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Original Article

# Tissue doppler imaging in thalassemia major patients: correlation between systolic and diastolic function with serum ferritin level

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## Abstract

***Background*** Thalassemia is a major public health problem in Indonesia. Cardiac diseases remain as the main cause of death in these patients due to iron overload. Although the T2* magnetic resonance imaging has been considered as the gold standard for assessing cardiac iron overload but it has limited availability. The tissue doppler imaging (TDI) echocardiography, a fairly new and easy method that is suggested, can detect early abnormal myocardial iron overload.

***Objective*** To assess myocardial systolic and diastolic function of thalassemic patients using TDI and examine their correlation with serum ferritin level.

***Methods*** A cross-sectional study was conducted from January to March 2011 at the Harapan Kita Women and Children Hospital. We performed clinical examination, serum ferritin level, as well as conventional and tissue doppler echocardiography on all subjects.

***Results*** We included 34 regularly-tranfused patients, of which 17 were boys. The mean age of the subjects was 11.6 (SD 4.7 years, range 2.6 - 20 years). Mean pulse rate and blood pressure were within normal range. Hemoglobin level at inclusion ranged from 5.8 to 6 g/dL. Almost all patients did not receive regular chelation therapy. Median serum ferritin level was 6275 ng/mL (range 2151 – 17,646 ng/mL). Conventional echocardiography showed normal systolic function, but some diastolic dysfunctions were found including E wave abnormalites in 4 patients, A wave abnormalites in 3, and E/A ratio abnormalites found in 3. The TDI showed decreased systolic function (Sa wave abnormality) in 9 patients and diastolic dysfunctions (Ea wave abnormality in 11 patients and Aa wave abnormaly in 2). No abnormality was found in Ea/Aa and E/Ea ratios. There was a weak negative correlation between ferritin level and Sa wave and Ea wave respectively and a moderately negative correlation between ferritin level and Ea/Aa ratio. There was no correlation between serum ferritin and Aa wave or E/Ea ratio.

***Conclusion*** TDI identifies a greater number of patients with systolic and diastolic myocardial dysfunction than was revealed by conventional echocardiography. There was a weak negative correlation between serum ferritin to Sa wave and Ea wave, and a moderately negative correlation between ferritin and Ea/Aa ratio. There was no correlation between serum ferritin and Aa wave or E/Ea ratio. **[Paediatr Indones. 2012;52:187-93]**.

***Keywords:*** *tissue doppler imaging, echocardiography, systolic function, diastolic function, ferritin, beta-thalassemia major*

Beta thalassemias are group of hereditary blood disorders characterized by anomalies in the synthesis of the beta chains of hemoglobin resulting in various phenotypes

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ranging from severe anemia to clinically asymptomatic individuals.[1-3] In Indonesia, thalassemia is one of the most common single gene disorders and causes a major public health problem.[4] Regular transfusion therapy and iron chelation are reported to improve patients' quality of life, but their life expectancy is limited by congestive heart failure associated with iron overload.[5-9] Cardiac disease remains the main cause of death in patients with iron overload.[1,9]

Detection of early cardiac abnormality is difficult.[8,10,11] The diagnosis of myocardial iron overload is often delayed because cardiac iron deposition is unpredictable. Also, symptoms and echocardiographic abnormalities arise late in the course of the disease. Usually, patients have normal exercise capacity, with systolic dysfunction occurring in the final state of disease.[9,12]

Tissue doppler imaging (TDI) is a fairly new and an easy method to detect abnormal myocardial iron overload in pediatric and adult patients with β-thalassemia. TDI has 88% sensitivity and 65% specificity compared to the gold standard, MRI T2*.[10-13] The MRI is not widely available, time-consuming, and expensive, limiting its application in developing countries where thalassaemia is most common.[10] In clinical practice, serum ferritin has been used to assess treatment effectiveness and is commonly used to assess the severity of iron overload.[11,13] The aim of this study was to assess cardiac systolic and diastolic functions using TDI and examine their correlation to serum ferritin in thalassemia patients with iron overload.

## Methods

We conducted a cross-sectional study from January to March 2011 at the Harapan Kita Women and Children Hospital, Jakarta on children with beta thalassemia. Subjects with >10 unit RBC tranfusion and agreed to participate in this study were enrolled and patients with congenital heart disease was excluded.

All subjects underwent clinical examination, serum ferritin measurements, as well as conventional echocardiography and TDI according to the standardized methods.[14-17] Outcome assessed were cardiac dysfunction. On conventional echocardiography, we measured left ventricular systolic function reflected by fractional shortening (FS) and ejection fraction (EF) as well as left ventricular diastolic function (the E wave, A wave, E/A ratio). The E wave reflected rapid ventricular filling phase while the A wave was the atrial contraction. The TDI measures myocardial systolic function (Sa wave), early myocardial diastolic function (Ea wave), late myocardial distolic function (Aa wave), Ea/Aa ratio, and E/Ea wave. TDI results was defined as abnormal if the Sa wave was <63 cm/sec, Ea wave <13 cm/sec, Aa wave <3,8 cm/sec, Ea/Aa ratio < 2 and E/Ea ratio >10.

Sample size was calculated using the correlation coefficient formula using 5% level of significance.[18] Numerical data was described as mean and standard deviation or median (range) as appropriate. Pearson's correlation analysis and simple linear regression were performed to assess the association between echocardiography/TDI parameters and ferritin level. Data was analyzed using SPSS version 11.5.

## Results

We examined 34 regularly-transfused patients, of which 17 were boys. Baseline characteristics are shown in **Table 1.** Mean pulse rate and blood pressures were within normal limits.

Conventional echocardiography showed normal systolic function, but some diastolic dysfunctions were found including E wave abnormalites in 4 patients, A wave abnormalites in 3, and E/A ratio abnormalites found in 3. The TDI showed decreased systolic function (Sa wave abnormality) in 9 patients and diastolic dysfunctions (Ea wave abnormality in 11 patients and Aa wave abnormaly in 2), as are shown in **Table 2**.

**Table 3** shows the distribution of TDI results. Pearson's correlation test revealed a weak correlation between serum ferritin level and Sa wave (r=0.360, P=0.036,). There was also a moderate correlation between serum ferritin level and Ea (r=0.434, P=0.010). No correlation was observed between serum ferritin level and Aa wave (r=-0.255, P=0.146,), nor between serum ferritin level and E/Ea ratio (r=-0.174, P=0.349). There was a moderately positive correlation between serum ferritin level and Ea/Aa ratio ( r=0.556, P=0.001).

Linear regression analysis between serum ferritin level and Sa wave revealed an association (P= 0.036, r=0.36), with Sa increased 1 cm/sec for every ferritin

**Table 1**. Subjects' characteristics

| Characteristics | Boys (n=17) | Girls (n=17) |
|---|---|---|
| Age [years, median (range)] | 10.1 (2.8-18.1) | 13 (5.3-20) |
| Age at diagnosis [months, median (range)] | 4 (2-72) | 8 (3-54) |
| Age at first transfusion [months, median (range)] | 4 (2-72) | 8 (3-54) |
| Body weight [kg, median (range)] | 24 (14-45) | 34 (15-43) |
| Body height [cm, median (range)] | 138 (92-168) | 127 (100-152) |
| Body surface area [$m^2$, median (range)] | 0.85 (0.58-1.53) | 0.87 (0.68-1.35) |
| Hemoglobin level [g/dL, median (range)] | 5.9 (6-6.2) | 6,1 (5.8-6.1) |
| Heart rate [mean (SD)] | 103 (3) | 101 (2) |
| Systolic pressure [mmHg, mean (SD)] | 100 (7) | 105 (5) |
| Diastolic pressure [mmHg, mean (SD)] | 70 (7) | 65 (5) |
| Serum ferritin [ng/mL , median (range)] | 6275 (2151-11,000) | 9822 (2199-17,646) |
| Regular DFO administration, n | 0 | 0 |
| Irregular DFO administration, n | 17 | 17 |

DFO: desferoxamine

**Table 2**. Distribution of abnormalities based on echocardiography and TDI findings

| Echocardiography and TDI | | Normal | | Abnormal | |
|---|---|---|---|---|---|
| | | n | % | n | % |
| Left ventricle systolic function | FS | 34 | 100 | 0 | 0 |
| | EF | 34 | 100 | 0 | 0 |
| Left ventricle diastolic function | E | 30 | 88 | 4 | 12 |
| | A | 31 | 92 | 3 | 8 |
| | E/A ratio | 31 | 85 | 3 | 8 |
| Systolic myocardial function | Sa wave | 25 | 76 | 9 | 26 |
| Diastolic myocardial function | Ea wave | 23 | 68 | 11 | 32 |
| | Aa wave | 32 | 100 | 2 | 6 |
| | Ea/Aa ratio | 34 | 100 | 0 | 0 |
| | E/Ea ratio | 34 | 100 | 0 | 0 |

Notes: FS = fractional shortening; EF = ejection fraction

**Table 3.** Distribution of TDI results and serum ferritin levels

| TDI parameter | Ferritin levels (ng/mL) | | | | | Number of subjects | |
|---|---|---|---|---|---|---|---|
| | <2500 | 2501-5000 | 5001-7500 | 7501-10000 | >10000 | n | % |
| Sa wave | 1 | 4 | 1 | 3 | 0 | 9 | 26 |
| E wave | 1 | 5 | 2 | 3 | 0 | 11 | 32 |
| Aa wave | 0 | 1 | 1 | 0 | 0 | 2 | 6 |
| E/Ea ratio | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ea/Aa ratio | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

level increase of 420.48 cm/sec (Y=-18.12 + 420.48 X + e). An Sa wave of 13% was influenced by increasing serum ferritin level (**Figure 1**).

Linear regression analysis between serum ferritin level and Ea wave revealed a correlation (P= 0.010, r=0.434), Ea increased 1 cm/sec for every ferritin level increase of 429.965 ng/mL (Y=-47.98 + 429.97 X + e). An Ea wave of 13% was influenced by increasing serum ferritin level (**Figure 2**).

In addition, linear regression analysis between serum ferritin level and Ea/Aa wave revealed a correlation (P= 0.001, r=0.556), with Ea/Aa ratio increased 1 unit for every ferritin level increase of 13,517 ng/mL (Y= -25,090 + 13,517 X + e). A 30% decrease of Ea/Aa ratio was influenced by serum ferritin level (**Figure 3**).

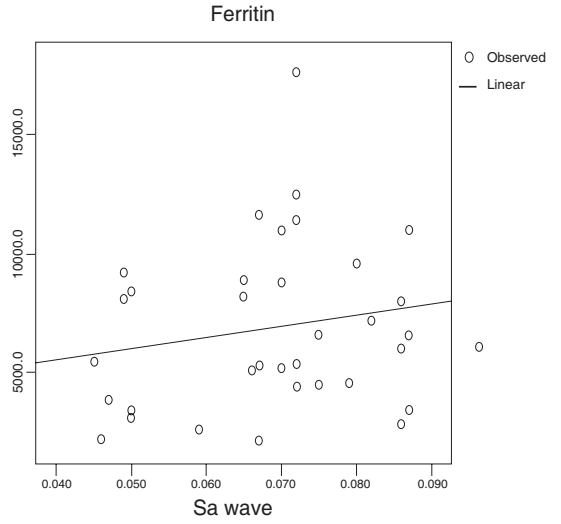


**Figure 1**. Correlation between serum ferritin and Sa wave

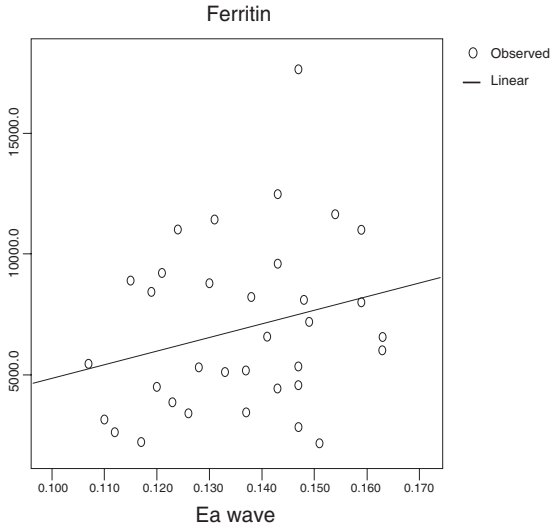


**Figure 2**. Correlation between serum ferritin and Ea wave

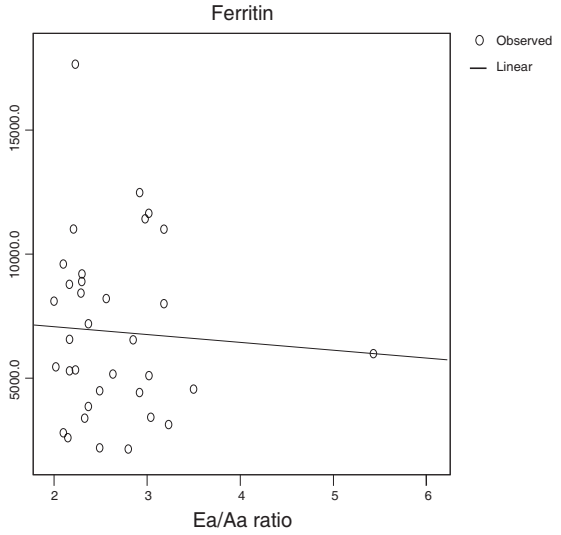


**Figure 3**. Correlation between serum ferritin and Ea/Aa ratio

## Discussion

There is no passive excretory mechanism of iron. In thalassemia patients, iron is easily accumulated by repeated blood transfusions. Free iron, non-transferrin-bound iron (NTBI), and labile plasma iron in the circulation, as well as the labile iron pools within cells, are responsible for iron toxicity. Labile unbound iron is able to redox cycle between $Fe^{2+}$ and $Fe^{3+}$, thereby generating reactive oxygen species (ROS), leading to lipid peroxidation and organelle damage. Ultimately this damage causes degeneration, fibrosis, cell death and dysfunction.[6,29-32] In hemochromatosis cases, microscopic examination revealed large amounts of iron in muscle cells and histiocytes. Focal degeneration and fibrosis were extensive. Myocardial fibers varied in size and in iron content. In some, as much as two-thirds of the cell appeared filled with iron. The hearts were dilated as well as hypertrophied, in some to more than twice the expected weight.[5]

Quantifying myocardial iron content is difficult.[29] The diagnosis of myocardial iron overload is often delayed because cardiac iron deposition is unpredictable. Symptoms and echocardiographic abnormalities arise late in the course of the disease.[12]

In clinical practice, serum ferritin has been commonly used to assess the severity of iron overload[11] and the effectiveness of treatment.[1,10] Serum ferritin does not correlate with myocardial iron load. Advantages of serum ferritin measurement are that it is easy to assess, inexpensive, amenable to serial measurements for monitoring chelation therapy, and correlates positively to morbidity and mortality.[12] However, serum ferritin measurements are not always reliable, since ferritin is an acute phase reactant and serum levels may be influenced by factors such as inflammatory disorders, liver disease and malignancy.

Echocardiography studies have shown

cardiovascular prognosis in β thalassemia patients to be excellent if serum ferritin is < 2500 ng/mL. Serum ferritin < 2500 ng/mL has been considered to be a safe level.[2,3,6]

A limitation in this study is that echocardiography and TDI were performed by only one person, possibly leading to a selective bias. However, this study should be viewed as preliminary study of TDI's correlation to the degree of iron overload in pediatric patients with β thalassemia.

In our study, subjects's characteristics were similar to those in other studies (**Table 1**).[19-21] Indonesian subjects' characteristics were common to those found in subjects from other developing countries. The few differences in characteristics may have been due to the number of subjects, age distribution, compliance to chelation therapy or serum ferritin level.[22-28]

In our study, conventional echocardiography showed no abnormalities in LV systolic function with normal fraction shortening (FS) and ejection fraction (EF). Kremastinos[33] found that β-thalassemia was not a pure iron storage disease and the pathophysiology of cardiac dysfunction was poorly understood and multifactorial in etiology. Systolic dysfunction was not correlated with serum ferritin and occured in a late stage of the disease.[7] Chronic iron myocardial deposition does not affect left ventricular relaxation. Engle et al. first reported in 1964 the co-existence of pericarditis and fatal arrhythmias with heart failure in β-thalassemia major patients. Pericarditis usually coincided to some degree with myocarditis, as both are inflammatory heart diseases, usually with an immunological background.[5] Patients with transfusion-dependent β-thalassemia are at risk of acquiring viral infections such as hepatitis B and C, as well as HIV.[34] The increased frequency of infections associated with β-thalassemia seems to be related to abnormalities of the immune system. Multiple transfusions represent a repetitive antigenic stimulus, together with iron chelation therapy itself.[33] Once systolic function of the left ventricle becomes impaired, survival is reduced, suggesting it to occur at a very late stage in the disease process.[29]

Diastolic LV dysfunction measurements included E wave > 0.70 m/sec in 4 subjects, A wave < 0.30 m/sec in 3 subjects and E/A ratio < 2 in 3 subjects (**Table 2**), findings which were similar to those of other studies.[22-24] Diastolic dysfunction preceeded systolic dysfunction. Early restrictive diastolic function occurred and correlated to severe serum ferritin level.[8,19,21 22-27]

TDI is a relatively new and an easy method with 88% sensitivity and 65% specificity compared to MRI T2* for earlier detection of abnormal myocardial iron overload.[10] TDI is superior and reproduceable in detecting myocardial dysfunction. Silvilairat *et al*. evaluated TDI in 31 patients with normal LVFS and found that diastolic myocardial dysfunction was absent in all patients with serum ferritin < 2500 ng/mL, but was present in all patients with serum ferritin > 5000 ng/mL.[11] We found that TDI revealed systolic myocardial dysfunction (Sa wave) in 26% of those subjects in which conventional echocardiography did not show any abnormalities. TDI also showed decreasing left ventricular myocardial diastolic function (Ea wave) in 32% of subjects and decreasing atrial contraction (Aa wave) in 6% of subjects. No abnormalities were found in Ea/Aa and E/Ea ratios of all subjects. There was a weak negative correlation between ferritin and Sa wave and Ea wave, but a moderately negative correlation between ferritin and Ea/Aa ratio (**Figures 1-3**). There was no correlation between serum ferritin and Aa wave or E/Ea ratio .

Using TDI, we observed that diastolic dysfunction was more pronounced than systolic dysfunction. Iron deposition in the heart may be patchy and not uniform. Iron is known to accumulate in the ventricular septum, as well as the free wall of the ventricles, with a tendency to be more concentrated in the epicardial layers.[27] Clinical and experimental studies have shown that iron is deposited within myocytes rather than within the interstitium. Wall motion abnormalities may represent an early sign of cardiac disease despite preserved global function. The regional abnormalities are related to iron overload and are easily detectable with TDI. The regional wall motion in patients with thalassaemia and iron overload is altered in the absence of global dysfunction. It is possible that at an early stage iron is predominantly deposited in the septum while at a later stage other areas become affected.[10,33]

Long-term prospective studies of echocardiographic assessment for systolic and diastolic ventricular function in larger numbers of pediatric patients with β-thalassemia is warranted. TDI should be a routine part of the echocardiographic assessment of pediatric patients with

β-thalassemia. In conclusion, TDI revealed a greater number of patients with systolic and diastolic myocardial dysfunction than was revealed by conventional echocardiography. There was a weak negative correlation between serum ferritin and Sa wave and Ea wave, and a moderately negative correlation between ferritin and Ea/Aa ratio. There was no correlation between serum ferritin to Aa wave or E/Ea ratio.

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