Diagnostic Accuracy of Electrocardiographic Criteria for Left Ventricular Hypertrophy in Thalassemia Syndrome

Sudigdo Sastroamoro, Deddy Ria Saputra, Bambang Madyono, Iset N Cesman, Sukman Tulus Putra

(Department of Child Health, Medical School, University of Indonesia, Jakarta)

ABSTRACT We compared the diagnostic accuracy of electrocardiographic (ECG) criteria for left ventricular hypertrophy (LVH) in 119 randomly selected from 400 patients with thalassemia major treated at the Department of Child Health, Medical School, University of Indonesia, Jakarta. Echocardiographically derived left ventricular hypertrophy (ECHO-LVH), both for body surface area (BSA)-indexed and height-indexed, served as the gold standard. There were 57 girls and 62 boys available, ranging in age from 5 to 27 years. ECG criteria for LVH was detected in 23 out of 119 patients, while echo-LVH was detected in 47 patients if BSA-indexed LVH was used, or 22 patients if height-indexed LVH was used. The sensitivity and specificity of ECG-LVH were 25.5% and 84.7% respectively if BSA-indexed LVH was used as gold standard, or 36.4% and 84.5%, respectively, when height-indexed echo-LVH was used. It is concluded that ECG criteria for LVH has a low sensitivity and high specificity in detecting increased left ventricular mass in children with thalassemia major. [Pediatr Indones 1995; 35:132-140]

Introduction

Thalassemia is the most frequently found intracorpuscular hemolytic anemia in Indonesia. In the Department of Child Health, Medical School, University of Indonesia, Jakarta, not less than 20 new patients with thalassemia major are diagnosed yearly. This inherited disease results from incompletely developed beta hemoglobin, resulting in continuing hemolysis. To maintain metabolism and normal growth, patients with thalassemia major need repeated blood transfusion to keep the hemoglobin level of 10 g/dl or more. This leads to the accumulation of iron in the organs (hemoside-
rosis), which may affect the organ func-
tion (hemochromatosis). Iron deposits in thalassemic patients can occur in the myocardium which might lead to myocardial thickening, conduction disturbances, dysrhythmias, pericarditis, or cardiac failure. Radi-
ological examination is not considered as a reliable tool to detect cardiac involvement in thalassemic patients, while the role of electrocardiography (ECG) is un-
clear. There has been no study evaluat-
ing the accuracy of ECG criteria for left ventricular hypertrophy (LVH) in patients with thalassemia major. ECG has a low sensitivity and specificity to determine LVH in adult patients with coronary heart disease, but it has a fair sensitivity and specificity in pediatric patients with rheumatic heart disease. This study aims to determine the sensitivity, speci-
ficity, predictive values, and likelihood ratios of ECG in detecting LVH in pa-
tients with thalassemia using echocardi-
graphy as the gold standard.

Methods
This diagnostic study was conducted at the Department of Child Health, Medical School, University of Indonesia - Cipto Mangunkusumo Hospital, Jakarta, from August 1991 through September 1993. Study subjects were recruited from thalassemic patients attending the Depart-
ment of Child Health. There were overall 400 patients with thalassemia major available.

We included patients of both sexes, those aged 5 years or more, and who had been diagnosed as having thalassemia by means of history, physical find-
ings, and hemoglobin analysis. Excluded were patients who had cardiac disease caused by other than thalassemia, and who refused to participate in the study.

Subjects were selected by random sampling. The sample size was calculated according to the formula for proportion. One hundred and fifteen patients were considered sufficient.

In all patients the following variables were determined: age, sex, body height and weight. Body surface area was calcu-
lated by using standard formula. ECG tracing was obtained by using "Manual Cardiosuny 501 D electrocardiography" by an experienced nurse, with the patients in a supine position. Standard 6 extremity and chest leads were taken from each patient; in addition a V3R or V5R was obtained. Standard M-mode electrocardiography was per-
formed using Toshiba Sonolayer SSH 65 A with 3.75 or 2.5 MHz transducer. Pa-
tients were examined in a left lateral decubitus position. The speed of M-mode tracing was set at 25 to 50 mm per sec-
ond. At least 3 prints were made. Left ventricular mass was calculated according to Devereux's formula:

\[
\text{LV mass} = 0.8 \times 1.04 \times (\text{LVDD} + \text{IVSD} + \text{LVPWD}) - 0.6 \times \text{LVDD}^3
\]

where \(\text{LV mass}\) = left ventricular mass; \(\text{LVDD}\) = left ventricular internal dimension at end-diastole; \(\text{LVPWD}\) = left ventricular posterior wall at end-diastole; \(\text{IVSD}\) = interventricular septal thickness at end-diastole.

All M-mode measurements were made according to leading edge to leading edge...
The echocardiograms were reviewed by one of the authors (SS) who was unaware of the result of clinical and electrocardiographic results of the patient. Each value was obtained by averaging 3 recordings.

The nutritional status of patients aged 5 years was determined using weight for age standard (NCHS). For those aged 6-17 years was determined by Jamadi's anthropometric standard, and for those aged 18 years or more was determined by using "Society of Actuaries" 1959. The classification of nutritional status followed the Workshop on Nutrition Department of Health (1975) and Center for Research and Development of Nutrition (1978).

Electrocardiographically determined left ventricular hypertrophy (ECG-LVH)

Diagnosis of ECG-LVH was established when one or more criteria of Liebman and Ziegler was fulfilled. The criteria were: (a) R wave in V6 >21 mm (b) S wave in V1 > 25 mm, (c) R/S ratio in V5 or V6 < 0.1; (d) q wave in V5, or V6 > 3 mm.

Echocardiographically determined left ventricular hypertrophy (Ech-LVH)

The diagnosis of Ech-LVH was established by echocardiography when the left ventricular mass, indexed for body height and body surface area, respectively, was more than 99.8 gram/m² or 103 gram/m² in boys, or more than 81.6 gram/m² or 84.2 gram/m² in girls.

Statistical analysis

The results of ECG-LVH were compared to Ech-LVH which served as the gold standard. The following values were calculated: sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios. For each value, 95% confidence intervals (95%CI) were calculated using standard formulas.

Chi-squared test for trend was used to compare changes in left ventricular hypertrophy with increasing age. All statistical tests were considered significant when the p value was < 0.05. The statistical analyses were done manually with the help of True-Epistat statistical program.

Results

From August 1991 through September 1993, there were 127 patients fulfilling study criteria. Eight patients were excluded from the study due to incomplete data. Therefore, 119 patients were available for analysis.

Age and sex distribution

There were 119 patients aged 5-27 years studied, consisted of 57 females and 62 males. The sex and age group distribution is depicted in Table 1.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Girls</th>
<th>Boys</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-</td>
<td>19</td>
<td>25</td>
<td>44</td>
</tr>
<tr>
<td>10-</td>
<td>24</td>
<td>28</td>
<td>52</td>
</tr>
<tr>
<td>&gt;15</td>
<td>14</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>62</td>
<td>119</td>
</tr>
</tbody>
</table>

Table 1. Age and sex distribution of study subjects

Nutritional status

The nutritional status of the 119 patients is depicted in Table 2. It appears that three-fifths of all patients were well-nourished, while one-third were under-nourished. Only few patients were overweight or malnourished.

<table>
<thead>
<tr>
<th>Nutritional status</th>
<th>No</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight</td>
<td>2</td>
<td>1.7%</td>
</tr>
<tr>
<td>Well-nourished</td>
<td>71</td>
<td>60.0%</td>
</tr>
<tr>
<td>Severely undernourished</td>
<td>36</td>
<td>30.3%</td>
</tr>
<tr>
<td>Severely malnourished</td>
<td>6</td>
<td>5.0%</td>
</tr>
<tr>
<td>Total</td>
<td>119</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Table 2. The distribution of nutritional status of 119 patients with thalassemia major

Electrocardiography

LVH was diagnosed by ECG in 23 patients, consisted of 8 girls and 15 boys. When stratified according to age group, it appears that in the age group of 5-10 years there were 11.4% patients with LVH, while in the age group of 10-15 years and more than 15 years the percentages were 17.3% and 39.1%, respectively. The trend was that the older the age group, the higher was the percentage of ECG-LVH. Statistical analysis showed that this trend was more clearly seen in boys than in girls. See Table 3.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Girls</th>
<th>Boys</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>10-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>62</td>
<td>119</td>
</tr>
</tbody>
</table>

Table 3. Proportion of ECG-LVH according to age and sex

was 3.8 (SD 0.60) cm, the mean left ventricular posterior wall thickness at end-diastole was 0.74 (SD 0.2) cm, and the mean interventricular septum thickness at end-diastole was 0.80 (SD 0.26) cm. In 22 (18%) patients the left ventricular internal dimension was the same as, or more than, that of 95% normal value for age. In thirty-seven (31%) patients the left ventricular posterior wall thickness was the same as, or more than, 95% percentile of normal value for age.

Body surface area (BSA)-indexed LVH was found in 47 patients, comprising 26 females and 21 males. In the age group of 5-10 years, LVH was found in 29.5%, while in 10-15 years and 15 years or more age group the percentages were 34.6% and 69.6% respectively. It is also shown that the percentage of BSA-indexed LVH increased with increasing age group. However, unlike ECG-LVH, chi-square for trend analysis did not show any significant difference between boys and girls. See Table 4.

Table 5 shows that height-indexed Echo-LVH was found in only 22 (18.5%) of the 199 patients. The percentage of height-indexed Echo-LVH was also increased with increasing age group in
both sexes, but the difference in trend was not statistically significant between boys and girls.

Table 4. Proportion of Echo-LVH (BSA-indexed) according to age and sex

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Girls</th>
<th>Boys</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-</td>
<td>7/19</td>
<td>6/25</td>
<td>13/44 (29.5%)</td>
</tr>
<tr>
<td>10-</td>
<td>8/24</td>
<td>10/28</td>
<td>18/52 (34.6%)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>11/14</td>
<td>5/9</td>
<td>16/23 (69.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>26/57</td>
<td>21/42</td>
<td>47/119 (39.5%)</td>
</tr>
</tbody>
</table>

Chi-square for trend; x²= 0.916; df=1; p = 0.339

Table 5. Proportion of body height-indexed Echo-LVH according to age and sex

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Girls</th>
<th>Boys</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-</td>
<td>3/19</td>
<td>0/25</td>
<td>3/44  (6.8%)</td>
</tr>
<tr>
<td>10-</td>
<td>4/24</td>
<td>5/28</td>
<td>9/52  (17.3%)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>7/14</td>
<td>3/9</td>
<td>10/23 (43.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>14/57</td>
<td>8/62</td>
<td>22/119 (18.5%)</td>
</tr>
</tbody>
</table>

Chi-square for trend; x²=6.022; df=1; p=0.430

Sensitivity and specificity of ECG-LVH

EGC LVH was found in 23 (19.3%) patients, and on echocardiography it was 47 patients (39.4%) if BSA index was used, or 22 patients (18.5%) if body height index was used. The sensitivity and specificity of ECG in detecting LVH was then 25.5% and 84.7% in BSA indexed echo was used as gold standard, or 36.6% and 84.5% if body height indexed echo was used as gold standard. Tables 6 and 7 describe the complete features of sensitivity, specificity, predictive values, and likelihood ratios of ECG-LVH using BSA-indexed or height-indexed Echo-LVH, respectively.

Discussion

Echocardiography has proven to be a reliable non-invasive method to evaluate cardiac chamber and wall dimensions, ventricular contractility, and other parameters. Using specific formula, left ventricular mass can also be determined by M-mode echocardiography, which is well correlated with autopsy.

To reduce the possibility of errors due to chance and bias in this cross sectional diagnostic test, several attempts have been made. These included randomselection of the patients, a strict operational definitions, and the binding of the reviewer when analyzing ECG or echocardiography.

Patient's characteristics

The boy to girl ratio of the 119 patients in this study was approximately 1.1:1. This was not very different to that reported by Wahidiyat (3:2) or by Dewi and Lumaga (4:3).

Echocardiography

Repeated blood transfusion in thalassemia patients results in the increase of transversal dimension of left ventricular chamber, increase in thickening of left ventricular wall, and increase in left ventricular mass. These phenomena is not only found in older patients, but also in

Table 6. Diagnostic accuracy of ECG-LVH in patients with thalassemia major using BSA-indexed Echo-LVH as the gold standard

<table>
<thead>
<tr>
<th>ECG-LVH</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>23</td>
<td></td>
<td>23</td>
</tr>
</tbody>
</table>

Sensitivity = 12/47 = 25.5% (95%CI = 13.0%; 38.0%)
Specificity = 61/72 = 84.7% (95%CI = 76.4%; 93.2%)
Accuracy = 73/119 = 61.3% (95%CI = 52.6%; 70.0%)
Positive predictive value = 12/23 = 52.2% (95%CI = 38.6%; 67.8%)
Negative predictive value = 61/96 = 63.5% (95%CI = 55.3%; 71.7%)
Positive likelihood ratio = 1.67 (95%CI = 1.13; 4.88)
Negative likelihood ratio = 0.88 (95%CI = 0.64; 0.95)

Table 7. Diagnostic accuracy of ECG-LVH in patients with thalassemia major using body height-indexed Echo-LVH as the gold standard

<table>
<thead>
<tr>
<th>ECG-LVH</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>23</td>
<td></td>
<td>23</td>
</tr>
</tbody>
</table>

Sensitivity = 8/22 = 36.4% (95%CI = 14.8%; 58.0%)
Specificity = 82/97 = 84.5% (95%CI = 77.3%; 91.7%)
Accuracy = 90/119 = 74.0% (95%CI = 77.4%; 90.6%)
Positive predictive value = 8/23 = 34.7% (95%CI = 15.6%; 53.8%)
Negative predictive value = 82/96 = 85.4% (95%CI = 78.4; 92.4%)
Positive likelihood ratio = 2.35 (95%CI = 0.81; 3.44)
Negative likelihood ratio = 0.78 (95%CI = 0.63; 1.22)
younger ones. In this study there was an increase of transversal dimension, thickening of left ventricular wall, and increase of left ventricular mass with increasing age. These were in accord with those reported by Henry et al.21 We did not examine the correlation between those cardiac measurements and the amount of blood transfusion received.

Accuracy of ECG-LVH

The use of electrocardiography in detecting LVH in cardiac patients has been questioned by many.22 In most adult patients, the sensitivity of ECG in detecting LVH is low, when compared with that obtained by echocardiography or autopsy. In this study the sensitivity of ECG in detecting LVH was low (25.5%) but its specificity was high (84.7%). This result was different with those reported by Sastrosomo23 who found good sensitivity (71.4%) and specificity (73.8%).

The corresponding predictive values and likelihood ratios of ECG-LVH (Tables 6 and 7) followed the sensitivity and specificity of ECG-LVH. The low sensitivity and high specificity in this study corresponded with low to moderate predictive values and high negative predictive values, with high positive likelihood ratios and low negative predictive values.

In contrast to absence of sex difference, the sensitivity of ECG to detect LVH showed significant difference with increasing age. ECG was more sensitive to detect LVH in patients more than 15 years of age than on those below 15 years. This was an accord with other report,24 which might be caused by paradoxical phenomena associated with the increased prevalence of LVH in older age as a result of repeated blood transfusion.

According to Devereux11 the best method in measuring LV mass by means of echocardiography is the Penn's method. This method excludes the endocardium in the myocardial thickness measurement but includes it in the left ventricular dimension. In this study we did not use this method because of the difficulty in determining endocardial thickness, especially in small children. In contrast to in adults, there is no standard values for LV mass measured by echocardiography.

In determining LV mass by means of echocardiography BSA-indexed LV mass is more often used than height-indexed LVH. However, some investigators reported that the use of height-indexed is more reliable when compared with BSA-indexed LV mass. In this study we used BSA-indexed LVH due to the many patients who were undernourished. In well-nourished children, BSA/height ratio usually gives larger value than in adults. The presence of undernutrition, as shown by low body weight and normal height will result in low BSA. This will result in lower body height-indexed LV mass when compared with BSA indexed LV mass.

Our results show that the role of ECG in detecting LVH in patients with thalassemia major was very low, especially in patients aged 5-10 years (Table 3). This makes echocardiography has the important place in the overall management of patients with thalassemia major, especially in its relation with cardiac involvement.

It must be borne in mind that in the management of thalassemia the use of deferoxamine, an agent that binds the iron, has the most important role in the prevention of iron deposit in the body organs, especially in the myocardium. In addition, splenectomy has to be seriously considered if frequent blood transfusion is needed (>180 ml/KgSw/year). Splenectomy will suppress the erythropoiesis and reduce the need for transfusion resulting in reduction of iron deposit.

In conclusion, our data indicate the following: (1) ECG can detect LVH in 19.3% of thalassemia patients aged 5 years or more; (2) BSA-indexed echo-LVH is more sensitive to detect left ventricular mass increase than height-indexed echo-LVH; (3) ECG has low sensitivity but high specificity in detecting LVH in thalassemia patients; (4) The sensitivity of ECG criteria for LVH is not different according to sex, but tends to increase with increasing age.

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Factors Influencing the Duration of Acute Infantile Diarrhea

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**ABSTRACT** A retrospective study was conducted on infantile diarrhea treated at the Gunung Weang General Hospital to evaluate the relationship of age, nutritional status and cause of diarrhea to the duration of episode of infantile diarrhea. From January 1991 up to December 1992, 584 infantile diarrhea cases out of 1109 infants were treated at the Division Gastroenterology Child Health Department. Three hundred and forty-four (58.7%) of them were male, and 56% of patients were less than 12 months of age. The nutritional status was evaluated using NCHS standard; 391 (67.0%) were well-nourished, 49 (8.4%) were moderately undernourished, and 5 (0.8%) were severely malnourished. Duration of diarrhea of 4 days of less was found in 70.8% of patients 13-24 months old, 43.9% in 7-12 months age group, 46.2% of infants 4-6 months age group, and 54.8% of infants 1-3 months age group, 60.6% of wellnourished infants, 56.8% of mildly malnourished infants, and 31.5% of moderate to severely malnourished infants. Chronic diarrhea was found in 5 infants (0.9%), 3 with severe malnourished infants suffered from carbohydrate intolerance with E. histolytica infestation and the other 2 infants due to E. coli. [Pediatr Indon 1995; 35:141-149]

**Introduction**

Based on the Survey on Illness and Management of Diarrhea in 1990, there are eight Provinces in Indonesia with second highest number of population, namely Aceh, Riau, Jambi, Yogyakarta, West Kalimantan, South Kalimantan, North Sulawesi and Bali. The morbidity rate of diarrhea for all age was 20.1/1000 (ranging 10.7 to 35.1/1000) and for children under five years of age was 103.6/1000, (range 62.8-137.1/1000). In North Sulawesi, the morbidity rate of diarrhea for all age was 10.7/1000 and for children under five years of age was 62.8/1000. For the age group under five years, the highest proportion is in the age group of