Chapter 1

Introduction

In Southeast (SE) Asia, ∝-thalassemia, B-thalassemia, hemoglobin E (HbE), and hemoglobin Constant Spring (Hb-cs) are common (1,2,3,4). The gene frequencies are as high as 30% for ∝-thalassemia, 3 to 9% for B^0-thalassemia, up to 54% or higher for HbE, and at least 4% for Hb-cs. Because of coexistence of several thalassemia and related genes in the same area, S.E. Asia witnesses the most complex thalassemia syndromes unparalelled by other parts of the world. In this part of the world, B^0-thalassemia predominates over B^+-thalassemia, which is commonly encountered among blacks and Mediterraneans (5). While among Mediterraneans homozygous B-thalassemia or Cooley anemia almost singularly represents B-thalassemia disease, in SE Asia B^0-thalassemia/HbE disease is more prevalent. This can be explained by the markedly high frequency of HbE gene and moderately high frequency of B^0-thalassemia gene in this region.

Though B-thalassemia/HbE (B-thal/HbE) patients have the seemingly same abnormal gene, the spectrum of disease varies commonly from asymptomatic one to severely disabled since childhood (6), an interesting feature different from other thalassemias. Wasi, P. et al (4) reported experience from over 1800 cases of B^0-thalassemia/HbE disease which shown out that the severity of anemia in this diseases varied greatly. The hemoglobin levels at steady state yary from 2.5 to 13.5 gram per decilitre with an average of 7.7 gram per decilitre. They are interested in the topic of what lead to the different degree of severity of anemia in these patients with apparently the same genotype. Several determinant factors were revealed as shown in Table 1.

Table 1. Factors that may modify severity of anemia in B-thalassemia

Acquired	inherent
1 Infections	1 ∝-thalassemia
2 Malnutrition	2 increased HbF production
3 hypersplenism	3 RBC superoxide dismutase activity
4 autoimmune hemolytic anemia	4 reticulo-endothelial function
	5 failure of erythropoiesis compensation
	6 erythrocyte proteolytic activity

Though there are a lot of research to find determinant factors of different severity of anemia in B-thal/HbE disease, only a little attention has been paid to cardiac problems in these patients, which is a major cause of their deaths (60%) (7).

Most echocardiographic studies (8 , 9, 10, 11) about thalassemia were conducted in B-thalassemia homozygote or in mixed varieties of thalassemia syndromes where a conclusion about B-thal/HbE disease, a major endemic health problem in Thailand, can be difficultly withdrawn. From studies in homozygous B-thalassemia, they found that 1 chronic, severe anemia from birth usually manifests signs of cardiac hemochromatosis during the second decade (12,13). 2 Most patients develop congestive cardiac failure and arrhythmia which led to death within a few months to a few years(12,13). 3 a considerable amount of iron from transfused erythrocytes and from dietary iron accumulates in the body. Iron is incorporated into tissues such as heart, liver, spleen,and pancreas as ferritin or hemosiderin. This results in pathologic changes in these tissue with necrosis, fibrosis, and subsequent organ failure (9). 4 Deferoxamine therapy (iron removal) improves LV function, decreased LV wall mass(14), and reduced cardiac arrhythmia(15).

Grusaru, D. et al (14) made serial echocardiographic studies in 35 homozygous B-thalassemia followed up for 5.5±2 years. Twenty patients received deferoxamine sulfate for 2±0.6 years (drug group) and 15 patients did not (non drug group). Blood transfusion were given to maintain pretransfusion hemoglobin levels at 9 gm/dl in both groups. They found that percentage shortening of LV diameter improved in the drug group (5±3.9%) and deteriorated in the nondrug group (-6.8±5.6%). Similarly, the maximum velocity of LV posterior wall motion improved in the drug group (16.1±20.1 mm/s) and deteriorated in the nondrug group (-18.3±19.0 mm/s). Left ventricular wall mass decreased in the drug group when compared with the nondrug group. They suggested that treatment of patients with thalassemia with modest blood transfusions and deferoxamine can prevent deterioration and may ever improve their LV systolic function.

Methods for the early detection of cardiac dysfunction has been reported. Systolic dysfunction has been reported to be abnormal in a study using radionuclide angiography to determine left ventricular ejection fraction during exercise in 24 patients with transfusion-dependent, congenital anemias, 21 of whom had severe beta thalassemia(16). Ejection fraction at rest was normal in 21 patients (>45 percent) and in all patients was 53± 2 percent (mean ± S.E.M.) -not significantly different from the value in normal subjects. However, ejection fraction during exercise was normal in only 11 patients. All eight patients who had received fewer than 100 transfusions but only three of 16 (19 percent, P <0.001) who had received 100 or more transfusions had normal responses during exercise. They concluded that radionuclide cineangiography during exercise is a highly sensitive technique for detecting preclinical systolic dysfunction in patients with systemic iron overload.

Nienhuis, A.W. et al (17) performed echocardiography, 24-hour monitoring of the cardiac rhythm by the standard Holter technique, and radionuclide cineangiography in 42 severe transfusion-dependent B-thalassemia patients. They used the calculated left ventricular

ejection fraction as a parameter that reflects left ventricular contractility. Only four of the patients studied fell outside the normal range of 65% to 85%. Two of these had congestive heart failure at the time of study, and all four died within a short period of time. This seemed to suggest that cardiac function as reflected in the resting left ventricular ejection fraction was well preserved during most of the course of cardiac iron deposition and that a fall in resting ejection fraction was a rather ominous prognostic sign.

Borow, K.M.et al(18) used the LV end-systolic pressure dimension (P_{ES}-D_{ES}) relation, which is independent of preload, incorporates afterload and is highly sensitive to contractile state, to assess LV performance in 20 asymtomatic, chronically transfused patients; ages 7-25 years, with thalassemia major. Their patients had normal resting systolic time intervals and exercise duration on treadmill. Baseline resting percent fractional shortening (% FS) on M-Mode echocardiography was normal in 14 patients (group 1) and abnormal in six patients (group 2). Echo and carotid pulse recordings were made at rest and during i.v. infusion of methoxamine to alter LV afterload. D_{ES} was measured directly from echo; P_{ES} was estimated from a calibrated carotid pulse tracing. The value for the slope of the P_{ES}-D_{ES} line was calculated for each patient. Values more than 2 standard deviations below the mean for 14 control subjects, ages 8-25 years were defined as abnormal. All group 2 patients and four of 14 group 1 patients had abnormal slopes. On clinical follow-up (mean 12$\pm$3 months), two of 10 patients with abnormal slopes developed overt signs of LV decompensation; all other patients remained asymptomatic. They suggested that the noninvasive determination of the LV P_{ES}-D_{ES} relation in patients with thalassemia major appeared to identify preclinical LV dysfunction not evident from resting or dynamic exercise studies. However, their data was still inconclusive.

Lewis, B.S. et al (10) studied left ventricular function in B-thalassemia and the effect of multiple transfusions. They divided 23 patients into 3 groups on the basis of their transfusion

requirement from birth until the time of study: group 1 (0-9 units) 7 patients, group 2 (10-80 units) 5 patients and group 3 (more than 80 units) 11 patients and measured left ventricular performance. They found that the left ventricle was enlarged in patients who had not received blood and larger still in patients who had received multiple transfusion. Echocardiography and systolic time interval measurements showed that systolic function of the LV was good in all the patients and that there was no statistical difference in systolic function in patients who had and those who had not received multiple transfusions. The diastolic closure rate (EF slope) of the anterior mitral leaflet and its amplitude of movement were increased, but less so in group 3; this may reflect an alteration in diastolic LV distensibility. They concluded that 1 LV performance is well preserved in patients with B-thalassemia, even in those who have received multiple blood transfusions 2 clinical cardiac failure is the consequences of volume overload and abnormal chamber compliance.

In summary, myocardial dysfunction in homozygous B-thalassemia can be divided into systolic & diastolic dysfunction. LV systolic function is rather well preserved until the very end stage of heart failure. LV diastolic dysfunction may be responsible for some degree in pathophysiology of heart failure from cardiac hemochromatosis, but there are no good clinical evidences at the present time.

B-thal/HbE disease has a distinctive cardiopulmonary pathology. In contrast to cases of homozygous B-thalassemia reported in the literature (13,19,20,21,22,23,24,25,26), patients with B-thal/HbE have remarkable little cardiac iron deposition(27). In an autopsy review at Siriraj hospital, of 47 B-thalassemia/hemoglobin E patients, 16 had trivial iron in the myocardium. This consisted only of small granules in scattered deposits mainly in subepicardial area, highly unlikely to affect overall myocardial function(27). These findings are consistent with a previous report on 20 B-thal/HbE patients by Bhamarapravati, N. et al(28). Furthermore, Sonakul, D. et al(29) found many cases of pulmonary arterial obstructive lesions in B-thal/HbE

during a review of a large series of autopsies of thalassemia patients at Siriraj Hospital. In 19 out of 43 patients, the lungs showed obstructive lesions in the pulmonary arteries, predominantly affecting muscular arteries 100-800 u in size and occasional larger arteries were also involved. These consisted of organized, recanalized thromboemboli partly or completely occluding the lumens. Of these 19 pulmonary arterial thromboembolism, 17 were splenectomized cases. Splenectomy in thalassemia is known to be followed by increased infections and thrombocytosis, both of which can predispose the patients to thromboembolism. The mechanism that leads to more pulmonary thromboembolism in B-thal/HbE is unknown.