Correlation Between T2* Cardiovascular Magnetic Resonance with Left Ventricular Function and Mass in Adolescent and Adult Major Thalassemia Patients with Iron Overload

Mulyadi M. Djer¹, Shirley L. Anggriawan², Djajadiman Gatot¹, Pustika Amalia¹, Sudigdo Sastroasmoro¹, Patricia Widjaja³

¹ Department of Child Health, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
² Eka Hospital, Pekanbaru, Riau, Indonesia.
³ Department of Radiology, Premier Hospital, Jakarta, Indonesia.

Correspondence mail: Department of Child Health, Faculty of Medicine, Universitas Indonesia. Jl. Salemba 6, Jakarta 10430, Indonesia. email: muldjer@yahoo.com, muldjer@gmail.com.

ABSTRACT

Aim: to assess for a correlation between T2*CMR with LV function and mass in thalassemic patients with iron overload. Methods: a cross-sectional study on thalassemic patients was conducted between July and September 2010 at Cipto Mangunkusumo and Premier Hospitals, Jakarta, Indonesia. Clinical examinations, review of medical charts, electrocardiography, echocardiography, and T2*CMR were performed. Cardiac siderosis was measured by T2*CMR conduction time. Left ventricle diastolic and systolic functions, as well as LV mass index were measured using echocardiography. Correlations between T2*CMR and echocardiography findings, as well as serum ferritin were determined using Pearson’s and Spearman’s tests. Results: thirty patients aged 13-41 years were enrolled, of whom two-thirds had β-thalassemia major and one-third had HbE/β-thalassemia. Diastolic
dysfunction was identified in 8 patients, whereas systolic function was normal in all patients. Increased LV mass index was found in 3 patients. T2*CMR conduction times ranged from 8.98 to 55.04 ms and a value below 20 ms was demonstrated in 14 patients. There was a statistically significant moderate positive correlation of T2*CMR conduction time with E/A ratio ($r = 0.471, P = 0.009$), but no correlation was found with LV mass index ($r=0.097, P=0.608$). A moderate negative correlation was found between T2*CMR and serum ferritin ($r = -0.514, P = 0.004$), while a moderate negative correlation was found between serum ferritin and E/A ratio ($r = -0.425, P = 0.019$). Conclusion: T2*CMR myocardial conduction time has a moderate positive correlation with diastolic function, moderate negative correlation with serum ferritin, but not with LV mass index and systolic function.

Key words: T2* cardiovascular magnetic resonance, diastolic dysfunction, iron overload, thalassemia major.

INTRODUCTION
Thalassemia is the most common hemolytic anemia in Indonesia. In the Thalassemia Unit at Cipto Mangunkusumo Hospital, there were 1,493 patients registered between 1994 and 2009. Iron overload caused by anemia, hypoxia and defective erythropoiesis is a major complication of thalassemia. In the heart, even small amounts of unbound iron may generate harmful reactive oxygen metabolites and toxicity. Iron deposition is reported to be greatest in the ventricular walls, with less deposition in the atria and conduction system. In patients with significant cardiac dysfunction, iron deposits occupy large areas of the myocardial fibers. The subsequent development of iron overload may result in heart failure. Cardiac siderosis manifests itself as cardiomyopathy, which causes death in 50-70% of thalassemia major patients. The cardiomyopathy may be reversible if iron chelation treatment is intensified in a timely manner, but the diagnosis is often delayed by the unpredictability of cardiac iron deposition, the late development of symptoms or echocardiographic abnormalities. Therefore, early identification of myocardial siderosis and improved treatment for heart complications are needed.

Cardiac iron clearance with chelation therapy is slower than by hepatic clearance, hence, measuring myocardial iron using MRI rather than hepatic iron index is more accurate in patient monitoring. Myocardial siderosis can be detected by T2*CMR, a non-invasive technique and has been suggested to be the gold standard examination to measure myocardial iron deposition. Significant iron overload in the heart is defined as a T2*CMR of <20 ms, in which a progressive and significant decline in LV ejection fraction and an increase in the LV end-systolic volume index and LV mass index are found. Furthermore, a T2*CMR <10 ms has been suggested to be associated with severe siderosis, indicating a need for iron chelation. The purpose of this study was to assess for a possible correlation between T2*CMR with LV function and mass in patients with thalassemia major and iron overload.

METHODS
An analytic cross-sectional study on thalassemic patients was conducted between July and September 2010 at Cipto Mangunkusumo and Premier Hospitals, Jakarta, Indonesia. All thalassemia major (TM) patients who were referred for cardiac examination to the Cardiology Clinic, Department of Child Health at Cipto Mangunkusumo Hospital were initially screened for recruitment. Screening included clinical examination and medical chart review, focusing on cardiovascular symptoms, transfusion index, chelation history, hemoglobin level, and ferritin level in the 1 year prior to the visit. Hemodynamic data, including heart rate and blood pressure were recorded. The sample size was estimated using a formula for single group correlation test. Based on this formula, the minimal subjects required were 30 patients. Subjects fulfilled the following inclusion criteria: had been receiving transfusions for at least 13 years, had hemoglobin level of more than 7 g/dL at the time of the examination, and received deferasirox with or without deferoxamine. Informed consent was obtained from all subjects.
and this study was approved by the Ethics Committee at Cipto Mangunkusumo Hospital, University of Indonesia.

Cardiac examinations included electrocardiography, echocardiography, and T2*CMR [Siemens® magnetom avanto 1.5 T, total imaging matrix (TIM) 76 x 18] at Premier Hospital, Jatinegara, Jakarta. For T2*CMR, we examined the region of the ventricular septum, encompassing all layers of myocardium from the right ventricle through the left ventricle endocardium. We excluded cardiac veins and lungs from the image to avoid causing artifacts. A single breath-hold technique (15 seconds) was required to acquire all images at lengthening echo times.

Data was analysed using CMR tools, a software package that provides integrated analysis and effective visualisation of CMR images. T2* conduction time between 10-20 ms was considered to be indicative of mild-to-moderate myocardial siderosis, while a value below 10 ms was considered to be indicative of severe myocardial siderosis.

Two-dimensional, Doppler (pulse wave, continuous wave and color), and M-mode echocardiography (Phillips® agilent sonos 4500) were performed at resting condition by one of the investigators (SLA). LV diastolic function was assessed by pulsed-Doppler recording of mitral inflow. Standard diastolic Doppler indexes were recorded, including early transmitial diastolic peak flow velocity (E) and late transmitial peak flow velocity (A), E-wave, deceleration time (DT), and LV isovolumic relaxation time (IVRT). In addition, duration of pulmonary vein reverse flow during atrial contraction (PVA), systolic wave S (PVS2), early diastolic wave D (PVD), S/D ratio, A wave (late diastolic reversal during atrial systolic) and duration of A wave were obtained from the pulsed-Doppler tracing of the right upper paraseptal pulmonary vein. The diagnostic criteria used for diastolic dysfunction were as follows: impaired relaxation was defined if it fulfilled one criteria or more: DT <240 ms, IVRT <90 ms, E/A >1.5, MVA < PVA, and PVS2 < PVD; pseudonormal was defined if it fulfilled one criteria or more: DT 160-240 ms, IVRT <90 ms, E/A 1–1.5, MVA < PVA, and PVS2 < PVD; and restrictive filling was defined if it fulfilled one criteria or more: DT <160 ms, IVRT <70 ms, E/A >1.5, MVA < PVA, and PVS2 < PVD.10

LV systolic function assessment included fractional shortening (FS), ejection fraction (EF), stroke volume, and cardiac index. Systolic dysfunction was defined as an FS of less than 28% and EF of less than 56%. Cardiac output and LV mass were indexed to body surface area. For patients aged 6-23 years, LV hypertrophy is defined as LV mass greater than 103 g/m2 in males or greater than 84.2 g/m2 in females. In adults, LV hypertrophy is defined as LV mass greater than 134 g/m2 in men or greater than 110 g/m2 in women.11,12

Data Analysis

Data are described as mean, median, or proportion, as appropriate. Pearson’s and Spearman’s tests were used to assess for correlations between echocardiography variables and T2*CMR. P values of less than 0.05 were considered to be statistically significant. All statistical analyses were performed with SPSS version 11.5.

RESULTS

We enrolled 30 patients (15 males and 15 females) into this study, with ages ranging from 13-41 years. Two-third of patients had β-thalassemia major and one-third had HbE/β-thalassemia. The median of stroke volume was 70.9 (42.5-127) mL and the median of cardiac output was 6 (3.7-11.2) L/minute. Subjects’ baseline characteristics are described in Table 1. Patients with T2*CMR of less than 20 ms had higher pulse rates and serum ferritin levels compared to those with T2*CMR of 20 ms or more. LV hypertrophy was identified in 4 patients and premature ventricular contraction (PVC) was noted in 1 patient.

Table 2 shows the echocardiographic findings in our subjects. Only 2 patients had mild tricuspid valve regurgitation with pressure gradients of 10-20 mmHg. One patient had mild diastolic dysfunction (impaired relaxation) and 7 patients had moderate diastolic dysfunction (pseudonormal). All patients had systolic function within normal range while increased LV mass index was noted in 3 patients.
significant moderately positive correlation between E/A ratio and T2*CMR (r = 0.471, P = 0.009). However, no significant correlation was observed between T2*CMR and LV mass index.

When looking at the correlation between T2*CMR and mean serum ferritin in the last 12 months prior to scan (Figure 2), we observed that the lower the T2*CMR, the higher the serum ferritin level (r = -0.514, P = 0.004). Accordingly, a negative moderate correlation was also found between serum ferritin and E/A ratio (r = -0.425, P = 0.019) (Figure 3).

**DISCUSSION**

In this study, we found that T2*CMR was moderately positive correlated with E/A ratio, in

<table>
<thead>
<tr>
<th>Variable</th>
<th>T2*CMR &lt;20 ms, n =14</th>
<th>T2*CMR ≥20 ms, n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>26 (16-30)</td>
<td>23.7 (13-41)</td>
</tr>
<tr>
<td>Mean heart rate (SD), x/minute</td>
<td>93.6 (9)</td>
<td>83.7 (7.1)</td>
</tr>
<tr>
<td>Median systolic BP (range), mmHg</td>
<td>110 (90-130)</td>
<td>110 (90-120)</td>
</tr>
<tr>
<td>Median diastolic BP (range), mmHg</td>
<td>70 (60-80)</td>
<td>65 (50-90)</td>
</tr>
<tr>
<td>Mean transfusion index (SD), mL/kg/year</td>
<td>176.1 (47.7)</td>
<td>149 (68)</td>
</tr>
<tr>
<td>Median duration of transfusion (range), year</td>
<td>23 (15 - 28)</td>
<td>18 (13 - 33)</td>
</tr>
<tr>
<td>Mean serum ferritin during 12 months prior to scan (SD), ng/mL</td>
<td>9,019.3 (3,889.4)</td>
<td>4,118.4 (2,373.6)</td>
</tr>
</tbody>
</table>

T2*CMR values ranged from 8.98 to 55.04 ms, with a mean time of 24.26 (SD 11.24) ms. Thirteen patients had moderate cardiac siderosis and only 1 patient had severe siderosis T2*CMR (<10 ms). Figure 1 shows a statistically

![Figure 1. Correlation between T2*CMR and E/A](image1)

![Figure 2. Correlation between T2*CMR and mean serum ferritin within 12 months prior to scan](image2)
which the lower the T2*CMR, the lower the E/A ratio, indicating diastolic dysfunction (impaired relaxation). However, no statistically significant correlation was found between T2*CMR and LV systolic function or LV mass index. We also found that T2*CMR had a moderately negative correlation with serum ferritin level.

One of the limitations of this study was that we had few numbers of patients with very low T2*CMR (<10 ms), so evaluation of the correlation between very severe hemosiderosis and diastolic function was not possible to be done. Moreover, with correlation, we could not assess the cause-effect relationship between T2*CMR and echocardiography findings. Because each of T2*CMR and echocardiography examination was done by a single independent examiner, so between-examiner potential bias can be excluded.

Serum ferritin is the most commonly used to indirect estimate of body iron stores. However, this measurement reflects only 1% of the total iron storage pool. The mean serum ferritin in this study was 6563.9 (SD 4488.4) ng/ml, similar to values from previous studies performed in the same centre, 7,301.9 (SD 3,788.2) and 5,590 (SD 4,614.7) ng/mL. These serum ferritin levels were higher compared to the recommendations by the Thalassemia International Federation Guidelines (approximately 1,000 ng/L) or another study, indicating poor compliance and limited availability of chelation drugs.

Chronic anemia usually increases the cardiac output when hemoglobin level is 7 g/dL or less. Increased cardiac output principally reflects a larger cardiac stroke volume. In our study, cardiac output and stroke volume, were within normal limits since we only included patients with hemoglobin above 7 g/dL.

A previous study on thalassemic patients reported that 21 of 30 patients had diastolic dysfunction. In contrast, we found only 8 of 30 patients with diastolic dysfunction, in which one had mild diastolic dysfunction (impaired relaxation) and 7 had moderate diastolic dysfunction (pseudonormal). These differences may have been due to the administration of combined chelation treatment (desferrioxamine and deferiprone) in our patients. Oral deferiprone has been suggested to be more effective than desferrioxamine for removing myocardial iron, as it is able to penetrate cells, including myocardial cells, and remove iron directly.

In our study, the mean E/A ratio, as one of the parameters to determine diastolic dysfunction, was 1.6 (SD 0.3), slightly above normal limits. However, other studies reported either lower E/A ratio, indicating impaired relaxation, or higher, suggesting restrictive diastolic dysfunction. However, as mentioned above, other parameters are required to diagnose the presence of diastolic dysfunction. A significant correlation between T2*CMR and E/A ratio in our study indicates that this echocardiographic parameter may be used as a means of early detection of significant cardiac siderosis, especially in centres lacking of T2* CMR facilities. Early detection of cardiac siderosis is useful to determine the best treatment for reducing iron overload.

Once systolic function of the LV becomes impaired, survival is typically reduced. It has been suggested that systolic dysfunction occurs at a very late stage in the disease process, whereas diastolic abnormalities may occur earlier. All of our patients had left ventricular fractional shortening (LVFS) and left ventricular ejection fraction (LVEF) within the normal ranges, similar to results of previous studies.

Increased ventricular mass index, reflecting myocardial structural changes, has been attributed to iron overload. However, in our study, the LV mass index was lower compared

![Figure 3. The correlation between serum ferritin and E/A ratio](image-url)
to that of a similar previous study, probably due to the combined chelation therapy administered to our patients.

In terms of T2*CMR, the mean value found in our study was relatively lower than that of a previous report [24.3 (SD 11.24) versus 26.1 (SD 4.6) ms, respectively], although the prevalences of significant myocardial siderosis were similar. However the difference was not clinically important. The age distribution of severe cardiac siderosis also differs among studies. A previous study found severe siderosis in patients below 15 years of age, whereas others, including ours, found it to be present in patients of older ages. This difference may reflect different patient characteristics, including biological and social factors, as well as different treatment approaches offered by various centers.

When looking at cardiac systolic function, we did not find a significant correlation between T2*CMR and LV systolic function. However, a previous study reported a progressive decline in patients with a myocardial T2*CMR of less than 20 ms (r = 0.61, P <0.0001), with an increase in LV end-systolic volume index (r = 0.50, P<0.0001) and LV mass index (r = 0.40, P<0.001). This difference may be due to our small number of subjects with T2*CMR of less than 20 ms so that we did not find a statistical significant result. In addition, previous studies showed a weak negative correlation between T2*CMR and serum ferritin, while we found a statistically significant moderate negative correlation.

CONCLUSION

T2*CMR has a moderate positive correlation with echocardiography diastolic function parameters (E/A ratio), moderately negative correlation with serum ferritin. However, it had no significant correlation with systolic function and LV mass index.

ACKNOWLEDGMENTS

This study was funded by Grant Riset Awal Universitas Indonesia 2010. A part of the data has been previously published in Journal of US-China Medical Science.