β-Thalassemia
Cardiovascular Complications

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Cardiovascular complications

- Individuals with TM or TI are at risk for a number of cardiopulmonary complications, including:
- **Heart failure**
- **Arrhythmias**
- **pulmonary hypertension**
- **Pericarditis**

- **Main etiology: Anemia-related cardiac dilatation, Cardiac iron deposition**
- **The principal interventions: transfusions & iron chelation**

Cardiac complications

The causes are multifactorial and include:

- Chronic anemia,
- High cardiac output related to chronic tissue hypoxia,
- Cardiac iron deposition,
- Splenectomy,
- Increased pulmonary vascular resistance,
- Vascular dysfunction due to oxidative stress,
- Pulmonary arterial hypertension,
- Vitamin D deficiency, and others.
- The general consensus is that iron accumulation plays the most significant role and can cause myocardial fibrosis and necrosis ⟶ **CHF**

Adaptive Cardiac Physiology in TM

- **Anemia** → **chronic high-output state** →

The larger cardiac dimensions, stroke volumes, heart rate → higher resting oxygen consumption and decreased reserves → increased oxidative stress*, independent of the free-radical effects of iron.*

- **lower the systemic vascular resistance** (peripheral arterial vasodilation) → low diastolic blood pressure. → endothelial toxicity of iron overload.

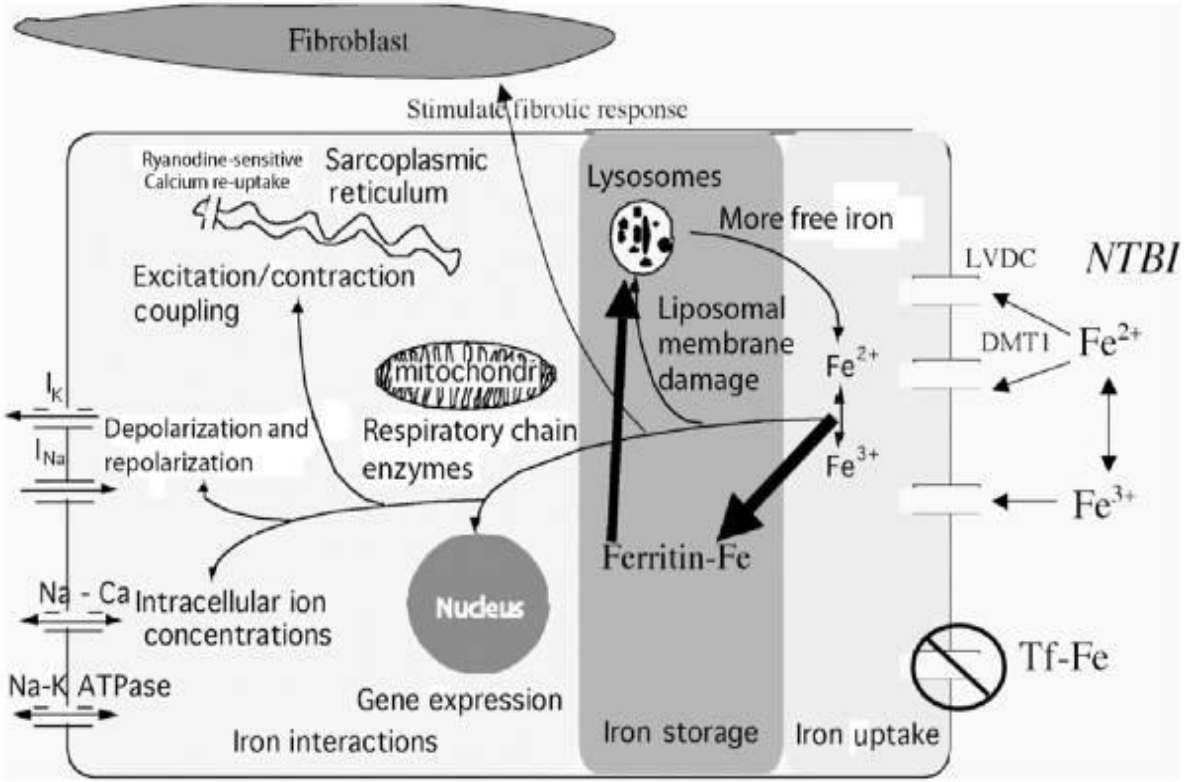
- Increased LVEF because of decreased afterload and increased preload.

Iron Overload

- **Iron mediated cardiac toxicity (*Increased iron absorption and blood transfusion therapy*).**
- **Iron-mediated endocrine toxicity**

- Iron is toxic to all the endocrine glands that support the heart.
- **Hyperglycemia** and insulin resistance are **powerful oxidative stressors** to the heart, worsening the effects of iron overload.
- Iron may also poison the thyroid and parathyroid gland, impairing metabolism and **calcium** regulation respectively.
- Iron-mediated adrenal insufficiency may also manifest itself during metabolic stress.
- Deficiencies of growth hormone and the sex steroids impair cardiac function.

IRON TOXICITYY



- NTBI is taken up by cells that have active uptake mechanisms such as the L-type calcium channel.(parenchymal cells of the liver, heart, and endocrine organs).
- **NTBI, which is capable of generating toxic oxygen free radicals, is immediately buffered by the cytosolic ferritin, degraded to hemosiderin, and stored in the lysosomes**.
- When the intracytosolic buffering mechanisms fail, toxic labile iron levels rise in the cardiomyocyte, resulting in oxidative damage to cell membranes and ion channels.
- **The free iron catalyzes the formation of hydroxyl radical, is highly reactive, and attacks lipids, proteins and DNA.**
- These reactive oxygen species in turn can cause tissue damage, inflammation, and fibrosis
- **Oxidative stress-mediated iron toxicity** also increases the lysosomal fragility and decreases mitochondrial inner membrane respiratory enzyme activity, protective antioxidant enzyme activity, myofibril elements, and number of mitochondria.

Iron toxicity mechanism

Increased levels of intracellular free iron are toxic.

mechanisms:

(1) damage to membranes by lipid peroxidation;

(2) damage to mitochondria and the respiratory enzyme chain;

(3) interference with electrical function, including ryanodine release channel interference;

(4) **promotion of cardiac fibrosis,**

(5) altered gene expression.

Leading to : **Heart failure, pericarditis, arrhythmias, and pulmonary hypertension**

Splenectomy

- **Splenectomy is a strong risk factor for intravascular thrombosis and pulmonary hypertension**

- The spleen plays a critically important role in removing **hematologic debris** from the cardiovascular system.
- Platelet fragments, and red cell fragments are **powerful pro-coagulants**. They also **inhibit nitric oxide, stimulate vasoconstricting substances** such as endothelin and vasoconstricting prostaglandins, and produce **endothelial proliferation**.
- The spleen also removes brittle senescent red cells from the circulation, suppressing intravascular hemolysis.
- Cell-free hemoglobin is a powerful oxidant and scavenger of nitric oxide.

Nutritional Deficiencies / lung disease

- The hemoglobinopathies are a hypermetabolic state and inherently produce chronic oxidative stress.
- Broad-spectrum nutritional deficiencies are prevalent and may reinforce disease toxicity.

  Fat-soluble vitamin depletion: vitamin A, D, E, and K, suggesting fat mal-absorption.
- Vitamin D deficiency is associated with increased cardiac iron toxicity and decreased function
- trace metals: selenium, zinc, and copper.
- B-vitamin levels are also low, (thiamine, riboflavin, and folate), most likely from consumption during ineffective erythropoiesis.

Lung Disease

Patients with thalassemia major develop mild, nonprogressive restrictive lung disease.

PULMONARY HYPERTENSION

Mechanisms

- A complex pathophysiology of pulmonary hypertension in thalassemia.
- **Increased cardiac output and diastolic dysfunction** cause abnormal loading of the pulmonary artery.
- Lung disease can exacerbate night-time hypoxia, a powerful stimulus for vasoconstriction.
- Iron, phosphatidylserine-expressing hematologic debris, free hemoglobin, and other circulating angiotrophic factors cause **vasoconstriction and intimal proliferation and thrombus formation** .

Clinical Cardiac Manifestations

- The most common clinical manifestations:
- **Dilated cardiomyopathy (HF)**
- **Arrhythmia, predominantly atrial fibrillation (AF).**

- **Frequency of Cardiomyopathy:** In a US survey in 2004, the number of TM patients of all ages receiving cardiac medication was found to be 10% (35/341). In a worldwide survey conducted in 2012, the incidence of HF at first T2* scan was 3.1% (107/3445).Alternatively, the prevalence of detectable left ventricular (LV) dysfunction is higher than the prevalence of clinically manifest HF. In one study of 167 Italian patients, LV dysfunction was found in 19 patients (11.4%)

- Ventricular diastolic dysfunction(restriction) , Decreased left atrial function, late onset LV systolic dysfunction
- Impaired right ventricular (RV) function
- Impaired endothelial function in iron overload
- Other relevant iron-overload complications that may affect the heart include hypothyroidism, diabetes mellitus, hypoadrenalism, growth hormone deficiency, and hypoparathyroidism.

CHF
Clinical sign & symptoms

- Many symptoms typically present in HF are common in anemia.
- More reliable clinical markers: changes in symptoms, such as increased exertional dyspnea.
- Additional symptoms: abdominal or back pain, nausea, dizziness/presyncope (arrhythmias).
- **Failure to tolerate standard transfusion**s.
- Orthopnea and peripheral edema are late symptoms.
- **The absence of the clinical features of HF does not exclude severe cardiac impairment.**
- **The classic signs of HF may appear late, and this has the potential to delay diagnosis and appropriate intensification of chelation.**
- An elevated BNP is expected but is a late sign.

Evaluation of cardiac dysfunction

- **The natural history and clinical course in untreated patients is: clinically silent myocardial iron accumulation for many years, followed by malignant arrhythmias / acutely impaired myocardial function in early adulthood.**
- In children who have received regular transfusions and iron chelation, cardiac loading before the age of 10 years is uncommon.
- **ECG**: New-onset electrocardiographic abnormalities are usually evident in TM patients with HF
- supraventricular arrhythmias, RV involvement (S_1Q_3 pattern and right-axis deviation), new-onset T-wave inversion beyond lead V_1, decrease in QRS height. In patients without HF, an abnormal ECG was found in 46% (T-wave abnormalities & RBBB)
- **Echocardiography** for early detection of subtle cardiac dysfunction.

- There were significantly lower values of myocardial performance index, longitudinal strain, circumferential strain, area strain, and radial strain in TM patients compared with the controls. The myocardial performance index was correlated with T2*MRI.

CMR T2*

- MRI to assess cardiac iron overload: as a baseline prior to starting chronic transfusion therapy. The timing of MRI depends on expected degree of iron overload.
- Myocardial iron deposition can be quantified reproducibly with myocardial T2*, a relaxation parameter that arises principally from local magnetic field inhomogeneities that are increased with iron deposition.

- Low T2* (< 20msec) indicates iron deposition. *The importance of using T2* MRI was illustrated in an international survey involving 3095 patients with beta thalassemia major. Approximately half had evidence of cardiac iron deposition on first MRI, and future development of heart failure correlated strongly with reduced T2* on MRI.*
- Cardiac T2* values <**10 ms**: at high risk of subsequent **cardiac decompensation** and warrant aggressive iron chelation therapy.

Cardiovascular Function and Treatment in β-Thalassemia Major

(A Consensus Statement From the American Heart Association)

- Acute decompensated heart failure in thalassemia is a medical emergency.
- Intensive **iron chelation therapy** could completely restore cardiac function in most patients with preclinical dysfunction and some with overt HF.
- Close electrocardiographic and hemodynamic monitoring;
- Correction of electrolyte, glucose abnormalities, and optimization of renal, hepatic, and thyroid function; searching for other precipitating factors such as infection; and initiation of chelation therapy.
- Recognition of severe cardiac siderosis by T2* CMR and intervention with suitable treatment, before the onset of symptomatic HF, is associated with improvements in ventricular function.

Prediction of HF in TM

- **ferritin , liver iron:** the serum ferritin level may not reflect the individual total body iron load and cardiac risk.
- **Cardiac Iron (T2*)** cardiac T2* is the most significant predictor of the development of HF
- The lower limit of normal is 20 ms, a threshold below which myocardial T2* in normal subjects does not occur.
- T2* calibration data suggest 20 ms equates to 1.1 mg/g iron dry weight, which is approximately twice the reported normal mean level of human myocardial iron.
- The probability of a reduced LVEF increases as cardiac iron increases (cardiac T2* falls).
- *The longitudinal follow-up of patients has shown that cardiac T2* <10 ms predicts HF.* ***Of patients who developed HF, 98% had a cardiac T2* <10 ms. Patients with a cardiac T2* <6 ms have a 50% likelihood of developing HF within 12 months if no change in iron chelation treatment is instituted.***

(low risk for HF, >20 ms; intermediate risk, 10–20 ms; and high risk, <10 ms).

A normal cardiac T2* has a very high predictive value for exclusion of HF for 12 months.

LV Ejection Fraction & CMR

- **Changes in LVEF are a late event** compared with the early warning of cardiac loading seen with intermediate levels of cardiac T2* (10–20 ms).
- As myocardial stores increase in the heart, ferritin breakdown increases into particulate hemosiderin, which is a form of ferrihydrite (hydrated iron oxide). This disrupts the local magnetic field homogeneity, causing reduced T2* values in inverse relation to iron concentration. Iron that is safely stored in ferritin or hemosiderin is nontoxic, yielding hearts with low T2* and normal function; however, high iron stores predispose patients to development of cardiac dysfunction in the future.
- The early decrement in LVEF may be modest and within the normal range until iron storage capacity is exhausted. The relation between the measured T2* and LVEF is therefore shallow until a critical level is reached, after which rapid deterioration may occur.
- The T2* technique can identify those patients who may benefit from earlier chelation therapy to avoid overt HF.
- Because T2* measures storage iron in the form of hemosiderin, and **acute toxicity is related to free iron**, LVEF can improve faster than the cardiac T2* with acute chelation treatment, which can drive the free iron to zero despite the presence of high tissue levels of hemosiderin.

Management

❑ Acute Decompensated HF

❖The aim of treatment in acute HF is to keep the patient alive so that iron chelator treatment can detoxify the cardiac iron.

❖ Immediate/ continuous **intravenous iron chelation** treatment with deferoxamine 50 mg·kg·d

1. The patient should have continuous electrocardiographic and hemodynamic monitoring.
2. Introduce **deferiprone** as soon as possible at a dose of 75 mg·kg·d
3. Avoiding aggressive **inotropic therapy.**
4. Only **minimum diuretic treatment** should be used because of the importance of maintaining preload.
5. Supportive hemodynamic therapy to maintain cerebral and renal perfusion,
6. Blood pressure is typically low in TM patients and should not attract specific therapy if renal and cerebral perfusion is maintained.

Management ; Additional notes

1. Cardiac arrhythmias are common and often respond to continuous iron chelation treatment.
2. normalization of electrolyte/ glucose abnormalities
3. use of magnesium infusion to stabilize ventricular arrhythmia. (amiodarone is the drug of choice to treat hemodynamically significant arrhythmias)
4. Hydrocortisone on the presumption of inadequate adrenal response to stress.
5. Check thyroid, liver, and renal function and calcium, magnesium, vitamin D, carnitine, and other metabolic parameters and correct these when necessary.
6. Maintain Hb between 10 and 12 g/dL. This may require frequent small-volume transfusions.
7. Search for precipitating conditions such as infections.
8. There is no evidence to support the initiation of ACE inhibitors or angiotensin 2 receptor blockers
9. The introduction of β-blockers as an antifailure treatment has the merit of reducing the propensity to arrhythmia
10. Cardiac T2* should be performed as soon as is practical. If cardiac T2* is >20 ms, then myocarditis should be considered as a cause of HF, using a standard CMR myocarditis protocol.

Management; drugs

- Baseline preload is high because of chronic anemia.
- Diuresis can lower wall stress and improve symptoms attributable to fluid overload, overdiuresis can precipitate acute renal failure by excessive reduction of preload
- Older patients may have a restrictive physiology that does not tolerate either overfilling or underfilling.
- Most inotropes **increase intramyocyte calcium levels**, may worsen **oxidative stress**, and **increase electrical automaticity**, which may act synergistically with iron-mediated toxicity to the detriment of myocyte function.
- Inotropes should be used with great caution and reserved for desperate situations and that doses should be minimized whenever possible.

Treatment of Patients With Cardiac Siderosis With Abnormal or Falling LVEF

❖**Subclinical HF,(asymptomatic):**

- Such patients require intensification of chelation. *This may only require dose adjustment of current treatment or measures to improve compliance.*
- Different responses in the LVEF to iron chelators.
- *Data from 2 randomized controlled trials:*
- *subcutaneous **deferoxamine** did not significantly improve LVEF in mild to moderate cardiac iron overload.*
- *significant increases in LVEF with **deferiprone**.*
- *LVEF does not increase with **deferasirox** treatment in cardiac siderosis.*
- The improvement in LVEF probably reflects relief of subclinical cardiotoxicity; it is associated with a lower risk of developing HF and is a good prognostic sign.
- If cardiac function fails to improve: consider additional factors, other cardiomyopathy or other concomitant pathology.

ARRHYTHMIA

Arrhythmias in TM are a mixture of triggered and reentrant arrhythmias.

❖**Mechanisms: 1-Chronic volume overload, 2- Iron toxicity**

- **Arrhythmias or sudden death may be present without signs of cardiac disease and only if myocardial siderosis is present**.
- Iron overloaded cardiomyocytes have a **shorter action potential** duration than iron-free cardiomyocytes in the same heart. **An alteration in ion currents characterized by reduced Na+ currents** may be an underlying mechanism.
- **This electrophysiological heterogeneity, including the patchy nature of cardiac iron deposition, may provide the substrate for triggered and re-entry activity.**
- Therefore, it is reasonable to assume that early detection of arrhythmic risk, through a careful ECG analysis, may have significant clinical impact in the management of these patients.
- **Strong evidence suggests that myocardial iron overload is less correlated with the development of arrhythmias than to heart failure…….**

Arrhythmia

- **Atrial fibrillation** (AF), atrial flutter (AFl), and intra-atrial re-entrant tachycardia are the most common rhythm disturbances.
- AF is a common finding on 24-hour Holter monitoring in patients without cardiac dysfunction with a prevalence up to 20%.
- The early detection of AF in patients is of pivotal importance for the management of clinical follow-up and for the optimization of medical therapy, in order to evaluate the opportunity of prophylactic anticoagulation treatment or nonpharmacologic approaches for stroke prevention
- Supraventricular ectopic beats may be present in the earlier stage of the β-TM cardiomyopathy, while malignant arrhythmias are usually present in the advanced stage of the disease.
- **Ventricular arrhythmias** are more specific for iron cardiotoxicity
- **SCD** accounts for about 5% of cardiac deaths and is associated with severe iron overload and increased QT dispersion (QTd), which suggests iron-mediated repolarization abnormalities and torsades de pointes as a causative mechanism.
- Cardioembolic stroke has been reported in 0.25–0.46% of patients.

ECG findings

- An abnormal ECG was found in 46% of β-TM patients without HF. (T-wave abnormalities/ RBBB)
- **P wave dispersion**: The association between PD and increased risk of atrial fibrillation also has been confirmed in clinical conditions. *a cut-off value of 111 ms for P max had a sensitivity of 80% and a specificity of 87%, and a cut-off value of 35.5 ms for PD had a sensitivity of 90% and a specificity of 85% for early detection of new onset of AF episodes in β-TM patients..*
- An increased dispersion of ventricular repolarization is considered to provide the electrophysiological substrate for life-threatening ventricular arrhythmias in several clinical conditions
- ***QT dispersion*** *cut-off value >70 ms and JTd cut-off >100 ms: high-risk sudden death*
- **Increased QRS duration, QRS fragmentation** : increased risk of arrhythmic events and mortality

Sudden Cardiac Death

A high incidence of sudden death among young men without clinical evidence of cardiac disease, with a 27% occurrence rate over a 26-year observation period.

ECG: **a higher degree of QT and JT dispersion.**

There is a need to reassess the thalassemia population for the incidence of electrocardiographic abnormalities that might increase the propensity to malignant ventricular arrhythmia.

Careful analysis of the ECG for QT and JT dispersion/ Holter ECG monitoring

CONCLUSION FOR ARRHYTHMIA

- **Cardiac arrhythmias (AF) are frequent in β-TM patients, particularly in the advanced stage of the disease.**
- **The ECG analysis should include the measurement of P wave and QT interval dispersion;**
- **The echocardiogram should include the evaluation of the atrial electromechanical delay or left atrial function analysis.**
- **These noninvasive tools may help to identify β-TM patients at high risk of atrial fibrillation onset or sudden cardiac death, even when cardiac function is conserved.**
- **Myocardial iron overload is less correlated with the development of arrhythmias than to heart failure.**
- **24-hours ECG Holter monitoring or cardiac loop recordings to early detect atrial fibrillation or malignant arrhythmias.**

Thalassemia Intermedia

Cardiovascular involvement represents a well-known complication and the primary cause of mortality both in TI.

1. **Iron overload**
2. **High output state**

- TI patients are exposed to prolonged tissue hypoxia(anemia , HbF,).

- The clinical course is complicated by the multiple effects of chronic hemolytic anemia and resultant tissue-hypoxia as well as by their compensatory reactions.

TI; clinical presentations/ complications

Long lasting hemolytic anemia / ineffective erythropoiesis

- **Anemia, high cardiac out put status**
- **Iron overload**
- **Pulmonary hypertension**
- **Hypercoagulation**
- **Thromboembolic disease(Hemolysis-induced tissue injury)**
- **Extramedullary hematopoietic state**
- **Splenomegaly**
- **Bone deformity**
- **Skin ulcer**

High cardiac output state in TI patients

chronic anemia + increased HbF

↓

prolonged tissue hypoxia

↓

extramedullary hemopoiesis, splenomegaly, hepatomegaly

high output state

through **peripheral vasodilatation** and **shunt development**.

Iron overload

Mechanisms:

1. Ineffective erythropoiesis,

2.Hemolysis,

3.Increased intestinal iron absorption.

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.*

Significantly, the pattern of myocardial iron distribution was frequently heterogeneous in TI patients.

Pulmonary hypertension; Right heart involvement

pulmonary hypertension (PHT) represents a prominent complication in TI.

Etiology: The combination of high output state and increased pulmonary vascular resistance

—*Almost 60% of cases in a large cohort of 110 TI patients had developed PHT. 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.*

- *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. 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.*

- Increased pulmonary vascular resistance in β-thalassemia is multifactorial.

1.Recently, the role of chronic **hemolysis** in the development of PHT through: the induction of **nitric oxide and arginine deficiency** resulting **in vasoconstriction** , coexistent **diffuse elastic tissue defect.**

2.**Endothelial dysfunction** promotes **hypercoagulability** and *in situ* **thrombus formation within the pulmonary vascular bed**.

3. iron overload and free-radical formation.

4. iron overload is associated with interstitial pulmonary fibrosis and may affect pulmonary vascular resistance.

5.hypercoagulability is 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 thalassemics in post-mortem autopsies.*

6. Lung infections, chest deformities, intrathoracic extramedullary hemopoietic masses and transient LV dysfunction may also contribute to pulmonary vascular resistance.

Hypercoagulability

Hypercoagulability is a well-established characteristic of β-thalassemia.

1.**Underlying genetic defect,**

2. **hemolysis** (The free α-globin chains), iron overload(the free iron): **oxidative tissue damage/ oxidative damage to the red blood cell membrane proteins.** exposure of negatively charged phospholipids which create **a precoagulant surface.**

3. Impaired endothelial function

4.**impaired NO bioavailability**. Oxidative damage resulting from hemolysis and iron load leads to an increase expression of adhesion molecules ICAM and VCAM and impaired NO bioavailability.

5.**Enhanced PLT aggregation**, while splenectomy increases platelet counts and induces membranes abnormalities that further increase platelet aggregation.

6. Deficiency of the coagulation inhibitors, protein C and protein S, the elevated levels of thrombin-ATIII complex due to splenectomy and/or liver dysfunction.

7. A strong inflammatory reaction .(elevated circulating levels of cytokines and adhesion molecules and the monocyte and neutrophil activation),

Hemolysis-induced tissue injury

vascular involvement and elastic tissue abnormalities

- **Chronic hemolysis** and **iron overload:** sources of strong oxidative stress.
- Free heme and the red cell membrane elements (a negative effect on nitric oxide and arginine availability) promotes vasoconstriction / endothelial/ elastic tissue injury dysfunction.

Thalassemia-related hypercoagulability + elastic tissue defects ⟶ **high frequency of thromboembolic complications.**

Elastic tissue abnormalities : ⟶ **vascular complications**

(fatal cerebral hemorrhages, anginal symptoms, ascending aorta aneurysm formation and gastrointestinal bleeding)

- the prevalence of such events was higher in splenectomized / or TI patients than in/ TM or non-splenectomized ones.

- Ischemic strokes have also been observed in combination with cardiac valvular lesions resulting from elastic tissue defect and/or atrial fibrillation.

- **thrombosis may be a sub-clinical process and may remain undetected.**

Left ventricular involvement

- **A continuous state of both volume and pressure overload.**
- less favorable interaction between left ventricular ejection and systemic arterial compliance and left ventricular impairment
- Peripheral vascular disorders, the coexistence of coronary arterial involvement, iron load and valvular lesions renders cardiac function more susceptible to decompensation.
- unstable angina and congestive heart failure(in a middle-aged TI patients)
- aortic valve calcification to severe stenosis
- **left cardiac status in TI patients consists of:**
- increase in **left ventricular diameters**, **volumes and mass**, **impairment of diastolic function** but **preservation of systolic function.**

-This condition represents an early, sub-clinical manifestation of left heart failure.

-Early diagnosis of subclinical LV dysfunction by echocardiography, CMR

-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 pulmonary hypertension, may be observed.

TI
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 RV failure dominates the clinical picture.
- systolic LV function is usually preserved in a steady-state condition.
- The key pathogenetic mechanism is **chronic tissue hypoxia** and its consequences.
- **Hemolysis-induced tissue injury**

- 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.(From a cardiovascular point of view)


سپاس