Chapter 3

Thalassemia heart disease

Cardiac complications represent the main cause of mortality in both thalassemia major (TM) and thalassemia intermedia (TI) forms of the thalassemia.[1] Heart involvement in TM is usually characterized by iron induced left ventricular (LV) dysfunction, leading to cardiac failure[2,3] and pulmonary arterial hypertension (PAH).[3-5]

In TI, age associated PAH and high output state with LV remodeling have been reported.[6]

Heart disease in thalassemia major (transfusion dependent β-thalassemia)

Direct iron related heart injury

Iron overload results mainly from the chronic regular blood transfusions. The patients receive 0.3 - 0.5 mg/ kg / day of iron by red cell transfusions. TM patients absorb more iron than normal people. The pathophysiology of increased iron absorption is related to paradoxical hepcidin suppression from the dyserythropoiesis.[7] The L-type Ca2+ channels are high capacity pathways for ferrous iron (Fe2+) uptake into cardiac-myocytes in situations ofiron overload.[8] Magnetic resonance imaging studies evaluated heart function, had cardiac iron overload in thalassemia case.[9,10]

Indirect iron related heart injury

Infections

Infection may aggravate cardiac failure. Iron overload is the principle etiologic factor that distress the balance of immune system in support of the infectious organisms growth.[11] The severe heart complications, myocarditis and pericarditis, are led to iron overload induced viral infection risk. Pericarditis cases were found fifty percent in TM with poor iron chelation in the past decade.[12] It is very rare nowadays, with the chelation treatment.[13]

Vascular involvement (afterload)

Systemic arterial disorder in TM patients, leading cause of cardiac abnormal function by heart after load affect.[14] The reduction of nitric oxide caused dysfunction of the vascular. The hemolysis is related and effected by three mechanisms;

- Arginase is released by red cell destruction which reduces arginine levels and its endothelium supplementation.

- Oxyhemoglobin is transformed to methhemoglobin after reacting with nitric oxide (NO) and changes it to NO_3 which inactive.
- Endothelial cell enzymes are inactivated by the oxidative stress. Moreover, the oxidative stress reduce nitric oxide formation.[15]

These vascular mechanisms contribution together with hypercoagulability is exposed to increase the resistance of pulmonary artery.[16]

Arrhythmias

Cardiac toxicity is induced by iron that is complicated by arrhythmias such as ventricular beats and extra atrial, paroxysmal atrial tachycardia, fibrillation and flutter. Ventricular tachycardia is rare. Short runs of ventricular tachycardia and atrial arrhythmias are common.

Endocrine abnormalities

Iron toxicity indirectly affect cardiac function by detrimental other organs. The abnormalities of endocrine diabetes mellitus and hypothyroidism can have an impact on heart function.[17] The diabetes onset is related with heart dysfunction. Chronic hyperglycemia is an oxidative stress on several organs, especially the heart. Hypothyroidism may precipitate pericardial effusion, left ventricular dysfunction, increase of peripheral vascular resistance and bradycardia. Hypocalcemia related to occult hypoparathyroidism may accelerate cardiac dysfunction.

Increased cardiac output effect (preload)

Disease associated with increase of cardiac output, resulting in increase of cardiac workload, lead to abnormal cardiac function in TM. Iron overload of liver or viral infection induced liver injury and cirrhosis can significantly increase cardiac output and cardiac dysfunction.[18]

Summary of the mechanisms of cardiac injuryin thalassemia major

The cardiac impairment from iron overload, is forced to maintain a high cardiac output through a vascular bed rigidity that mentioned damage of vascular and is therefore subjected to a continuous state of pressure and volume overload cause to become the LV decompensation. In TM patients the concurrence of high cardiac output state and increase of

pulmonary vascular resistance lead to the PAH, which provokes right ventricular dysfunction and failure.[16] Infections, with a indirect or direct effect also have an impact on cardiac function. In well treated TM, the inhibition of these mechanisms, result in a reduction of LV dysfunction, damage of vascular, development of PAH and right ventricular failure.[19,20]

Cardiac disease in thalassemia intermedia (non-transfusion dependent)

Heart involvement is a complication and the main cause of death in TM and TI.[21] However, heart complication in TI is different. The patients are untransfusion and live longer. Therefore, hemoglobin levels and iron overload in TI are lower than in TM.[6] Multiple factors interrupt in the pathogens is of cardiac complication in TI. These affect right and left heart, so contribute to ventricular remodelling and cardiac failure.[6,19]

Cardiovascular consequences

Vascular manifestations

The hemolysis and hypercoagulability related elastic tissue abnormalities lead to multiple vascular abnormalities such as cerebral hemorrhages, angina pectoris, ascending aorta aneurysm and gastrointestinal hemorrhages.[22-24] Elastic tissue abnormalities may contribute to the leg ulcers which are found in TI.[25] These also explain the transfusion induced arterial hypertension development in sickle cell anemia and β-thalassemia patients.[26]

Thalassemia related hypercoagulability, thromboembolic event were found in TM and TI patients, with a frequency of 4.3% and 5.2%, respectively.[27] The prevalence of these events was higher in postsplenectomy thalassemic patients than in non-splenectomized patients. Thromboembolic events were even more frequent in untransfusion TI with postsplenectomy (29%), compared to regularly transfused TM patients (2%). This emphasizes the role of blood transfusion treatment in the inhibition of hypercoagulability in thalassemias.[28] Thromboembolic complications included thrombosis of deep vein (40%) and portal vein (19%), pulmonary thromboembolism (12%), cerebral occlusion (9%), recurrent arterial thrombosis and others events (20%).

Right heart involvement

Pulmonary arterial hypertension (PAH) is a well-known complication in TI patients. Almost 60% of cases in 110 TI patients cohort study had PAH.[6] PAH is a typical characteristic of untransfused TI patients[19] and is the leading cause of right cardiac failure in TI patients (5.4%)[6,19,29] The increase of pulmonary vascular resistance and high cardiac output state are the potential factors leading to the PAH development in TI (non-transfusion dependent) patients.[6,19]

Left ventricular involvement

Left ventricular impairment

The left ventricle has to preserve a high cardiac output state through a dilated and stiff vascular bed and is therefore in a continuous state of pressure overload and volume. The compromised left ventricle function leads to an unfavorable interaction between systemic arterial compliance and left ventricular ejection.[30]

The combination of coronary arterial disorder, iron overload and valvular abnormalities cause to becomes more susceptible to decompensation of cardiac function. In fact, unstable angina and cardiac failure were found in a middle aged TI with severe anemia and calcified coronary arteries.[23] In addition, left heart status in TI comprise of an increased left ventricular diameters, mass and volumes, with diastolic dysfunction but preserve systolic function.[6,19] Left sided heart failure with PAH may be observed in old TI, who are untransfused because incompatibilities of red cell, and who have arteries become calcified and rigid.[19]

Summary of cardiac disease in thalassemia intermedia

Heart involvement in TI is influenced by both ventricles have to preserve a high cardiac output through a rigid vascular bed. PAH results from right side cardiac failure dominates the clinical feature, although left ventricular systolic function is commonly preserved in a steady state.

Conclusion

In TM patients blood transfusions and iron chelation treatment have significantly reduced the morbidity and improved the survival.[21,31] In the past eighty percent of TM patients had died by the age of sixteen and at least eighty percent survive with the age more than forty years nowadays. Nevertheless, cardiac complications still explain significant morbidity and the main

cause of mortality in transfusion dependent TM patients.[21] In TI with PAH, early transfusion with iron chelation therapy may prevent cardiac damage by reduced critical factors that cause and sustain heart deterioration, such as high cardiac output, hypercoagulability and hemolysis.[19]

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