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Research Article

Correlation of myocardial performance index and serum ferritin levels in children with beta thalassemia major

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ABSTRACT

Background: Cardiac complications are the major causes of mortality and morbidity in β Thalassemia major. Early recognition of cardiac iron overload by 2D and Doppler echocardiography which is economical guides early intervention and hence minimise morbidity and mortality. The objective of the study was assessment of myocardial performance index (MPI) and serum ferritin (SF) in children with β-Thalassemia and to establish relation of myocardial performance index in to serum ferritin level and age.
Methods: A Cross -sectional descriptive analytical study including 34 patients in the age group 3 years to 17 years with β-thalassemia on regular blood transfusion were included in the study. M-mode, 2D and Doppler echocardiography is used for analysis of isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT), ejection time (ET) and MPI. SF was measured by ELISA.
Results: Mean age was 9.21(+/-3.9) years. SF ranged from 365 to 18826µg/L. MPI varied from 0.35 to 0.62. Similarly IVRT varied from 35ms to 74 ms (60.26+/-12.36ms), IVCT from 36 to 75ms, ET from 108 to 280ms. MPI was 0.39±0.04 (Mean±SD) at SF≤1000 µg/L against 0.49±0.04 at SF of 1000 µg/L to 2499 µg/L. Rate of increase of MPI was maximum from SF 582 µg/L to 1962µg/L.
Conclusions: Mean MPI is abnormal at SF levels more than 1000 µg/L. Although MPI value is within the normal limit for the age at SF levels less than 1000 µg/L, MPI starts increasing with increasing SF from as low as 582 µg/L. Serial evaluation could give better information even if myocardial performance index falls within normal range for the age.

Keywords: Myocardial performance index, β Thalassemia major, Serum ferritin, Cardiac MRI

INTRODUCTION

A serum ferritin (SF) level greater than 1800 µg/L was associated with the increased concentration of cardiac iron, and that serum ferritin greater than 2500 µg/L was associated with the increased prevalence of cardiac events in β Thalassemia major patients.[1]

Several studies in the last decade demonstrated that serum ferritin is not suitable for its use as a predictive indicator of myocardial iron deposition due to its lack of relationship with cardiac iron.[2,3] CMR T2 imaging is recognized as the method of choice for evaluation of cardiac iron deposition in TM patients.[4] However, the limitation of this CMR is its rather expensive cost and availability in limited medical centres in developing countries like India.

Myocardial performance index (MPI) and isovolumic relaxation time (IVRT) have been observed to increase in β thalassemic children compared with normal control subjects. Measurement of MPI and IVRT have been reported to be simple and useful in early detection of left ventricular(LV) dysfunction in asymptomatic children in an early reversible stage of the disease when iron overload has not yet caused systolic dysfunction.[5] There are reports of many unexplained cardiac deaths in β Thalassemia major patients were found even though they had low serum ferritin levels emphasizing the unreliable use of serum ferritin as a predictor for iron overload cardiomyopathy in β Thalassemia major patients.[6] Hence, we undertook study to correlate serum ferritin and MPI, IVRT, isovolumic contraction time (IVCT) and ejection time (ET).

METHODS

34 consecutive children with β Thalassemia major admitted to Vanivilas Women and Children Hospital, Bangalore Medical College and Research Institute, Bengaluru were studied. Inclusion criteria were: children more than 3 years of age with regular blood transfusion. Exclusion criteria were: acute infections, inflammatory diseases, collagen diseases, hepatic diseases, malignancy which causes increase in serum ferritin levels .[7]

Clinical history included age at diagnosis, blood transfusions frequency and chelation therapy. Echocardiography was carried out by trained echo technicians who were blinded to study population. The echocardiographic examination was done using standard views and techniques according guidelines of the American Society of Echocardiography.[8] Echocardiographic examination images were taken in the left lateral decubitus position with an echocardiography machine (Philips Envisor Ultrasound Machain, with a 3.5/5 and 2.5/3.5 MHZ transducer with a 5 MHz transducer for children and 3.75 MHz for adolescents at/ after 48 hours of last transfusion. Doppler and M-mode views were recorded at 50 mm/s velocity. Pulsed Doppler method was used for blood flow measurements from cardiac valves (mitral, aortic, tricuspid and pulmonary): flow velocity during early filling (E), flow velocity during atrial contraction (A) and ET. For recordings of the mitral inflow velocity pattern, the sample volume 2 mm in size of the pulsed Doppler has been placed between the tips of the mitral leaflets in the apical four-chamber view. Accordingly, the left ventricular outflow velocity was recorded from the apical long-axis view with the sample volume of the pulsed doppler positioned just below the aortic annulus. M-mode, 2D and Doppler echocardiographic parameters were averaged over 3 cardiac cycles for all echocardiographic measurements. MPI was obtained from the apical five- chamber view.

ET was measured as the time from LVOT opening to the closing click of the aortic valve. IVRT was measured as the time from the end of aortic flow to the beginning of the mitral inflow. IVCT is measured from the end of mitral flow and beginning of aortic flow. The MPI is measured by the ratio of total isovolumic activity to the ET with formula: MPI = IVCT + IVRT / ET.

SF was measured by ELISA from patient's blood sample collected by venepuncture. Collection was done before transfusion with packed RBCs. About 3 ml of patient's blood sample was collected by a venepuncture and Ferritin levels were measured by ELISA. Statistical analysis: All data were coded and entered to computer by using statistical package for social sciences (SPSS) window version 20 (SPSS Inc., Chicago, IL, USA). Data was expressed in Mean +/- standard deviation unless specified. Echocardiographic indices were correlated between groups of SF ≤1000 µg/L and ≥1000 µg/L using Independent-samples T test. One way annova mean plot was for correlating IVRT, IVCT, ET and MPI in relation to serum ferritin concentration.

RESULTS

Thirty four children with β Thalassemia major patients were analysed for MPI. Mean age was 9.21 (+/-3.9) years with youngest and oldest being 3 and 17 years respectively. SF ranged from 365 to 18826µg/L (4704.6+/-5564.546µg/L). MPI varied from 0.35 to 0.62 with mean of 0.4812 (+/- 0.061). Similarly, IVRT varied from 35ms to 74 ms (60.26+/-12.36ms), IVCT from 36 to 75ms (59.85+/-11.64ms), ET from 108 to 280ms (248+/-31.185 ms) (Table 1). All Echocardiographic parameters paralleled with SF (Figure 1).

Seven children were observed in below 5 years of age. SF ranged from 365 to 1020 µg/L (mean 537.1+/232µg/L). Majority of less than 5 years (86%) had SF less than 1000µg/L. MPI in this age was 0.41+/-0.027 (range 0.39-0.47). IVCT, IVRT, ET values were observed to increase with SF concentrations. Highest MPI of 0.47ms was observed in 5 old children with SF of 1020µg/L. This particular child had low ET (180ms) compared to rest. Six children below 5 years had SF 360-614µg/L and MPI of 0.39 to 0.42. MPI correlated well with SF than the age. Ten children were observed in the age of 5 to 9 years with mean age of 7.8+/-1.135 years (range 6-9 years). MPI varied from 0.35 to 0.54 (0.46+/-0.06). Similarly, progressive increase in IVCT, IVRT was seen. Eight of 10 children (80%) between 5-9 years had SF above 1000µg/L. One six years old had 910 µg/L and other 8 years old -716µg/L. MPI in these children were respectively 0.35-0.46. However, a 7 year old child with SF 2828µg/L had MPI of 40. Rest of all in this age group showed direct correlation of MPI with age and SF rather than either alone. There were 17 patients aged more than 10 years with mean age of 12.35 +/-2.45years. SF ranged from 2100 to 18826 µg/L (8128+/-6187.62 µg/L). MPI was significantly elevated in all these children with minimum of 0.46 and maximum of 0.62 (0.52+/-0.039). MPI measurement correlated with SF and age.

Relation of MPI and SF

SF less than 1000µg/L: 9 children were observed in this sub group. SF values were varied from 365 to 910µg/L (582+/-218.76µg/L). In two of 9 (22.2%), MPI did not correlate with serum ferritin level. All but one had MPI less than 0.42 with highest of 0.46 in one case. All the children were less than 8 years at evaluation and seven were less than 5 years at evaluation (Table 2).

Table 1: Mean±SD of S. Ferritin and echocardiographic parameters.

	N	Range	Mean	Std. Deviation	N
	Statistic	Statistic	Statistic	Std. Error	Statistic
Age (years)	34	14	9.21	.682	3.97
S. ferritin	34	18461	4704.62	954.312	5564.54
IVRT	34	35	60.26	2.098	12.23
IVCT	34	36	59.85	1.997	11.64
ET	34	108	248.03	5.348	31.18
MPI	34	0.27	0.48	0.01	0.06

Table 2: Echocardiographic parameters (Mean±SD) at different Ferritin levels.

Serum ferritin	Less than 1000µg/L	1000µg/L- 2499 µg/L	2500µg/L-4999 µg/L	More than 10000 µg/L
S. ferritin	582.78+/-218.76	1962.13+/-297.10	3932.82+/-616.132	15950.67+/-2853.84
IVRT	43.33+/-7.78	64.63+/-4.14	65.64+/-7.50	70.33+/-3.07
IVCT	43.67+/-6.87	63.25+/-4.23	66.09+/-6.53	68.83+/-3.06
ET	220.56.17+/-31.4	260 .75+/-21.85	264.36+/-15.29	255.17+/-23
MPI	0.39/-0.04	0.49+/-0.04	0.50+/-0.05	0.55+/-0.05

Table 3: Independent-samples T test values of Echocardiographic parameters (Mean±SD) against ferritin levels of <1000 µg/L versus >1000 µg/L.

Group Statistics					
	S. ferritin	N	Mean	Std. Deviation	Std. Error Mean
IVRT	>= 1000	26	65.54	7.44	1.46
	< 1000	8	43.13	8.29	2.93
IVCT	>= 1000	26	64.88	7.21	1.41
	< 1000	8	43.50	7.33	2.60
ET	>= 1000	26	257.88	24.47	4.80
	< 1000	8	216.00	30.23	10.69
MPI	>= 1000	26	0.50	0.46	.91
	< 1000	8	0.40	0.03	0.01

SF between 1000 and 2500 µg/L: There were eight children with SF between 1000 to 2499 µg/L in the age of six to 12 years. SF varied from 1620 to 2500µg/L (1962+/-297.10). MPI was 0.49+/-0.03 with minimum of 0.42 .One with lowest valve of 0.42 was six years old female with SF of 1980 µg/L and did not correlate (12.5%) (Table 2).

SF between 2500 and 4999microgm/L: There were eleven children in this subgroup. Mean and standard deviation of ferritin was 3932.82+/-616.13µg/L.MPI was varied from 0.40 to 0.53 (0.49+/-0.04). One seven year old child with MPI of 0.4 had ferritin of 2828µg/ L in contrary to expectation (9%) (Table 2).

SF above 5000microgm/L: There were six children with SF above 5000 µg/L. Values varied from 10850 to 18826 µg/L with mean of 15940.67+/-2853.84 µg/L .All were between ten to seventeen years. MPI varied from 0.50 to 0.62 (0.55+/-0.05) (Table 2).

All had significantly increased MPI ,IVCT, IVRT and ET increased sharply from the level of serum ferritin of 582 µg/L till 1962 µg/L there after rate of increase was slower as depicted by one way annova mean plot (Figure 2-5). ET started decreasing after SF value 3932 µg/ (Figure 5).

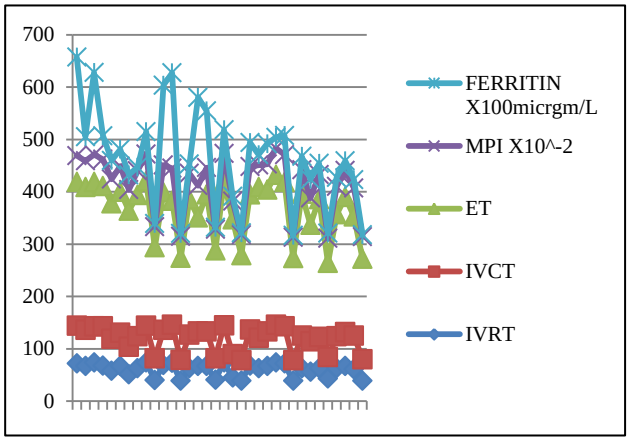

Figure 1: Line diagram representing trend of Echocardiographic parameters and S. ferritin values of all subjects.

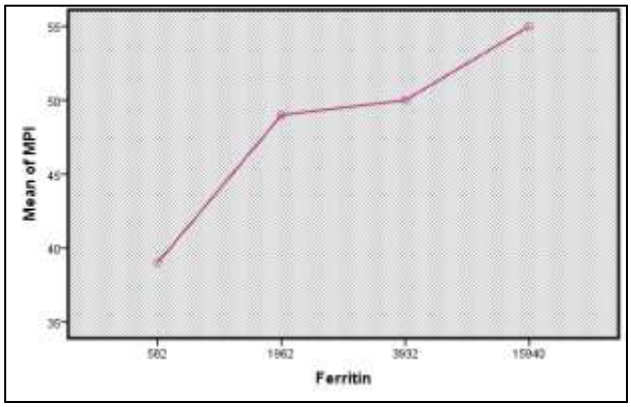

Figure 2: One way ANOVA mean plot of MPI and S. Ferritin.

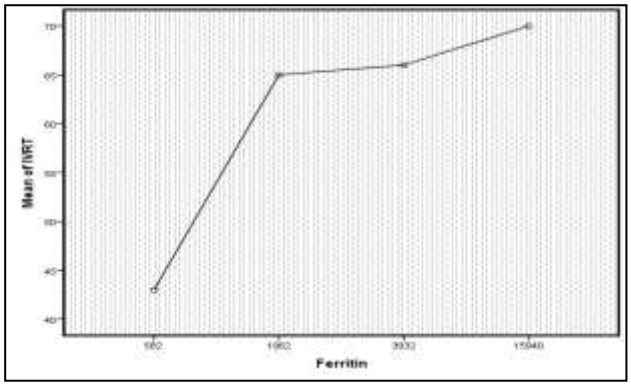

Figure 3: One way ANOVA mean plot of IVRT and S. ferritin.

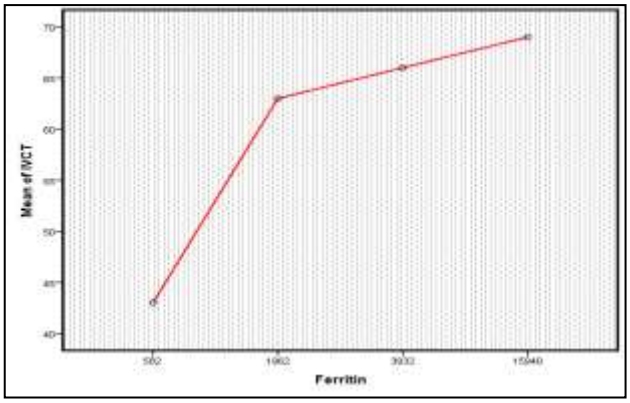

Figure 4: One way ANOVA mean plot of IVCT and S. ferritin.

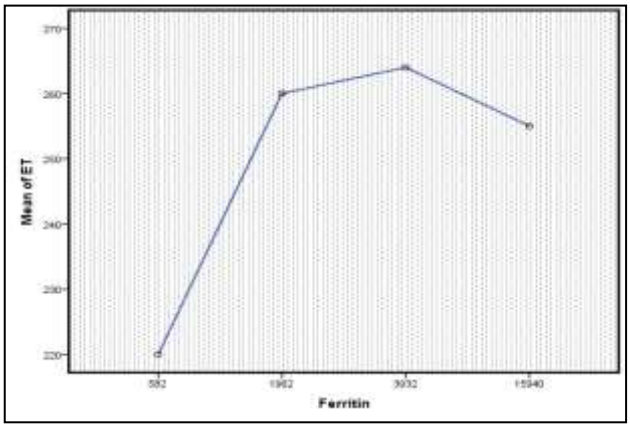

Figure 5: One way ANOVA mean plot of ET and S. ferritin.

Indices for SF less than 1000µg/l versus more than 1000 µg/L: IVRT was 43.13+/-8.2 ms, IVCT was 43.50+/-7.3ms, ET- 216+/-30ms, MPI 0.40+/-0.03 when the SF of less than 1000 µg/L, against 65.54+/- 7.436ms, 64.88+/-7.213ms, 0.50 +/- 0.04 respectively. For SF more than 1000 µg/L (Table 3). For the upper limit of MPI in pediatric age group (0.45), serum ferritin was 936.33+/-875 µg/L.

DISCUSSION

Iron overload cardiomyopathy is one of the most important features of cardiac complications of beta thalassemia major. L-type Ca^{2+} channels are the major transport pathway of iron entry in to cardiac myosites. Oxidative stress induced cellular damage is the main mechanism behind cardiac hemochromatosis. Myocardial performance index is calculated by calculated by dividing the sum of isovolumetric contraction and relaxation times by the left ventricular ejection time.[8-11] This indicates the combined systolic and diastolic function of the myo-cardium. The Tei index is considered abnormal if it was more than 0.46 (normal 0.38 ± 0.07 in children and 0.41 ± 0.05 in adults) in the left ventricle.[8,9]

IVRT is considered significant when if more than 65 ms in adults or 55 ms or more in children.[12] MPI is independent of heart rate, blood pressure and severity of mitral valve regurgitation and is simple, reproducible and reliable and correlates well with invasive measurements of systolic and diastolic function.[10,12,13] It has been shown that early recognition and intervention may alter outcomes.[14,15]

Diastolic left ventricular dysfunction develops early, but most patients die of systolic dysfunction. However, with regular chelation and anticongestive therapy, the systolic dysfunction was seen to improve.[10,13]

In current study, it is observed that IVRT, MPI started increasing from serum ferritin of as low as 582 µg/L as derived from mean PLOT in one way annova test. IVCT also changed with raising ferritin level but lagged IVRT prolongation suggesting diastolic dysfunction or relaxation abnormalities occur earlier than systolic dysfunction.

In a study by Asaad AA et al that included 421 β Thalassemia major patients against 100 controls, MPI was 0.42+/-0.06 in β Thalassemia major patients and 0.38+/-0.02 in control which was statistically significant with p value of 0.03. IVRT was 73.52+/-17.51 in thalassemic patients versus 42.90+/-15.38 with p = 0.04. MPI was more among β thalassemic patients and this difference proved to be of statistical significant. (P=0.03).[16]

Similarly, MPI has been reported to increase in β thalassemic patients compared with normal control subjects (0.42 +/-.06 vs. 0.34 +/- 0.04, P value=0.015).[5] IVRT was increased in patients vs. compared to controls (60+/-11 ms vs. 42+/-6 ms, P value=0.020). Measurement of MPI and IVRT were proved to be simple and useful in early detection of LV dysfunction, especially in asymptomatic young patients in an early reversible stage of the disease when iron overload has not yet caused systolic dysfunction.[5] IVRT appears to be the most accurate variable that is able to differentiate patients with early diastolic dysfunction from healthy subjects. Observations in current study are consistent with other studies.[5,17] This abnormal diastolic filling pattern could be explained by the existence of LV hypertrophy and therefore reduced LV compliance.[17]

Olson et al showed that iron is stored predominantly in the subepicardial layers, causing abnormal subepicardial motion observed in this study by measurement of IVRT, while LV systolic function remains unchanged, unlike a later stage of disease as the subendocardial layer is spared.[18]

Olivieri et al reported that the cardiovascular prognosis in patients with homozygous β Thalassemia major was excellent if serum ferritin was below 2500 ng/mL.[20] The MPI in current study showed increasing trend at SF as low as near 600 µg/L (582 µg/L) although absolute value fell with in normal range (Figure 2). This implies that MPI provides useful information regarding latent LV diastolic dysfunction provided serial MPI is evaluated. Inference that could be drawn is that chelation is to be considered even if serum ferritin concentration is less than 1000µg/L if evidence of abnormal MPI for the age or progressive change on serial measurement if MRI confirmation is not available for assessing cardiac Iron overload. In 9% to 22% of cases in our study, MPI did not correlate with serum ferritin. This disparity could go in lines with recent studies that showed ferritin level was not correlated well with cardiac iron.[20-22]

In current study rate of increase of MPI, IVCT, IVRT and ET was observed to be higher up to SF of 1962µg/L, thereafter the change was slower. This observation in current study is consistent with observation made by A. Shahmohammadi et al in which there was no significant change in MPI for SF levels between less than 2000 µg/L and more 2000 µg/L.[5]

Limitations

SF and MPI were not correlated with Cardiac T2 MRI which is gold standard investigation for cardiac iron overload. Controls were not used to calculate normal values for the age and sex, but derived from other studies. Study sample size is small and was conducted in a single centre.

CONCLUSION

Iron-overload cardiac disease in patients with β-thalassemia is often fatal and unfortunately is a common complication of β- thalassemia. Although Cardiac T2 MRI is the investigation of choice for evaluation of cardiac iron status, MPI gives valuable information provided it is done by trained personnel. Combined SF and MPI are better in assessing cardiac iron overload than either alone. Mean MPI is abnormal at SF levels more than 1000 µg/L. Serial MPI gives more valuable information even if the SF is less than 1000 µg/L in absence of availability of cardiac T2 MRI. CMR could use in case of disparity of serum ferritin and myocardial performance index in resource poor situations.

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