



Heart disease in thalassemia intermedia: a review of the underlying pathophysiology

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Acknowledgments: the authors wish to express their appreciation to Dr. K. Tsomi for her valuable input regarding the histopathology figures.

Manuscript received October 15, 2006.

Manuscript accepted March 8, 2007.

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ABSTRACT

Heart disease is the leading cause of mortality and one of the main causes of morbidity in β -thalassemia. The clinical spectrum of the thalassemia syndrome ranges from the severe, transfusion-dependent thalassemia major and the asymptomatic carrier state. Thalassemia intermedia represents a milder form and is usually transfusion-independent. Two main factors determine cardiac disease in this form. One is the high output state that results from chronic tissue hypoxia and from hypoxia-induced compensatory reactions. The other is the vascular involvement that leads to an increased pulmonary vascular resistance and an increased systemic vascular stiffness. Valvular abnormalities and iron overload also contribute to a less extent. As a result, both right and left ventricles have to maintain a high cardiac output level through a stiff vascular bed. Right heart involvement with age-related pulmonary hypertension followed by congestive heart failure dominates the clinical picture. Although the left heart is also affected, systolic left ventricular function is usually preserved but this may also be decompensated under conditions characterized by excessive cardiac work load.

Key words: β -thalassemia, thalassemia intermedia, heart disease, pulmonary hypertension, high output state.

Haematologica 2007; 92:658-665

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Thalassemia intermedia (TI) is an inherited hemoglobin disorder characterized by a significant genetic and clinical heterogeneity.^{1,2} It represents up to one fourth of β -thalassemia patients. The remainder are made up of the more prevalent and severe form, thalassemia major (TM).² A wide spectrum of different genotypes – homozygous, heterozygous and compound heterozygous – have been thought to be responsible for TI. The clinical phenotype ranges between the severe, transfusion-dependent TM and the asymptomatic carrier state.^{1,2} Patients with TM have severe anemia. This starts during the first year of life and requires life-long transfusion therapy. Patients with TI usually have a later clinical onset with a milder anemia. At least during the first few years of life transfusions are not required.¹

If they remain untreated, the clinical course of both forms of thalassemia is complicated by the multiple effects of chronic hemolytic anemia and resultant tissue-hypoxia as well as by their compensatory reactions. These include increased erythropoiesis with bone marrow expansion and increased intestinal iron absorption.³ Nowadays, these manifestations are completely or partially inhibited in TM patients due to the early application of regular transfusion-chelation therapy. However, they are still present in TI patients.

Cardiovascular involvement represents a well-known complication and the primary cause of mortality both in TM and in TI.⁴ Nowadays, in TM, iron overload constitutes the main cause of heart disease.^{4,5} Cardiovascular involvement in TI, howev-

er, is quite different. Patients live longer and are usually transfusion-independent, at least for the first decades of their life. Hemoglobin levels are therefore lower and, compared to TM, a lower iron load is also maintained.³ Several factors have been reported to interfere in the pathophysiology of cardiovascular abnormalities in TI. These affect left and right heart, therefore leading to ventricular remodelling and, finally, heart failure.^{3,5}

Pathogenetic mechanisms

The relatively mild clinical course of TI, the reluctance of patients, and the restrictive experience on transfusion and chelation therapy in TM patients gave rise to the concept that TI patients should not be transfused. In fact, before 1975, TI patients were rarely transfused. After this, some patients received blood transfusions on a palliative basis. As a result, in a 1995 study of 165 TI patients, 47.5% had never been transfused, while 25.5% had been transfused only occasionally and 27% had become transfusion-dependent during adulthood.⁶ Modern medical trends adopt an earlier application of transfusion-chelation therapy in TI. However, therapeutic strategies are still primarily based on patients' symptoms and the incidence of complications, such as bulky extramedullary hemopoiesis, splenomegaly, cardiomegaly and bone deformities. The significant fall in hemoglobin levels is also an important factor.² Given that patients become transfusion-dependent during adulthood, the transfusion target in TI is usually to keep a reasonable hemoglobin level and not, as in TM patients, to suppress native erythropoiesis. As a result, most literature on TI refers to non-transfused or only occasionally transfused patients while other studies refer to patients who have been started on regular transfusions for palliation late in life.

In this context, TI patients are exposed to prolonged tissue hypoxia. This is followed by the development of bone marrow expansion, increasingly ineffective erythropoiesis, and increased intestinal iron absorption. These are also present in poorly treated TM patients as well as in the other hemoglobinopathies. Consequently, these same mechanisms affect the cardiovascular system in all hemoglobinopathic patients in many ways and with different degrees of severity. Nowadays, TI patients are particularly affected. As a result, some evidence derived from different hemoglobinopathies other than TI is relevant. This is used here to support the description of cardiovascular involvement in TI.

High cardiac output state

A constant finding in TI is the high output state. This represents one of the basic pathophysiological mechanisms of cardiovascular involvement in these

patients.^{3,5,7,8} More specifically, echocardiographic measurements revealed an almost two-fold increase in cardiac output levels compared to normal subjects (Table 1).³ Indications for the presence of a high output state were also provided by a cardiac magnetic resonance imaging (CMR) study in TI patients.⁹

Chronic hemolytic anemia, resulting from ineffective erythropoiesis, is the hallmark of all thalassemia syndromes.¹ Chronic anemia, however, is not always severe in TI. Hemoglobin levels usually range between 7 and 11 g/dL and is apparently not the only cause of a high output state in these patients. In normal subjects, resting cardiac output is kept within normal limits when hemoglobin levels range between 8-10 g/dL.¹⁰ Besides the overall hemoglobin level, the proportions of the different hemoglobin types, especially the high percentage of fetal hemoglobin (HbF), are also important. More specifically, HbF reduces tissue oxygen delivery due to its increased oxygen affinity.¹¹ Figure 1 depicts a typical TI case with a high cardiac index level (6.1 L/min/m²). Although the patient's hemoglobin concentration was close to normal (11 g/dL), 95% of it was HbF.

Thus, both chronic anemia and increased HbF percentage result in prolonged tissue hypoxia. This leads to a compensatory bone marrow expansion with extramedullary hemopoiesis, splenomegaly and hepatomegaly, all of which also contribute to the high output state through peripheral vasodilatation and shunt development.^{3,12-14} Vessels in TI are also more susceptible to pulse pressure-driven dilatation due to a co-existent elastic tissue injury. This is discussed in detail below. The contribution of peripheral vasodilatation and intramedullary shunting seems to play an important role in the high output state. Indeed, it has been shown that the abolishment of splenic shunt and the increase in hemoglobin levels following splenectomy are not sufficient to counteract the pre-existent high cardiac output levels in TI patients.^{13,14}

Iron overload

Chronic iron overload is currently considered to be the primary cause of mortality in β -thalassemia, mainly due to the induction of left-sided cardiac failure.⁵ Iron overload results from a number of mechanisms associated with the disease itself. These mainly include ineffective erythropoiesis, as well as peripheral hemolysis, and increased intestinal iron absorption. The main cause is repetitive blood transfusions, also used in a number of TI patients.¹ Therefore, although iron overload is mainly a problem for transfusion-dependent TM patients, it also involves to a lesser extent TI cases.

In the case of increased intestinal iron absorption, the recently identified hepatic peptide hepcidin seems to influence iron load in thalassemia patients. This peptide interferes in iron homeostasis by inhibiting

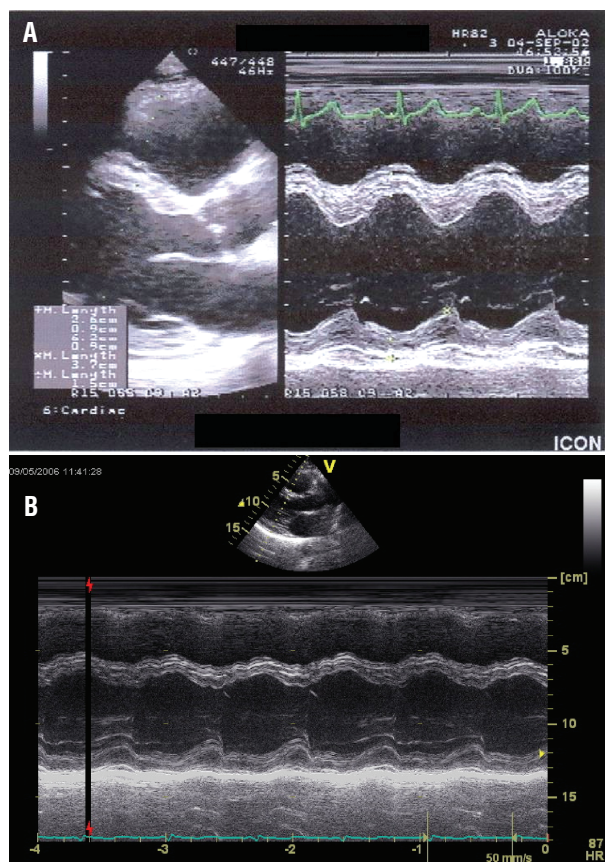


Figure 1. A. Simultaneous two-dimensional (left panel) and M-mode (right panel) echocardiogram in a 39-year-old thalassemia intermedia patient in high output state (cardiac index 6.1 L/min/m²), with a hemoglobin level of 11 g/dL and a 95% of hemoglobin F. Left ventricular dilatation with normal contractility (left ventricular end-diastolic diameter=62 mm, left ventricular end-systolic diameter=37 mm, fractional shortening=40.3%). B. Corresponding two-dimensional and M-mode echocardiographic frames in a normal subject, matched for age and body constitution.

iron absorption from duodenal enterocytes and iron release from hepatocytes and macrophages that recycle iron from senescent erythrocytes.^{15,16} Anemia and the resulting tissue hypoxia lead to the reduction of hepcidin levels, which in turn leads to iron hyperabsorption and maldistribution.^{15,16} Thus, urinary hepcidin was found to be suppressed in TM and TI patients.¹⁷ Sera from these patients decreased hepcidin expression in human hepatoma cell cultures, to an unexpectedly higher degree in TM.¹⁸ In a recent study, hepcidin mRNA levels from the liver of TM patients were inversely correlated to serum levels of erythropoietin and transferrin receptor, indicating that the down-regulation of hepcidin is proportional to the increase of erythropoietic activity.¹⁷

The heart, along with liver and endocrine glands, is one of the main organs where iron deposition causes severe complications.¹⁹ Iron overload interferes in the cardiomyocyte capacity to catalyze the formation of deleterious oxygen free radicals.¹⁹ Serum ferritin concentration is the most widely used marker of iron load,

Table 1. Data of patients and controls.

	Patients (n=110)	Controls (n=76)	p
Right ventricular diameter (mm)	23±4	19±3	<0.001
Left atrial diameter (mm)	42±6	33±3	<0.001
Left ventricular end-diastolic diameter (mm)	55±5	48±2	<0.001
Left ventricular end-systolic diameter (mm)	32±4	27±2	<0.001
Interventricular septum thickness (mm)	9.7±1.0	8.6±0.9	<0.001
Posterior wall thickness (mm)	9.6±1.0	8.5±0.8	<0.001
Left ventricular mass index (g/m ²)	126±30	86±10	<0.001
Shortening fraction (%)	43±5	44±3	NS
Ejection fraction (%)	73±6	75±3	<0.05
Cardiac index (l/min/m ²)	5.45±1.33	3.82±0.80	<0.001
Peak early transmitral diastolic velocity - E (cm/sec)	99±20	80±15	<0.001
Peak late transmitral diastolic velocity - A (cm/sec)	69±19	58±12	<0.001
E/A	1.51±0.48	1.42±0.34	NS
E deceleration time (msec)	152±34	164±33	NS
Isovolumic relaxation time (msec)	47±15	51±10	NS
Peak systolic tricuspid gradient (mmHg)	33.15±14.06	20.77±4.23	<0.001
Total pulmonary resistance (dynes.sec.cm ⁻²)	451±294	245±93	<0.001

Data derived from a cohort previously published by Aessopos et al. (Blood 2001;97:3411-6).

although it is not the best. At present, it is usually low in TI rarely exceeding 1,000 ng/mL. Confirmation of myocardial iron content is not generally easy and only T2* CMR has provided reliable estimates in a large number of TM patients.²⁰ An assessment of cardiac iron by T2* CMR in 31 TI patients revealed that 23% had cardiac iron overload, defined as a T2* value <20 msec.⁹ Significantly, the pattern of myocardial iron distribution was frequently heterogeneous in TI patients, a fact that may have an effect on cardiac iron toxicity.

Hemolysis-induced tissue injury – vascular involvement and elastic tissue abnormalities

Chronic hemolysis and iron overload, both of which characterize the hemoglobinopathies, are currently considered sources of strong oxidative stress. Reports have shown that the free heme and the red cell membrane elements that are produced during hemolysis have a negative effect on nitric oxide and arginine availability, which in turn promotes vasoconstriction.²¹ They also lead to further endothelial dysfunction, resulting in a more pronounced nitric oxide reduction, as well as to diffuse elastic tissue injury. The presence of such an elastic tissue defect has been recently described with a high prevalence in patients with hemoglobinopathies, especially in those with either of the two forms of β -thalassemia.²²⁻²⁴ The defect resembles hereditary pseudoxanthoma elasticum (PXE), a rare (1:70,000 to 1:160,000) connective tissue disorder, and covers the whole clinical spectrum of PXE. This mainly consists of skin (small yellowish papules or



Figure 2. Fundoscopic appearance of a thalassemia intermedia patient with a diffuse pseudoxanthoma elasticum-like elastic tissue disorder: typical findings called angioid streaks.

larger coalescent plaques), ocular (breaks of the elastic lamina of Brush membrane called angioid streaks [AS]) (Figure 2) and vascular manifestations (degeneration of the elastic lamina of the arterial wall, often with calcification [Figure 3]).²²⁻²⁴ Endocardium, cardiac valves and pericardium may also be involved.^{3,22}

Clinical expression of the elastic tissue injury is age-related. TI patients are therefore more affected by PXE lesions because of their prolonged survival. In fact, it has been shown that TI patients aged >30 years (mean age 41.4 years) presented a 55% occurrence of tibial artery calcification as part of elastic tissue abnormalities.²⁵ Interestingly, Tsomi and colleagues showed that the arterial involvement in hemoglobinopathies, including TI, had a much earlier sub-clinical onset. Since PXE-like tissue pathology was found in splenic artery specimens even from the first decade of life (Figure 4).²⁶ On the other hand, the degenerative arterial lesions observed in the elastic lamina and adventitia²⁶ make vessels more susceptible to dilatation by pulse pressure increase. Finally, the functional component of the arterial involvement was recently studied in TM, sickle-cell anemia and sickle-thalassemia patients. Increased arterial stiffness with endothelial dysfunction was observed and attributed to the two common pathogenetic mechanisms, hemolysis and iron load.^{27,28}

Valvular involvement

In a large group of 110 patients, electrocardiographs confirmed a high frequency of endocardial degenerative lesions, in the form of thickening and calcification, which affected cardiac valves, mitral annulus and papillary muscles. These were often followed by moderate valvular regurgitation and occasionally by aortic stenosis.³ Leaflet thickening was present in 48% of patients, endocardial calcification in 21%, mitral regurgitation in 47%, aortic regurgitation in 15%, while there were 3 cases of mild to moderate aortic stenosis.³ It has been suggested that the hyperkinetic



Figure 3. Lateral X-ray of the tibia in a 45-year-old patient with thalassemia intermedia. Calcification of the anterior and posterior tibial arteries.

state due to the high output state, the iron overload and primarily the elastic tissue abnormalities discussed previously are the pathogenetic mechanisms responsible.^{3,5} Although the hemodynamic consequences of the mild or moderate valvular abnormalities are not usually significant, they may contribute, along with the other pathogenetic mechanisms, to the development of heart disease. Atrioventricular conduction disturbances and the risk of cerebrovascular thrombotic events in the context of a coexistent hypercoagulable state have also been discussed in literature.^{3,29}

Hypercoagulability

Hypercoagulability is a well-established characteristic of β -thalassemia.³⁰ A number of pathogenetic mechanisms have been discussed in relation to the underlying genetic defect and its sequences, namely hemolysis and iron overload, and the resulting oxidative tissue damage. In fact, the free α -globin chains that result from the decreased synthesis of the β -chains, together with the free iron, provoke oxidative damage to the red blood cell membrane proteins. This results in the exposure of negatively charged phospholipids which create a pre-coagulant surface.^{30,31} Furthermore, data obtained from TM and sickling syndromes, as described above, showed that endothelial function is

also impaired.^{27,28} Oxidative damage resulting from hemolysis and iron load leads to an increase expression of adhesion molecules ICAM and VCAM and impaired NO bioavailability. This provokes hypercoagulability and decreasing NO-dependent, flow-mediated dilatation.^{27,32} Platelets are also activated with enhanced aggregation, while splenectomy increases platelet counts and induces membranes abnormalities that further increase platelet aggregation.³² The observed deficiency of the coagulation inhibitors, protein C and protein S, the elevated levels of thrombin-ATIII complex due to splenectomy and/or liver dysfunction as well as the co-inheritance of several coagulation defects, such as factor V (Leiden) and factor deficiency, may all contribute to the pathogenesis of hypercoagulability in thalassemia.^{30,33} Finally, a strong inflammatory reaction has been observed. This has been expressed by the elevated circulating levels of cytokines and adhesion molecules and the monocyte and neutrophil activation, hence promoting hypercoagulability.³²

Cardiovascular consequences

Vascular manifestations

The combination of hypercoagulability and hemolysis-related elastic tissue abnormalities may lead to a wide spectrum of vascular complications. Elastic tissue abnormalities have been associated with a number of vascular complications sometimes observed in TI patients. These include fatal cerebral hemorrhages, anginal symptoms, ascending aorta aneurysm formation and gastrointestinal bleeding.^{29,34,35} Elastic tissue abnormalities may also contribute to the leg ulcerations frequently observed in TI patients. They may also explain the observed development of transfusion-induced arterial hypertension in sickle cell anemia and β -thalassemia patients.^{36,37}

Thalassemia-related hypercoagulability, sometimes in combination with elastic tissue defects is thought to be responsible for a high frequency of thromboembolic complications. Thromboembolic events were encountered in two large cohorts of thalassemia patients, including both thalassemia major and TI patients, with a frequency of 4.3% $\kappa\alpha$ and 5.2%, respectively.^{38,39} It must be noted that the prevalence of such events was higher in splenectomized patients than in non-splenectomized ones. In particular, thromboembolic complications were even more frequent in transfusion-independent splenectomized TI patients (29%), compared to regularly transfused TM patients (2%). This emphasizes the role of transfusion therapy in the inhibition of hypercoagulability in thalassemia patients.⁴⁰ Thromboembolic events included deep vein thrombosis (40%), portal vein thrombosis (19%), pulmonary thromboembolism (12%), cerebral thrombosis

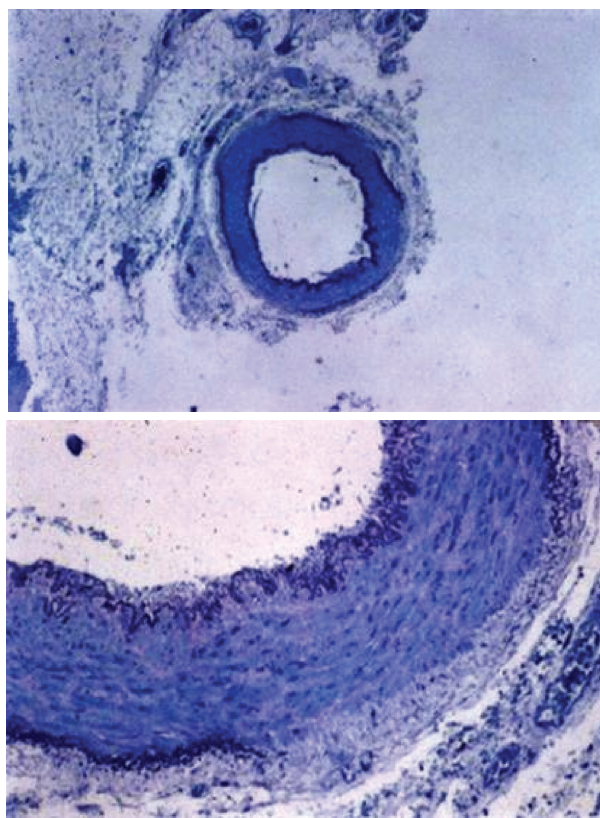


Figure 4. Upper panel: Cross section of an extrasplenic artery in a child with thalassemia intermedia. Irregular conformation of the internal elastic lamina and defects of the adventitia. Lower panel: Part of the same artery. Adventitial defect along with debris of the fragmented original elastic lamina and multiple secondary elastic layers at the endothelial aspect of the arterial wall (Pinkus staining for elastic tissue - Dr. Tsomi's collection).

(9%), as well as recurrent arterial occlusion and others (20%). A recently published multinational study of 8,860 thalassaemia patients from the Mediterranean region and Iran showed that thromboembolic events were 4.38 times more frequent in TI than in TM, and were particularly prevalent in splenectomized patients and patients with profound anaemia (hemoglobin level <9 g/dL).⁴¹ Ischemic strokes have also been observed in combination with cardiac valvular lesions resulting from elastic tissue defect and/or atrial fibrillation.²⁹ However, thrombosis may be a sub-clinical process and may remain undetected. In fact, autopsy findings of thrombi in the microvasculature of lungs and brain have been observed in the absence of clinical manifestations or other known risk factors.⁴²

Right heart involvement

Despite the variable echocardiographic cut-off values for trans-tricuspid pressure gradient applied in different studies, pulmonary hypertension (PHT) represents a prominent complication in TI. Almost 60% of cases in a large cohort of 110 TI patients had developed PHT.³ More specifically, peak systolic tricuspid gradient values >30 mmHg indicative of pulmonary

hypertension were present in 59.1% of patients, while values >50 mmHg were present in 7.3% of cases.³ Other reports have confirmed these findings.⁴³⁻⁴⁵ A recent study showed that pulmonary hypertension is a typical feature of non-transfused TI patients and not a simple age-related effect due to their prolonged survival.⁵ Pulmonary hypertension seems to be the leading cause of congestive heart failure in TI, due to the subsequent right heart insufficiency. In the two largest cardiological studies carried out on TI patients, congestive heart failure was encountered in 5.4% of 110 patients aged 32.5 years and 2.7% of 74 patients aged 28.2 years, respectively.^{3,5} It is important to emphasize that all TI patients with congestive heart failure in both studies had severe pulmonary hypertension and normal systolic left ventricular function. More specifically, echocardiographically determined left ventricular ejection fraction was normal in all cases, while right cardiac catheterization in patients with congestive heart failure showed a normal capillary wedge pressure.^{3,5,43} The combination of high output state and increased pulmonary vascular resistance is thought to be responsible for the development of PHT in TI.^{3,5}

Increased pulmonary vascular resistance in β -thalassemia is multifactorial. The fact that most sub-types of chronic hemolytic anemia may develop pulmonary hypertension suggests that there is a pathogenetic link between the two conditions.⁴⁴ Recently, the role of chronic hemolysis in the development of PHT through the induction of nitric oxide and arginine deficiency resulting in vasoconstriction, has received particular attention.²¹ Hemolysis has also been associated with the coexistent diffuse elastic tissue defect. In fact, degenerative elastic tissue lesions have been encountered in pulmonary autopsies in patients with hemoglobinopathies such as sickle cell disease.⁴⁶ Furthermore, endothelial dysfunction promotes hypercoagulability and *in situ* thrombus formation within the pulmonary vascular bed. In β -thalassemia in particular, the oxidative stress resulting from chronic hemolysis is enhanced by the presence of iron overload and free-radical formation and the expected effect seems to be more pronounced. In addition, iron overload is associated with interstitial pulmonary fibrosis and may affect pulmonary vascular resistance.⁴⁵ As discussed above, hypercoagulability is a well-described, co-morbid state in β -thalassemia, particularly common in non-transfused TI patients. Extensive thromboembolic lesions resulting in the reduction of the total pulmonary vascular bed have been found in the pulmonary arterioles of splenectomized thalassems in post-mortem autopsies.⁴² Lung infections, chest deformities, intrathoracic extramedullary hemopoietic masses and transient LV dysfunction may also contribute to pulmonary vascular resistance.³

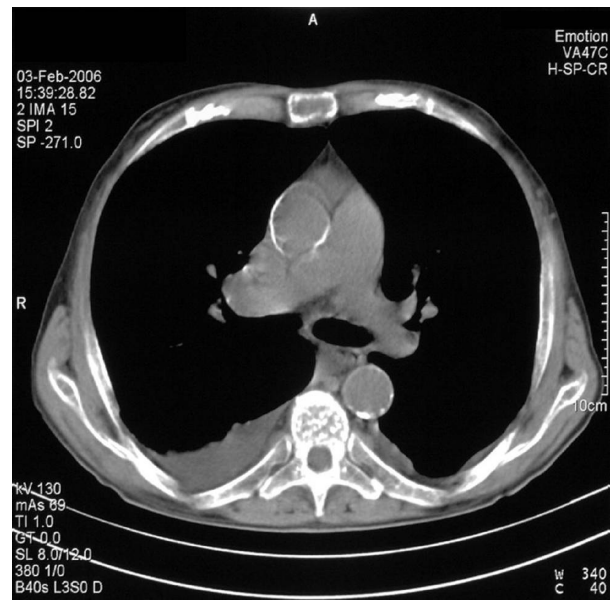


Figure 5. Computed tomography scan of the thorax in a 59-year-old thalassemia intermedia patient with a hemoglobin level of 7 g/dL. Heavily calcified ascending and descending aorta along with pleural effusion due to left heart failure.

Left ventricular involvement

Although right heart failure dominates cardiac involvement in TI, the left ventricle is also affected. As stated above, the left ventricle has to maintain a high cardiac output through a dilated and yet rigid vascular bed, and is therefore in a continuous state of both volume and pressure overload. This compromised left ventricle function leads to a less favorable interaction between left ventricular ejection and systemic arterial compliance. This may contribute to left ventricular impairment.^{47,48} These changes are aggravated by advancing age and are therefore of particular importance in older TI patients.

Besides peripheral vascular disorders, the coexistence of coronary arterial involvement, iron load and valvular lesions renders cardiac function more susceptible to decompensation. Indeed, unstable angina and congestive heart failure were reported in a middle-aged TI patient with severe anemia and heavily calcified, although patent, coronary arteries. Fast evolution of aortic valve calcification to severe stenosis, requiring aortic valve replacement, was observed in another case.^{34,49} Accordingly, the reported left cardiac status in TI patients consists of a pronounced increase in left ventricular diameters, volumes and mass, with impairment of diastolic function but preservation of systolic function. This condition represents an early, sub-clinical manifestation of left heart failure.^{3,5} Thus, during physical exercise or other conditions requiring increased cardiac work load, such as fever or significant anemia exacerbation, a clinically evident left-sided heart failure, usually in combination with pul-

monary hypertension, may be observed. This condition is often seen in older patients, who are often unable to be transfused due to red cell incompatibilities, and whose arteries have become rigid and calcified (Figure 5).⁵

Conclusion

Cardiac involvement in TI is primarily determined by the fact that both ventricles have to maintain a high cardiac output level through a stiff vascular bed. Pulmonary hypertension followed by right heart failure dominates the clinical picture, while systolic left ventricular function is usually preserved in a steady-state condition. The key pathogenetic mechanism is chronic tissue hypoxia and its consequences. From a

cardiovascular point of view, early transfusion therapy, combined with correct iron chelation, may prevent heart damage by reducing a number of crucial factors that cause and maintain cardiac deterioration, such as high output state, hemolysis and hypercoagulability.⁵ However, a complete evaluation of patients' condition is necessary before this kind of treatment is adopted.

Authors' Contributions

AE: concept, design, drafting of the manuscript, final approval of the manuscript submitted; MK: design, drafting of the manuscript, final approval of the manuscript submitted; DF: concept, design, drafting of the manuscript, final approval of the manuscript submitted.

Conflict of Interest

The authors reported no potential conflicts of interest.

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