 , all 5(100%) patients had abnormal value of Et value. In SFL group <2500, 96.3% patients had abnormal value of At, in SFL group 2500-5000, 94.4% patients had abnormal value while in SFL group >5000, all 5(100%) patients had abnormal value of At value. In SFL group <2500, 100% patients had abnormal value of St , in SFL group 2500-5000, 94.4%patients had abnormal value while in SFL group >5000, all 5(100%) patients had abnormal value of St value. Mean values of Et(Early Systolic Peak at tricuspid) in SFL group <2500 was 11.57±1.88, in SFL group 2500-5000 was 12.10±1.71 and in SFL group >5000, it was 10.06±2.21 and the difference was found statistically insignificant (p>0.05). Mean values of At (Late Systolic Peak at tricuspid) in SFL group <2500 was 6.35±1.33, in SFL group 2500-5000 was 6.41±1.15 and in SFL group >5000, it was 5.65±0.39 and the difference was found statistically insignificant (p>0.05). Mean values of St(Peak systolic Velocity at Tricuspid) in SFL group <2500 was 7.78±1.13, in SFL group 2500-5000 was 8.33±1.97 and in SFL group >5000, it was 8.01±1.21 and the difference was found statistically insignificant (p>0.05). All mean values of TDI at Tricuspid valve are shown in figure 3.

Table 1: Distribution of cases according to cardiac structure parameters in relation to serum ferritin level

Parameters	Percentile	Serum Ferritin Level (ng/ml)						Total	
		<2500		2500-5000		>5000			
		No.	%	No.	%	No.	%	No.	%
IVSd	>97	16	59.3	17	94.4	5	100.0	38	76.0
	3-97	11	40.7	1	5.6	0	0	12	24.0
IVSs	>97	6	22.2	11	61.1	3	60.0	20	40.0
	3-97	21	77.8	7	38.9	2	40.0	30	60.0
LVPWd	>97	6	22.2	7	38.9	4	80.0	17	34.0
	3-97	21	77.8	11	61.1	1	20.0	33	66.0
LVPWs	>97	6	22.2	7	38.9	1	20.0	14	28.0
	3-97	21	77.8	11	61.1	4	80.0	36	72.0

Table 2: Statistical analysis of cardiac structure parameters in relation to serum ferritin level

Parameters (cm)	Serum Ferritin Level (ng/ml)						F	p
	<2500		2500-5000		>5000			
	Mean	SD	Mean	SD	Mean	SD		
IVSd	0.76	0.13	0.84	0.08	0.99	0.16	8.901	0.001
IVSs	1.10	0.16	1.19	0.13	1.29	0.24	3.740	0.031
LVPWd	0.69	0.12	0.77	0.09	0.97	0.15	13.766	<0.001
LVPWs	1.09	0.23	1.21	0.14	1.20	0.15	2.478	0.095

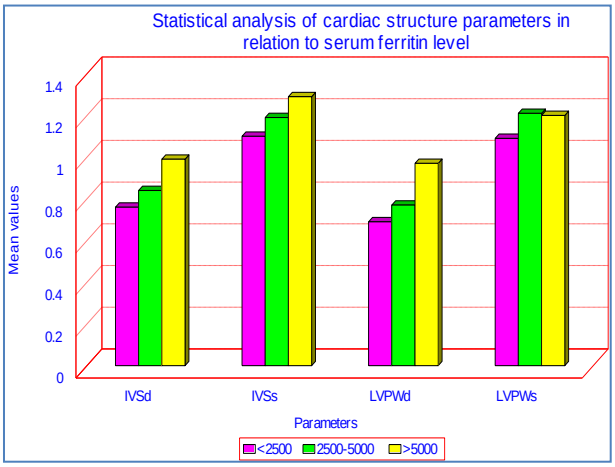

Figure 1:

Table 3: Distribution of cases according to left ventricular diastolic function variables in relation to serum ferritin level

Parameters	Grades	Serum Ferritin Level (ng/ml)						Total	
		<2500		2500-5000		>5000			
		No.	%	No.	%	No.	%	No.	%
E (cm/sec)	>1SD	9	33.3	10	55.6	4	80.0	23	46.0
	Normal	18	66.7	8	44.4	1	20.0	27	54.0
A (cm/sec)	>1SD	17	63.0	13	72.2	5	100.0	35	70.0
	Normal	10	37.0	5	27.8	0	-	15	30.0
E/A	<1SD	12	44.4	7	38.9	2	40.0	21	42.0
	Normal	15	55.6	11	61.1	3	60.0	29	58.0
DT (ms)	<1SD	17	63.0	9	50.0	5	100.0	31	62.0
	Normal	10	37.0	9	50.0	0	-	19	38.0
IVRT (ms)	>1SD	17	63.0	13	72.2	5	100.0	35	70.0
	Normal	10	37.0	5	27.8	0	-	15	30.0

Table 4: Statistical analysis of left ventricular diastolic function variables in relation to serum ferritin level

Parameters	Serum Ferritin Level (ng/ml)						f	p
	<2500		2500-5000		>5000			
	Mean	SD	Mean	SD	Mean	SD		
E (cm/sec)	105.61	14.57	116.86	20.53	120.66	17.23	3.163	0.051
A (cm/sec)	62.06	11.08	66.23	13.12	64.64	6.22	0.720	0.492
E/A	1.74	0.31	1.80	0.31	1.87	0.26	0.468	0.629
DT (ms)	117.56	22.64	125.39	26.30	119.60	22.26	0.580	0.564
IVRT (ms	83.92	15.71	88.72	19.30	99.40	9.15	1.932	0.156

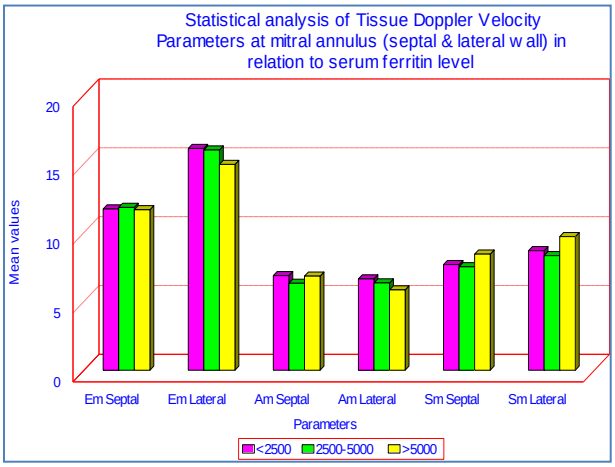

Figure 2:

Table 5: Distribution of cases according to tissue Doppler velocity parameters at mitral annulus (septal & lateral) in relation to serum ferritin level

Parameters	Grades	Serum Ferritin Level (ng/ml)						Total	
		<2500		2500-5000		>5000			
		No.	%	No.	%	No.	%	No.	%
Em Septal	<2SD	17	63.0	14	77.8	4	80.0	35	70.0
	Normal	10	37.0	4	22.2	1	20.0	15	30.0
Em Lateral	<2SD	10	37.0	11	61.1	4	80.0	25	50.0
	>2SD	1	3.7	1	5.6	0	0	2	4.0
	Normal	16	59.3	6	33.3	1	20.0	23	46.0
Am Septal	<2SD	2	7.4	2	11.1	1	20.0	5	10.0
	>2SD	14	51.9	6	33.3	3	60.0	23	46.0
	Normal	11	40.7	10	55.6	1	20.0	22	44.0
Am Lateral	<2SD	9	33.3	6	33.3	2	40.0	17	34.0
	>2SD	8	29.6	3	16.7	1	20.0	12	24.0
	Normal	10	37.0	9	50.0	2	40.0	21	42.0
Sm Septal	<2SD	10	37.0	8	44.4	2	40.0	20	40.0
	>2SD	7	25.9	2	11.1	2	40.0	11	22.0
	Normal	10	37.0	8	44.4	1	20.0	19	38.0
Sm Lateral	<2SD	14	51.9	12	66.7	4	80.0	30	60.0
	>2SD	5	18.5	0	0	0	0	5	10.0
	Normal	8	29.6	6	33.3	1	20.0	15	30.0

Table 6: Statistical analysis of Tissue Doppler Velocity Parameters at mitral annulus (septal & lateral wall) in relation to serum ferritin level

Parameters (cm/sec)	Serum Ferritin Level (ng/ml)						F	p
	<2500		2500-5000		>5000			
	Mean	SD	Mean	SD	Mean	SD		
Em Septal	11.71	1.79	11.82	1.49	11.65	1.67	0.028	0.973
Em Lateral	16.10	2.77	15.99	2.79	14.94	2.59	0.376	0.689
Am Septal	6.87	1.60	6.31	0.76	6.83	0.87	1.055	0.356
Am Lateral	6.63	1.51	6.34	1.38	5.83	1.67	0.681	0.511
Sm Septal	7.67	0.96	7.51	0.87	8.43	1.47	1.765	0.182
Sm Lateral	8.68	1.67	8.32	1.47	9.70	2.39	1.342	0.271

Table 7: Distribution of cases according to Tissue Doppler Velocity Parameters at tricuspid valve in relation to serum ferritin level

Parameters	Grades	Serum Ferritin Level (ng/ml)						Total	
		<2500		2500-5000		>5000			
		No.	%	No.	%	No.	%	No.	%
Et	<2SD	27	100	17	94.4	5	100.0	49	98.0
	Normal	0	0	1	5.6	0	0	1	2.0
At	<2SD	26	96.3	17	94.4	5	100.0	48	96.0
	Normal	1	3.7	1	5.6	0	0	2	4.0
St	<2SD	27	100.0	17	94.4	5	100.0	49	98.0
	Normal	0	0	1	5.6	0	0	1	2.0

Table 8: Statistical analysis of Tissue Doppler Velocity Parameters at tricuspid valve in relation to serum ferritin level

Parameters (cm/sec)	Serum Ferritin Level (ng/ml)						F	P
	<2500		2500-5000		>5000			
	Mean	SD	Mean	SD	Mean	SD		
Et	11.57	1.88	12.10	1.71	10.06	2.21	2.406	0.101
At	6.35	1.33	6.41	1.15	5.65	0.39	0.814	0.449
St	7.78	1.13	8.33	1.97	8.01	1.21	0.732	0.487

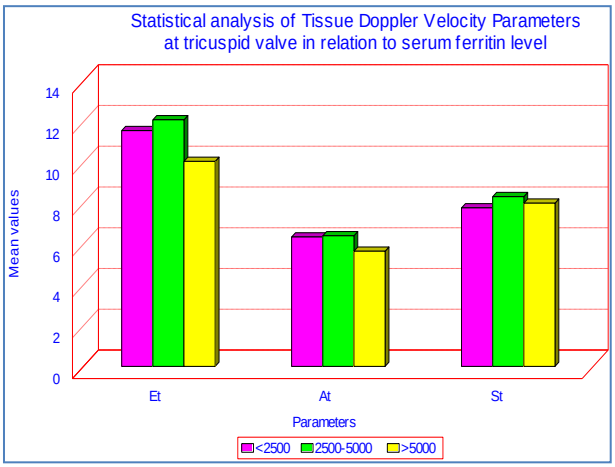

Figure 1

Discussion

The present study was undertaken to evaluate the cardiac functions of ß-thalassemia major patients, in the Department of Pediatric Medicine and HRMC , Sardar Patel Medical College, Bikaner. A total of 50 ß - thalassemia major children (between age 3 to 17 years) on regular blood transfusions were taken and assessed for their cardiac functions. All children were evaluated for cardiac functions using 2D- Echocardiography with Tissue Doppler Imaging (TDI) and a 12 lead ECG. Mean serum ferritin and mean annual hemoglobin level of preceding 1 year was calculated.

The following parameters were assessed viz. interventricular septal wall thickness, left ventricular posterior wall thickness both in systole and diastole (IVSs, IVSd, LVPWs and LVPWd), Peak Mitral early and late diastolic velocity (E and A), E wave deceleration time (DT), Isovolumetric relaxation time (IVRT), septal and lateral wall velocities in systole, early and late diastolic velocities at tricuspid and mitral valve were measured. All parameters were correlated with serum ferritin.

In the present study, interventricular septal wall thickness and left ventricul posterior wall thickness both in diastole and systole (IVSd, IVSs, LVPWd ar LVPWs) increases with increase in ferritin levels. In the studies of Taksande et al[18], Sayed et al[23], Hyder al[19] mean value compared between Thalassemia and normal above which was considered higher. In this study the above parameters were considered abnormal if their value were >97th centile for body surface area (BSA).

In this study, SFL group 2500-5000, who had abnormal level of E, A, EA and IVRT, the percentage of patients were increased in comparison to below 2500 ng/ml SFL group. In SFL group <2500, 17(63.0%) patients had abnormal value of DT, in SFL group 2500-5000, 50%

patients had abnormal value of DT while in SFL group >5000, all 5(100%) patients had abnormal value of DT. This left ventricle abnormal restrictive pattern in concordance Similarly Taksande et al[18], Silvilairat et al[24], Hyder et al[19], Sayed e al[23], Yaprak et al[21] noted increasing trend of E and A velocity isovolumic relaxation time (IVRT) but decreasing trend of DT and E/A ratio, which is suggestive of restrictive pattern of left ventricle.

In contrast, Favilli et al study on 25 ß thalassemia major patients in age group of 10 to 22 years did not reveal any correlation between transmitral flow patients and controls[22].

In our study, LV and RV tissue doppler indices were compared from other studies. In present study, septal Sm, Em & lateral Em, Sm, Am and RV Et, At, St were reduced early in majority of patients. Same findings were found by Magri et al[20]. Possible reason for early involvement of septum and RV are : 1. Early involvement of septum can be explained by larger iron deposition in septum than the free LV wall[25] 2. RV involvement earlier than LV can be multifactorial : i) Relatively small thickness of RV free wall can be involved by iron deposition earlier than LV free wall. It is also contributed by different geometry & difference at ultrastrutucal level in RV &LV[26] ii) Pulmonary iron overload also effect RV diastolic functions[27]

Conclusion

Tissue Doppler Imaging is superior to conventional echocardiography in giving an early evidence of diastolic myocardial dysfunction in non symtopmatic and normal LV function thalassemic patients. Hence, TDI can be applied as an integrated part of assessment of children & adolescents with ß-thalassemia. Our study showed early involvement of septum and RV in thalassemic patients.

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