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Original Article

Correlation between hemoglobin level and left ventricular systolic functions and dimensions in children with chronic severe anemia

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Abstract

Background Chronic severe anemia is a common disease. Cardiac output may increase when the hemoglobin (Hb) level decreases to < 7 g/dL for 3 months or more. Alteration of left ventricular (LV) function occurs frequently in children with chronic severe anemia, in the form of concentric LV hypertrophy, LV dilatation with or without LV hypertrophy, or systolic dysfunction.

Objective To examine the correlation between Hb level and alteration of LV systolic function in children with chronic severe anemia.

Methods We conducted a cross-sectional study in Adam Malik Hospital from October to December 2009. Subjects were chronic severely anemic children. Left ventricular systolic function (ejection fraction/EF, fractional shortening/FS) and dimensions (left ventricular end diastolic diameter/LVEDD and left ventricular end systolic diameter/LVESD) were measured using Hitachi EUB 5500 echocardiography unit. Univariate analysis and Pearson correlation were performed.

Results Thirty children were enrolled in the study. The mean of age was 113.5 months (SD 53.24). Hb values ranged from 2.1 to 6.9 g/dL with mean value of 4.6 g/dL (SD 1.44). Mean duration of anemia was 3.9 months (SD 0.70). Chronic severe anemia was not associated with decreased LV systolic function [EF 62.2% (SD 9.16), r = 0.296, P= 0.112; FS 33.8% (SD 7.26), r = 0.115, P= 0.545], nor LV dimension changes [LVEDD 40.2 mm (SD 6.85), r = -0.192, P= 0.308; LVESD 26.2 mm (SD 4.98), r= -0.266, P= 0.156].

Conclusion There was no correlation between Hb level in chronically anemic children and changes in LV systolic function or dimension. **[Paediatr Indones. 2011;51:79-83]**.

Keywords: *chronic severe anemia, LV function, LV dimensions*

Anemia is a public health problem that affects populations in rich and poor countries. Anemia is defined as reduction of red blood cell (RBC) volume or hemoglobin (Hb) concentration below the range of values for age and sex, based on standards established from the normal population.[1,2] The World Health Organization (WHO) defines anemia as a Hb concentration of less than 11 g/dL for children aged > 6 months to 5 years, and less than 12 g/dL for those aged ≥ 5 to 14 years. In its 1993-2005 study, the WHO reported the highest prevalence of anemia to be in preschool-age children (47.4%, 95% CI 45.7 to 49.1).[3] Iron deficiency anemia (IDA) is the most common cause of anemia in children.[4] Based on data of a family health survey in Indonesia, the prevalence of IDA is 40.5% in preschool-age and 47.3% in school-age children.[5] According to the WHO and the National Cancer Institute (NCI), severe anemia is defined as Hb level within the range

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of 6.5 to 7.9 g/dL.[6,7] Chronic severe anemia is the most common cause of increased cardiac output (CO), particularly when the Hb level is < 7 g/dL for 3 months or more.[8-11]

Echocardiography is a sophisticated, non-invasive imaging tool that has contributed significantly to the assessment of patients with chronic severe anemia.[12] A study of retrospective cohorts showed that during the course of one year, new chronic severe anemia patients was the cause of 9.6% of left ventricular (LV) dysfunction.[13] Another study concluded that for every 1 g/dL increase in baseline Hb in anemic children, the mortality risk was 15.8% lower and the risk of mortality or hospitalisation for heart failure (HF) was 14.2% lower.[14] The aim of this study was to determine if there is a correlation between Hb level and alterations in LV systolic function and/or LV dimension in children with chronic severe anemia.

Methods

We conducted a cross-sectional study on 30 children with chronic severe anemia in Adam Malik Hospital, Medan, from August to December 2009. Participants were children and adolescents aged 12 months to 15 years who suffered from chronic severe anemia with Hb levels under 7 g/dL for at least the three previous months. We calculated the minimal number of subjects needed for this study to be 29. We excluded children who suffered from cardiac diseases, congenital malformations, acute hemorrhage, thalassemia major (TM), and/or those who received multiple blood transfusions. Informed consent was obtained from the parents. Ethical approval was obtained from the Medical Ethics Committee, University of North Sumatera Medical School.

Study enrollment and initial physical examination were conducted by way of a standardized interview to assess medical history, height, weight, and blood pressure. Height was measured using a stature meter 2M (sensitivity 0.5 cm) and weight was measured using Camry® scales (sensitivity 0.1 kg). Blood pressure was measured with a Riester® sphygmomanometer. The following demographic and hematological data were obtained: age, duration of anemia, and Hb level at diagnosis. Duration of anemia was defined as the time from clinical diagnosis of anemia to the time of enrollment in our study. The diagnosis of anemia was made by clinical assessment and Hb estimation by cyanmethemoglobin method. The cutoff criteria for diagnosis of severe anemia was Hb level $\leq$ 7 g/dL, while chronic severe anemia was established when these Hb levels lasted for 3 months or more.

We used a Hitachi EUB 5500 (Japan) for echocardiographic examinations. Complete cross-sectional echocardiography imaging of all cardiac chambers was done to exclude the presence of congenital abnormalities or significant valve lesions. Two-dimensional echocardiography, Doppler and M-mode, were used to evaluate LV systolic function and dimension, i.e., ejection fraction (EF), fractional shortening (FS), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD). Systolic dysfunction was defined as an EF less than 54% and/or FS less than 28%. We looked for end systolic and end diastolic LV dimensions above the normal limits. Echocardiography was done by a pediatric cardiologist. LV functions were calculated using standard formulae. Left ventricular dimensions were analyzed using M-mode echocardiographic measurements for children.

The statistic program used for data processing was SPSS version 14.0. Data was presented in mean values with SD. Hematological data and echocardiography findings were tested using Pearson correlation and linear regression analysis. Differences were considered significant at $P < 0.05$ with a 95% confidence interval.

Results

Out of 52 participants, 30 met the inclusion criteria. Twenty-two subjects were excluded due to rheumatic heart diseases (7), pericardial effusion (2), lupus carditis (1) and various congenital heart diseases (12). Subjects' ages ranged from 12 to 178 months, with a mean of 113.5 months. Twenty subjects were children and the remainder were adolescents. Characteristics of subjects are summarized in **Table 1**.

We evaluated for alterations in left ventricular systolic function based on EF and FS values. Echocardiography results are also summarized in **Table 1**. The mean EF was 62.2%, ranging from 50.2% to 88.9% and mean FS was 33.8%, ranging from 24.3%

Table 1. Characteristics of subjects.

Characteristics	Mean (SD)
Gender, n	
Male	15
Female	15
Ages, months	113.5 (53.24)
Body weight, kg	25.3 (11.33)
Body height, cm	125.4 (25.57)
Systolic blood pressure, mmHg	107.3 (13.88)
Diastolic blood pressure, mmHg	68.3 (10.85)
HR, times/min	124.1 (14.58)
RR, times/min	34.1 (6.97)
Hb, g/dL	4.6 (1.44)
Duration of anemia, months	3.9 (0.70)
EF, %	62.2 (9.16)
FS, %	33.8 (7.26)
LVESD, mm	26.2 (4.98)
LVEDD, mm	40.2 (6.85)

to 58.1%. Dilatation of the left ventricle was assessed by way of LVESD and LVEDD measurements. The mean LVESD was 26.2 mm, ranging from 13.8 to 35.8 mm. Mean LVEDD was 40.2 mm, ranging from 26.3 to 52.2 mm.

In our study, the relationship between left ventricular systolic function and Hb level was analyzed using Pearson correlation and linear regression. **Figure 1** shows that there was no significant correlation between EF and Hb level in chronic severe anemia patients ($r = 0.296$, $P = 0.112$). There was no significant correlation between FS and Hb level in chronic severe anemia patients, as shown in **Figure 2** ($r = 0.115$, $P = 0.545$). Linear regression revealed that Hb levels cannot be used to predict EF values, nor those of FS.

We also analyzed dilatation of the left ventricle

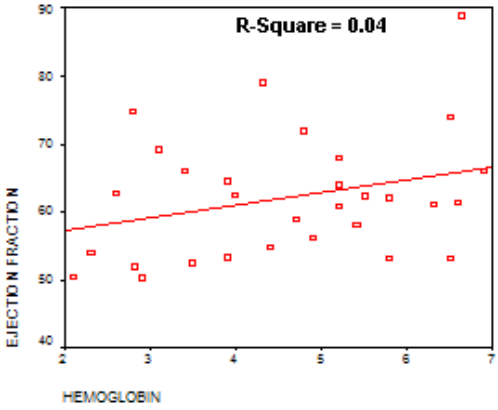

Figure 1. Realtionship of EF to Hb level

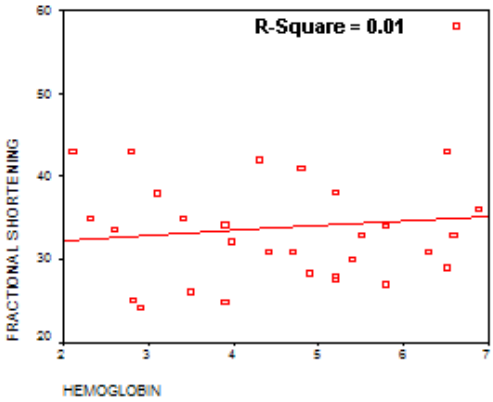

Figure 2. Relationship of FS to Hb level

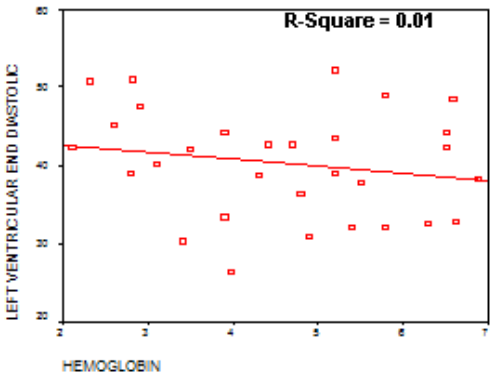

Figure 3. Relationship of LVEDD to Hb level

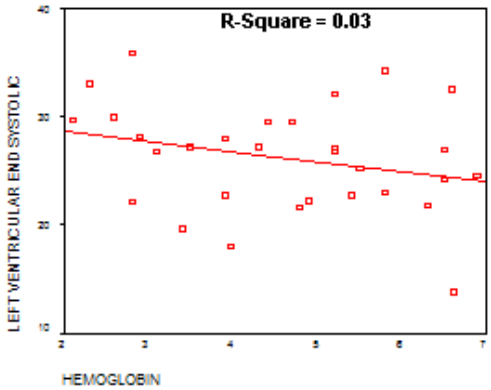

Figure 4. Relationship of LVESD to Hb level

using Pearson correlation and linear regression analysis. **Figure 3** shows there was no significant correlation between LVEDD and Hb level in chronic severe anemia patients (r = -0.192 ; P = 0.308). Likewise, **Figure 4** shows there was no significant correlation between LVESD and Hb level (r = -0.266 ; P = 0.156).

Discussion

The impact of chronic severe anemia on LV function and dimensions in children has been extensively studied. However, there has been no consensus as to how anemia duration affects changes in LV function and dimensions.[15] Myocardial function is associated with the severity and duration of anemia.[9,10,16] We used a cutoff point of 3 months or more to classify the subjects' anemia as chronic. Mean duration of anemia in our subjects was 3.9 months, ranging from 3 months to 1 year. A coronary hemodynamic study was conducted in 14 chronic severe anemia patients with anemia of at least 4 months and Hb values $\leq$ 6.5 g/dL (ranging from 1.6 to 6.5 g/dL, average 4.4 g/dL). They showed that coronary blood flow was significantly raised in patients with chronic severe anemia when compared to normal subjects. After the subjects' anemia was corrected, they observed that changes in coronary hemodynamic parameters noted in the anemic state were completely reversible.[14] Another study of anemia in chronic kidney disease (CKD) patients used 6 months as the cutoff point for chronic anemia duration.[17]

At the onset of our study, the diagnosis of anemia was made by clinical assessment, interviews with parents or guardians and confirmed by testing Hb levels. Chronic anemia usually increases cardiac output (CO) when Hb level is < 7 g/dL,[14,18,19] but significant cardiac enlargement occurs only with an extreme reduction in Hb (< 4 g/dL).[20] Based on these reports, our cutoff criteria for diagnosis of severe anemia was Hb level $\leq$ 7 g/dL. Most of the studies used the same value cut-off point of anemia.[14,18-21]

The mean Hb level was 4.6 g/dL (SD 1.44), ranging from 2.1 g/dL to 6.9 g/dL. Thus, all participants suffered from severe anemia, which tends to be life threatening.[6,7] Another study showed lower Hb level in chronic severe anemia patients compared to our study (an average 4 g/dL).[21] The youngest participant in our study was 12 months old, and the oldest was 178 months. An Indian study of LV systolic function enrolled older children as participants, with a mean age of 9.4 years,[20] but in general our findings were similar to theirs.

Our study was in agreement with other reports on the hemodynamic consequences of chronic severe anemia.[14,18-22] Resting heart rates (HR) of subjects tended to be in the tachycardia range. These findings can be explained by hemodynamic mechanisms already induced in anemic children resulting in higher resting HR. Tachycardia occurs in order to increase the CO in patients with chronic severe anemia, in response to chemoreceptor stimulation due to hypoxia and increased sympathetic activity, to fulfill oxygen demand and perfusion to vital organs.[11]

In our study, systolic blood pressure (SBP) varied from 80 to 140 mmHg and diastolic blood pressure (DBP) varied from 50 to 90 mmHg. Average pressure was 107.3 /68.3 mmHg. According to age-specific percentiles of SBP and DBP in boys and girls,[23] these values were slightly high (in between P_{50-75}). However, our findings appears to show hemodynamic compensation of chronic severe anemia, which is activated by neurohormonal activities to maintain BP in order to adequately perfuse vital organs.[11,24,25]

Anemic patients have hyperdynamic ventricular function with increased FS and velocity of circumferential fiber shortening (VCFc), which increases with progressive hemodilution. It has been shown that chronic severe anemia leads to a hyperdynamic state with improved LV function and decreased peripheral resistance. However, chronic severe anemia alone does not lead to ventricular dysfunction in patients with no other underlying cardiac or systemic disease.[26]

We evaluated LV systolic function by EF and FS. Alteration of LV function was established when one or both of these parameters were below the normal limits. We observed the mean FS to be 33.8%, ranging from 24.3% to 58.1%. We found 6 subjects with FS < 28%, suggesting altered systolic function. However, we found no significant relationship between FS and Hb level in chronic severe anemia patients. It is possible that a masking effect of subclinical LV dysfunction in anemic children was present, which was not readily appreciated in EF measurements. Similarly, a study

of subclinical LV dysfunction in anemic children concluded that exercise is helpful in demasking subtle LV dysfunctions in anemic subjects that are not detected during testing. They concluded there were no significant systolic or diastolic dysfunctions in any of their study groups during rest, but after exercise significant systolic dysfunction was seen in all severely anemic subjects.[20]

The EF values of our study ranged from 50.2% to 88.9%, with a mean of 62.2%. We found eight subjects with EF < 54%, suggesting systolic function alteration. However, there was no significant relationship between EF and Hb level in our subjects. Although the Hb level was very low, the compensatory mechanism of the heart was still performing well. The heart was still able to increase CO by increasing workload to fulfill oxygen demands.[11]

Ventricular hypertrophy and remodeling are important compensatory processes that develop over time in response to hemodynamic burdens.[11] LV systolic and diastolic dimensions increased with increasing degrees of anemia. Specifically, there was a negative correlation between Hb level and LVEDD ($r = -0.6$). Load-dependent indexes of ventricular function (FS, corrected ejection time/ETc, and VCFc) were not adversely affected by patient age, increased severity or duration of anemia.[15] Since long-term severity of anemia may not be properly represented by a single Hb value, we evaluated the relationship between ventricular dilatation (LVEDD and LVESD), a more reflective measure of the chronic severity of anemia, and Hb level. Although we found no correlation, as a continuous variable the persistent anemia may negatively impact the LVEDD and LVESD. However, we did not observe a relationship in our study ($r = -0.192$; $P = 0.308$, $r = -0.266$; $P = 0.156$, respectively). In contrast, a study of pediatric sickle cell anemia (SCA) patients found significantly increased LV dimensions and mass,[27] with confirmation by others.[28,29] It has been proposed that abnormal loading conditions associated with chronic severe anemia lead to chamber dilatation and myocardial remodeling that progress to ventricular dysfunction.

We performed Pearson correlation and linear regression analyses. Our inclusion and exclusion criteria were designed to reduce the risk of bias in our study. A limitation of this study was that duration of anemia was provided only by patient history. Therefore, we did not know the exact onset of anemia. We also did not perform multivariate analyses to evaluate other risk factors for alteration of LV systolic function and LV dilatation. Further investigation is needed to study the diastolic and systolic LV function in chronic severe anemia patients. Finally, alteration of LV function and dimension is a slowly progressing phenomenon, implying the cumulative effect of chronic anemia is more important than the short-term magnitude of a single Hb measurement. It is likely that the chronic severe anemia patients had variations in anemia severity over the months, which may not be properly represented by a single Hb measurement as was used for data analysis in this study. Thus, further study should include a longer duration of anemia and several testings of Hb levels.

We conclude there was no significant correlation between Hb level and left ventricular function (EF, FS) and dimensions (LVESD and LVEDD) of children and adolescents with chronic severe anemia lasting at least 3 months.

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