Mechanisms of and obstacles to iron cardiomyopathy in thalassemia

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1. ABSTRACT

   Thalassemia is anemia of variable severity, arising from mutations of genes encoding the hemoglobin alpha and beta chains. Severe thalassemia is associated with iron overload, tissue lesions, and high risk for cardiovascular complications, and iron-mediated cardiomyopathy is the main cause of death in this condition. Thalassemia major (TM) patients exhibit cardiovascular abnormalities consistent with chronic anemia; these include enlargement of the ventricular chambers, increased cardiac output, and reduced total vascular resistance. Cardiac iron overload in TM patients due to long-term transfusion can cause further chamber dilation, decreased contractility, and arrhythmia. Paradoxically, many such patients remain asymptomatic until decompensation occurs. For decades, magnetic resonance imaging and echocardiography have been performed to detect advanced cardiac dysfunction; however, reliable evaluation tools for the early detection of cardiac abnormalities are currently in demand. This article reviews the mechanisms underlying the development of heart disease in thalassemia and strategies for therapeutic intervention in TM patients with congestive heart failure.

2. INTRODUCTION

   Homozygous beta-thalassemia is a genetically inherited hemoglobin (Hb) disorder characterized by dyserythropoietic anemia (1,2) that affects people in various parts of the world, from the Mediterranean basin to Asia. Regular transfusion therapy improves the quality of life of patients but results in a catastrophic iron overload. Following saturation of the reticuloendothelial iron stores, iron deposition increases in parenchymatous tissues, including, the endocrine, hepatic, and myocardial parenchyma. Cardiac iron deposition typically exhibits no harmful effects for many years but causes arrhythmia, systolic/diastolic dysfunction, and congestive heart failure (CHF) during the second or third decade of life. Chelation therapy prolongs life and improves its quality but may induce cardiac toxicity, which is the leading cause of death, generally in the third or fourth decade of life (3). Noncompliance with chelation therapy contributes to these deaths, and some patients die despite apparently adequate liver iron chelation (4).

   Conventional cardiac surveillance comprising
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annual electrocardiography (ECG), Holter monitoring, and echocardiography has proven quite ineffective for detecting preclinical cardiac iron overload. Changes recorded during ECG mainly reflect left ventricular (LV) hypertrophy and nonspecific ST-T wave changes due to volume overload. Conduction abnormalities, which mainly comprise atrioventricular and bundle-branch block, typically appear following the appearance of symptomatic disease. Holter ECG monitoring is useful for detecting atrial or ventricular arrhythmia in thalassemia major (TM) patients experiencing palpitations (5).

Echocardiographic abnormalities in ventricular systolic function are almost universally observed in TM patients but are often not detectable until a state of overt CHF ensues (6). By performing tissue Doppler echocardiography (TDE), regional myocardial wall motion abnormalities can be detected during the early phases of preclinical cardiac dysfunction (7). Radionuclide angiography and magnetic resonance imaging (MRI) have been shown to be effective for detecting preclinical systolic dysfunction (8).

The detection of impaired myocardial relaxation is valuable for the early diagnosis of cardiac iron toxicity; however, this approach has not been well documented in the case of thalassemic cardiomyopathy (9). Standard echocardiographic techniques for assessing diastolic function are usually confounded by cardiac volume overload, which is inevitable in chronic anemia (10). Only patients with advanced cardiac injury exhibit restrictive cardiomyopathy, although most patients exhibit some degree of systolic dysfunction or severe pulmonary hypertension (10). Prior to the introduction of iron chelators in clinical settings, any type of marked cardiac systolic dysfunction was usually a predictor of impending cardiac death; today, continuous deferoxamine (DFO) infusion or oral deferiprone (L1) therapy or a combination of these has proven effective in restoring failing hearts to a satisfactory status (8,11-13). This review summarizes the basis of cardiac injury and therapeutic intervention strategies for TM patients with CHF.

3. PATHOPHYSIOLOGY OF IRON-MEDIATED CARDIOMYOPATHY

3.1. Normal cardiac physiology in TM

Transfusions are used for increasing the concentration of normal Hb, which is required for transfer of oxygen to tissues. That is initiated to arrest the destructive effects of ineffective erythropoiesis and marrow expansion in TM. It is typically performed by maintaining the pretransfusion Hb levels at 9–10 g/dL as a transfusion trigger; this induces mild chronic anemia that the patient’s body compensates for with increased cardiac output (CO) (14), which results in chamber dilatation and myocardial hypertrophy (15-17). However, cardiac compensation for chronic anemia may not always be effective, and some patients manifest left-sided heart failure, exertional dyspnea, cough, fatigue, lung rales, and cardiac gallop rhythm. Right ventricular (RV) dysfunction arises more frequently than LV dysfunction. Further, TM patients usually experience fatigue, abdominal pain, and liver distention, which are possibly of non-cardiac origin (18). Thus, TM represents a chronic, high-output state that is induced by volume-loaded ventricles rather than by an increased heart rate.

In order to maintain the mean systemic blood pressure within the normal range in the presence of high CO, the body is required to lower the systemic vascular resistance (14). Similar to the physiological compensation that occurs during exercise, systemic vascular resistance is reduced via peripheral arteriolar vasodilation, which leads to wide pulse and low diastolic pressures. The systolic blood pressure of thalassemia patients is reported to be comparable with that of age-matched control subjects; however, the diastolic pressure of thalassemia patients is significantly lower than of non-thalassemic patients (19), and the hearts pump greater blood volumes against lower peripheral resistance in the former. Further examination reveals a positive hepatojugular reflux with neck vein distention when in the appropriate position. A third heart sound, peripheral edema, and ascites may be observed. Chest x-ray frequently reveals cardiomegaly; however, features of pulmonary congestion are not always observed. An echocardiogram is expected to demonstrate biventricular dilation and reduced function in both ventricles (20) in the case of early RV decompensation due to iron deposition (5). Understanding the normal physiological parameters at baseline is crucial for interpreting cardiac tests and evaluating responses to pathological stimuli.

3.2. Pathophysiology of cardiac iron deposition

Iron accumulates to a greater extent in the ventricular septum and free walls than in the atria, and it tends to remain concentrated in the epicardium (21,22). In the heart, iron exists in 3 forms, namely, as labile cellular iron, ferritin, and hemosiderin (23), and it changes from one form to another. Although labile cellular iron is the most toxic form that stimulates the generation of free radicals, which harm cells via peroxidation of the membrane lipids and proteins, this form is considered the most amenable to chelation. In the heart, peroxidation impairs the mitochondrial respiratory chain function, and this is clinically manifested as impaired cardiac muscular contractility and the development of CHF. Histological examination of the iron-loaded myocardium reveals hypertrophy of individual myocytes and deposition of brown granular material within the cytoplasm. Iron granules are limited to the perinuclear area in cases of mild cardiac dysfunction but may occupy large areas in the myocardial fibers in cases of significant dysfunction. Only mild fibrosis is observed in most cases, suggesting that cardiac dysfunction may be reversible with proper treatment.

Intracellular lysosomes store the relatively nontoxic forms of hemosiderin and ferritin; However, once this storage capacity is overwhelmed, iron that is nontransferrin bound can be released, which is highly toxic, leading to the reduction of ferric to ferrous iron and the promotion of hydroxyl radical formation through the Haber-Weiss reaction. Cytoplasmic granules or siderosomes contain many iron particles, and these
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Structures can be assessed by performing X-ray microanalysis (24). Histopathology is iron overload states lends further support toward a deleterious effect of iron on the cardiovascular system (25,26). In cases of advanced iron overload, rust-brown coloration in the myocardium due to preferential iron deposition in the subepicardial layers is a common autopsy finding. Mild to moderate fibrosis in the absence of inflammation is also observed. Electron microscopy reveals the disruption of sarcomeres together with iron-containing granules present between myofibrils. Other pathological findings such as impairment of the cardiac conduction system, myocardial hypertrophy, chamber dilation, pericardial effusion, and focal myocardial degeneration are invariably noted (24,27-29). In cases of less advanced iron loading, autopsy reveals an intermediate phenotype with a similar but less extensive pattern of iron distribution (25,26,30,31). Other relevant findings include chronic pulmonary arterial hypertension, RV abnormalities, coronary wall infiltration, pericarditis, and valvar disease (26,30-32). Physiologically, chronic anemia in TM causes volume overload and increases the heart contractility (Frank-Starling’s Law), which leads to early heart dysfunction when combined with cardiac iron loading. Cardiac involvement includes heart failure, arrhythmia, and pericarditis. Although ventricular failure is predominantly left-sided, right-sided failure is also recognized to play a significant role in early cardiac dysfunction (33). It is vital to note that patients with high CO exhibit higher ejection fraction (EF) cut-off values than those suggested for normal individuals. An EF of more than 60% is considered normal (34).

3.3. Oxidant injury and non-transferrin-bound-iron (NTBI) uptake in iron-mediated cardiotoxicity

Nitric oxide (NO) from the blood or endothelial cells diffuses into red blood cells (RBCs) but cannot perform its vasodilatory function following diffusion. NO entering RBCs first binds to the heme moiety in Hb and is then transferred to cysteine 93 of the beta-chain, forming Hb-derived S-nitrosothiol that is associated with the RBC membrane; it then binds to the cytosol face of band 3 to form AE1-S-nitrosothiol. NO is usually released from this membrane site due to deoxygenation, following which it enters circulation and performs its vasodilatory function. In thalassemia, Hb may be oxidized at the cysteine 93 site of the beta-chain (35), and band 3 undergoes oxidative clustering (36). These alterations inhibit the release of NO; thus, lack of vasodilator activity may contribute to pulmonary hypertension that is reported to occur in beta-thalassemia intermedia (17). The increase of plasma iron turnover in beta-thalassemia results in saturation of the iron storage and transport proteins, and emergence of “free” plasma iron pool (37). Cardiomyocytes are sensitive to the activity of redox-active iron and the accompanying elaboration of the hydroxyl (OH) radical. Iron-mediated oxidative stress causes lipid peroxidation, mitochondrial injury, membrane disruption, and contractile dysfunction, accompanied by myocyte death (37-40). In vivo, endothelial dysfunction, increased oxidative stress, L1 and DFO administration, and iron deficiency exert beneficial biological effects in thalassemia (41-45).

The characterization of iron transport mechanisms may provide a critical, independent therapeutic method to complement chelation. Iron uptake primarily occurs via the uptake of NTBI (46-49). NTBI in plasma is believed to catalyze the formation of reactive radicals in the circulating blood of patients with iron overload, resulting in the accumulation of oxidation products. Both ferric and ferrous ions are absorbed during tissue culture, and membrane-bound enzymes facilitate their conversion from one species to another (46). Dimethyl transferase 1 (DMT1) has been implicated in iron transport across the intestine but has not been definitively linked to cardiac iron transport (47). L-type voltage-dependent channels (LVDCs) have been noted to mediate murine cardiac iron transport, accounting for at least 50% of the cardiac iron uptake (49). NTBI uptake is considerably rapid in cell cultures (48). Further, the iron uptake rate increases dramatically when myocytes are preexposed to iron, suggesting the involvement of a positive-feedback regulatory mechanism (48,50).

The above indicates that relatively brief periods of very poor chelator compliance may lead to significant cardiac iron deposition in vulnerable individuals. Abnormal cardiac MRI T2* values are rarely recorded for patients aged less than 10 years, even in cases where the liver iron concentration is high (19). The prevalence of abnormal T2* values increases to more than 50% in late adolescence and early adulthood; this indicates relatively “precipitous” iron loading. This transition corresponds to the age at which chelation compliance is most difficult; however, developmental factors such as puberty cannot be excluded. Both the level and duration of NTBI exposure are probably vital factors influencing cardiac iron uptake. The NTBI level is apparently correlated with a function of transferrin saturation and the ability of the liver to buffer and store iron. Diseases such as cirrhosis that impede this function of the liver could also increase the vulnerability of a patient to extrahaepatic iron deposition (24).

Although high liver iron levels probably increase the risk to the heart, it cannot be stated that low liver iron levels are definitely protective. Chronic exposure to low levels of NTBI may be sufficient to induce cardiac iron overload. The levels of labile iron species are suppressed during DFO therapy but increase once again within hours from the time at which infusion is discontinued (51). Therefore, the duration for which DFO infusion is performed per day may be as important to the heart response as is the dose of the drug administered per day. Oral L1 treatment increases the plasma NTBI levels due to iron mobilization but does not produce labile plasma iron (LPI), indicating that L1-chelated iron in plasma is not redox active. Further, oral L1 treatment is reported to eliminate LPI species in patients. A previous study described an approach that enabled the assessment of LPI susceptibility to in vivo or in vitro chelation and the potential of LPI to cause tissue damage, such as is observed in iron overload (51). On entry into a myocyte, NTBI is rapidly buffered by ferritin, and this limits its potential to induce redox damage or participate in other harmful cellular interactions. Within hours, ferritin-iron complexes are visible in intracellular siderosomes for long-term storage (52-54).
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From a magnetic perspective, “free-iron” species at physiological concentrations have minimal effects on the MRI T2 or T2* values. On binding to ferritin, iron decreases homogeneity in a magnetic field, resulting in detectable changes in the T2 and T2* values. When compared with freely diffusing ferritin molecules, clusters of these molecules or the products of their breakdown, such as those present in siderosomes, produce considerably larger changes in the T2 or T2* values for the same iron concentrations (55). MRI predominantly detects long-term storage deposits of iron rather than functionally active iron. This observation explains why some individuals do not exhibit cardiac symptoms despite massive cardiac iron deposition. Nevertheless, all buffering systems have a limited capacity or can be disrupted by other factors. In such situations, the free iron levels within the cell increase, causing destruction via redox reactions, gene modulation, and direct interactions with ion channels (40,54,56,57). Iron catalyzes the production of free radicals via the Haber-Weiss reaction, thus causing oxidative membrane damage throughout the cell. The oxidation of iron in siderosomes renders these structures more fragile and competent; this in turn may lead to the release of additional redox-active iron species, indicating the possibility of a positive-feedback system (57,58). This may explain the occurrence of catastrophic hemodynamic collapse in some patients. Mitochondrial membranes may also be involved in iron-mediated cardiotoxicity. Iron is avidly taken up by mitochondria (54,59), and this is observed to impair oxidative phosphorylation, although the mechanisms underlying this disruption are not entirely understood. Chronic impairment of energy production by the mitochondria causes dilated cardiomyopathy in many diseases and may constitute a mechanism underlying the development of asymptomatic functional abnormalities in early iron cardiomyopathy (60).

Elevated myocyte iron levels alter gene expression (61). However, it is unclear whether these changes mediate controlled interactions occurring via iron-response elements or exert nonspecific redox effects. Myocytes appear to tonically suppress fibroblast proliferation, and this paracrine effect is diminished by iron overload in the myocytes (62). This observation suggests a potential mechanism underlying the development of iron-induced cardiac fibrosis in thalassemic hearts. The size and charge of the ferrous ion is similar to that of the calcium ion; further, the former is a major mediator of excitation-contraction coupling and a major determinant of the cardiac action potential. Thus, it is not surprising that iron overload leads to arrhythmia and poor cardiac function (5,8,56,63). Ferrous ions directly interact with the ryanodine-sensitive calcium channel in the sarcoplasmic reticulum (64), which activates contraction and modulates calcium reuptake. Ryanodine channel dysfunction is the common denominator for many congenital and acquired arrhythmogenic cardiomyopathies (65). Intracellular iron impairs membrane-bound fast sodium channels and delayed-rectifier potassium currents (56); the former control the rapid upstroke of the cardiac action potential. Channel blockage or other interference slows cardiac conduction; this broadens the QRS interval observed in electrocardiograms (56,63), and a delayed action potential spreads across the myocardium (63). Modifications in calcium or potassium channels may induce repolarization abnormalities such as early or delayed afterdepolarization and QTc prolongation. Further, these modifications link both triggered ventricular arrhythmia and reentrant mechanisms such as torsade de pointes (65).

Arrhythmia and cardiac dysfunction both warrant aggressive chelation, regardless of the total iron load it presents. Continuous DFO therapy is a treatment system used that provides a continuous “sink” for free iron species (8,11), while overcoming the unfavorable kinetics of DFO transport across myocyte membranes. Cardiac symptoms typically stabilize within weeks or months if the free iron levels are consistently suppressed. However, sustained recovery often demands continued therapy for years, wherein the cardiac iron reserves are depleted at a slower rate (8,11). Plots constructed based on MRI reveal that the rate of iron elimination from the heart is approximately 6-fold slower than that from the liver (45,66). The rate-limiting step in cardiac iron excretion has not yet been identified but appears to reflect ferritin turnover. Cardiac iron load and elimination asymmetry contrasted with that of the liver effectively weakens or destroys cross-sectional correlation between liver and cardiac iron. Elevated liver iron levels are not predictive of the cardiac iron levels but may reflect the prospective risk of cardiac iron overload. MRI offers a unique tool for studying the interplay between the hepatic and extrahepatic iron levels.

4. EARLY DETECTION OF IRON-MEDIATED CARDIOMYOPATHY

Assessment of the cardiac status requires consideration of the past history and functional class of heart failure, the rate of disease progression, and the severity of myocardial dysfunction. Echocardiography or LV rest/stress radionuclide ventriculography should be periodically performed for early detection of myocardial dysfunction. The aforementioned findings are alarming in the context of high iron load (33,67). Liver biopsy is the method currently used for estimating the iron load and related cardiac risk (2); however, many TM patients consider this method cumbersome for serial examinations. The need for a noninvasive and precise method for risk estimation will probably be fulfilled by a novel technique of cardiovascular MRI T2* by which the cardiac iron overload can be accurately quantified (66). The myocardial T2* value is inversely correlated with the left ventricular ejection fraction (LVEF) albeit not with the liver iron or ferritin levels. Severe cardiac iron overload that has been noted in certain patients with only moderate hepatic iron load (66) challenges the notion that cardiac iron overload represents a late stage of iron overload that occurs in unavoidable circumstances (68); however, MRI is costly and/or unavailable in poor countries where the disease is most prevalent.

Cardiac function remains normal until late in the course of iron-mediated cardiomyopathy; therefore, other predictive parameters should be assessed in order to
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anticipate and prevent iron cardiomyopathy. The liver iron levels provide a good index of the total iron reserves in the body, and high levels may foreshadow cardiac risk (69). The liver iron levels that have traditionally been estimated by performing biopsy or by using a superconducting quantum interference device (SQUID) can now be accurately estimated by performing MRI. The presence of iron reduces the values of the MRI-related parameters T2 and T2* (and increases those of R2 and R2*) in a predictable and reproducible manner. MRI can be used to assess the iron levels in the heart as well as in the liver. Myocardial T2 and T2* are both shortened in thalassemia patients (12,19,66,70,71). The cardiac function is normal in patients exhibiting normal T2* values; however, the relative prevalence of myocardial dysfunction and arrhythmias increases with a decrease in the T2* values (19,66,71,72). Using a range of echo times enables accurate quantification of the iron overload (T2* < 20 ms), and this technique is sensitive to low tissue iron levels. This suggests that it may be possible to successfully apply the T2* technique to other sites in the body and with other scanners and yet obtain comparable T2* results; further, this technique can be used at geographic locations where the number of patients with thalassemia and consequent cardiac iron loading is high.

Ventricular function is impaired in approximately 10% patients exhibiting a T2* value of 10 ms and in approximately 70% of those exhibiting a value of 4 ms (72). Similar to many other biomarkers such as serum cholesterol, an abnormal T2* value only reflects the relative risk, and many patients with a relatively high iron load do not show any symptoms at the time of investigation. The predictive efficiency of an abnormal T2* value has been strongly implied but has not been demonstrated to date. For many years, the liver iron level has been used as a surrogate for the cardiac iron level (69,73); however, the association between these parameters is considerably complicated. Some patients develop ventricular dysfunction despite low liver iron concentrations, and little or no correlation is noted between the cardiac T2* value and the liver iron level in cross-sectional analyses performed for these patients (74-76). This may be explained by the phenomenon of organ-specific iron transport and elimination (77,78). Another tool for diagnosis during the early stages of iron cardiomyopathy is TDE, which is used to detect regional abnormalities in the myocardial wall motion when the global ventricular systolic function is preserved (7).

5. THERAPEUTIC APPROACH FOR CHF IN TM PATIENTS

5.1. Decompensated CHF

The 3-month mortality from the time of heart failure due to iron overload is reported to be 58% prior to chelation therapy (29,79-81). However, Kremastinos et al (10) have reported an improved prognosis for long-term chelation, i.e., a 5-year survival rate of 48%, positively associated with LV systolic function. Further, all deaths reported in another study occurred due to biventricular cardiomyopathy that arose shortly after the involvement of a nonfailing ventricle (74). These reported improvements in the survival rates are explained by the widespread use of chelation therapy in addition to better management of anemia and the use of angiotensin-converting enzyme inhibitors (ACE-Is) (74,82). Cardiomyopathy is reversed following intensified chelation in a substantial minority of patients (6,11,33,67,83). In contrast, insufficient chelation may be associated with a fulminant course of the disease (33). Following the development of cardiac dysfunction or arrhythmias, aggressive chelation should be initiated, regardless of the total iron load.

In a series of recent studies, the prevalence of heart failure remains at 2.5% among well-treated patients, although it is reported to have decreased by more than 50% (14,29,33,74,84). The age of onset has modestly been prolonged in adolescents, primarily due to suboptimal chelation (75). Pump failure is the principal cause of mortality in beta-TM (29,33,67,69,74,75,85,86), and sudden death is notably uncommon (33,74), although a previous report has revealed the existence of a proarrhythmic substrate (63). TM patients exhibiting signs and symptoms of CHF should be hospitalized and closely monitored. To gain the patients’ cooperation and confidence, hospitalization should be proposed and the need for it, clearly explained to them by the physicians because various psychological issues may arise at this juncture. Extensive laboratory tests should be performed, including arterial blood gas analysis, endocrine profile determination, and liver and renal function tests. Chest x-ray may reveal cardiomegaly, lung congestion, pleural effusion, as well as a prominent pulmonary artery in the presence of marked pulmonary hypertension. Further, ECG often reveals certain other abnormalities such as wide QRS, low QRS voltage, LV hypertrophy, inverted T waves, non-specific ST-T changes, prolonged A-V conduction, or any type of arrhythmia. Doppler echocardiography (10) should also be performed to assess the severity of left and right ventricular dysfunction as well as the degree of pulmonary hypertension. It is noteworthy that patients who provide echocardiographic evidence of LV systolic dysfunction often present with clinical signs and symptoms of isolated right-sided heart failure. Pericardial effusion or pericardial thickening should be assessed. Recent MRI studies have confirmed that almost all patients with decreased LV function exhibit severe iron overload (66). MRI measurements are adequate for ascertaining the degree of iron overload during follow-up.

Complications such as arrhythmia, blood volume overload following transfusion, infection, and severe anemia should be identified and treated. If significant arrhythmia persists, antiarrhythmic agents that exert minimal negative inotropic effects should be selected for treatment. In general, amiodarone is administered by infusion at a loading dose of 150 mg in 100 mL 5% distilled water (D/W) for 10 min, followed by an IV drip of 900 mg in 500 mL D/W for 6 h (0.5 mg/min) (87). Electric cardioversion can be performed in cases of atrial fibrillation or atrial flutter but only in the absence of CHF. Electric cardioversion is best avoided for patients with severe CHF and atrial fibrillation/flutter; a poor outcome of cardioversion has been reported for some TM patients with intermittent ventricular tachycardia. If normal sinus
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tachycardia persists, a low dose of a beta-blocker such as carvedilol may be administered (3.125 mg twice a day). Daily measurement of the body weight, blood pressure, and 24-h urine output is of paramount importance. Further, frequent monitoring of the hematocrit (Hct), Hb, blood electrolyte, urea, creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and uric acid levels in the blood is also mandatory.

An intensified course of iron chelation therapy, including intensive IV DFO infusion and oral L1 administration, is extremely important for both asymptomatic high-risk patients and patients with heart failure (88). Recent studies have suggested that this combination produces cumulative chelation effects (89,90). DFO should be administered at a dose of 60–80 mg·kg⁻¹·d⁻¹ via continuous IV infusion and L1, in 3 separate doses of 75–100 mg·kg⁻¹·d⁻¹ (13) to avoid fluid overload during the continuous DFO infusion. The Hb concentrations of patients should be maintained at more than 10 g/dl by performing blood transfusion, and endocrine abnormalities, if any, should be appropriately managed. ACE-Is should be administered immediately after the LVEF approaches a value of 50% (8,33,91). Angiotensin II receptor blockers can be used as an alternative or a supplement to ACEs. Further, diuretics and digitalis glycosides are required for treating symptomatic patients, and beta-blockers may be required in for patients in whom compensation has occurred (88).

In the event of pulmonary hypertension, sildenafil citrate titrated at a dose of 25–75 mg/d once a day (92), which releases NO, has proven effective for reducing the pulmonary pressure (93,94). Hypoalbuminemia due to liver dysfunction is a common presentation in TM patients with CHF. The liver is injured by the combined effects of excessive hepatic iron, viral or other infections, and congestion. However, low serum albumin levels can be masked by treatment with diuretics. It is important consider the fact that CHF patients with hypoalbuminemia and those under treatment with strong diuretics exhibit a low renal flow rate and are at high risk for acute renal failure. Both albumin administration and diuretic infusion should be carefully moderated by administering 50 mg human albumin once or twice a day, followed by bolus infusion of 20 mg furosemide, in order to gradually attain a negative fluid balance. In the event of oliguria, IV administration of positive inotropic agents in titrated doses of dopamine (2–5 µg·kg⁻¹·min⁻¹ in 250 or 500 mL 5% D/W) and/or hemodialysis should be considered.

It is evident that treatment should be personalized in terms of the choice of medication as well as the route and dose of administration. Advanced or complete A-V block necessitates the implantation of a pacemaker device. Interestingly, malignant ventricular tachyarrhythmias are a rare occurrence (33,67,74) and may be related to the recovery of myocardial function in some cases and to the rapid decline of pump function in others (33). Cardioverter-defibrillator implantation is necessary in rare cases. In exceptional cases and when the outcome of dysfunctional myocardium cannot be predicted, the use of automatic wearable defibrillators may be an option. Heart transplant has been recommended for selective patients with end-stage disease (95).

5.2. Compensated CHF

Treatment should be continued for patients who survive the acute phases of cardiac iron overload (13,96). General clinical examination, echocardiography, and MRI T2* should direct subsequent treatment modifications toward either treatment with cardiac drugs and beta-blockers or chelation. In some cases, normal heart function can be restored. In rare cases complicated with constrictive pericarditis, surgical intervention is essential. RV involvement and attendant asynergy LV contraction is common in end-stage heart failure. Cardiac resynchronization via atrial-synchronized biventricular pacing improves both the heart contractility and the symptoms of refractory systolic heart failure (97); this therapeutic modality should therefore be considered when resynchronization is indicated.

Patients with beta-TM are at a greater risk for the development of malignancy (86). Chelation should be intensified during chemotherapy with drugs that are known to exert iron-mediated toxicity, such as anthracyclines (98), in order to minimize the risk of fulminant cardiomyopathy (33). Regular anticoagulant therapy is indicated for patients with atrial fibrillation, ventricular thrombus, and/or pulmonary hypertension. If hepatic disease coexists with these conditions, the anticoagulant should be administered at a dose lower than the usual one. Restoration of sinus rhythm via electric cardioversion requires appropriate pretreatment with anticoagulants to dissolve intracardiac thrombi. Prophylactic antithrombotic therapeutic measures such as surgery or prolonged immobilization may be recommended for patients who are at risk for transient thromboembolic events (99).

6. CARDIOPROTECTIVE CHELATION THERAPY FOR THALASSEMIC PATIENTS

The primary aim of chelation is to prevent iron-induced organ damage and premature death. To achieve this, it is necessary to effectively remove iron from the heart (the target lethal organ in iron overload) (100). DFO treatment improves survival and delays the onset of iron overload (101). The standard therapy system involves subcutaneous DFO infusion at a dose of 20–40 mg·kg⁻¹·d⁻¹ for 8–24 h for 5–7 d/wk (102), and it is usually initiated in children following the initial 10–20 blood transfusions. In many cases, continuous 24-h parenteral infusion of DFO to drain cardiac iron can reverse arrhythmia and CHF (8). Anderson et al (45) followed patients in whom IV administration of DFO had been initiated for iron-induced cardiomyopathy over a period of 12 months to confirm that siderotic heart failure can often be reversed by iron chelation via IV administration of DFO. During recovery, the myocardial T2* value along with the LV volume and function is reported to improve; however, iron clearance is noticeably slower from the heart than from the liver. A retrospective study by Anderson et al (103) compared the levels of myocardial iron in relation to cardiac function...
between 15 patients under long-term L1 treatment (80.5 mg·kg⁻¹·d⁻¹) and 30 matched controls under DFO treatment (37.4 mg·kg⁻¹·d⁻¹, for 5.1 d/wk). MRI T2* revealed that the myocardial iron levels were distinctly lower in the L1-treated group than in the DFO-treated group (p = 0.02). The odds ratio for the presence of excess myocardial iron following DFO treatment was 5.5 (95% confidence interval (CI), 1.2–28.8). The cardiac function exhibited a greater improvement in the L1 treated group; i.e., this group exhibited a higher mean LVEF value (p = 0.004) and reduced LV dilatation in systole (p = 0.03) and diastole (p = 0.01). These findings were recently confirmed in a larger, prospective, controlled trial conducted by Pennell et al (104), wherein 61 patients who were already under DFO treatment were randomized to continue the treatment (43 mg/kg for 5.7 d/wk) or to switch to L1 treatment (92 mg·kg⁻¹·d⁻¹). During the 1-year-long study, compliance was similar between the groups (93% and 94% for the DFO- and L1-treated groups, respectively; p = 0.023); further, the improvement in the myocardial T2* was noticeably greater in the L1-treated group when compared with the DFO-treated group (27% and 13%, respectively; p = 0.023). The LVEF demonstrated an appreciably greater increase with L1 treatment (3.1% vs. 0.3%; p = 0.0034). The serum ferritin level at baseline did not significantly predict T2* improvement (104). Prospective trials demonstrating superior efficacy in treating cardiac siderosis and better outcome for LVEF receive support from outcome studies looking at survival and clinical complications. A retrospective study conducted by Piga et al provided the first survival data comparing the effects of L1 and DFO (105). In their study, 54 L1-treated patients and 75 DFO-treated patients, all of whom had previously been under DFO treatment, were compared for an average duration of 6 years. The results revealed that the cardiac disease-free survival rate improved considerably with L1 treatment over a period of 5 years (p = 0.003). Cardiac dysfunction was diagnosed in 2 (4%) of the L1-treated patients and in 15 (20%) of the DFO-treated patients (p = 0.007). A recent multicenter natural history study conducted by Borgna-Pignatti et al (106) demonstrated that the outcome of heart disease and the survival rates were better for L1-treated patients. Their study involved 359 patients under DFO treatment (30–50 mg·kg⁻¹·d⁻¹, 5–6 times per week) and 57 patients who switched from DFO to L1 treatment (75 mg·kg⁻¹·d⁻¹, 3 times a day) at 7 Italian centers during 1995–2003. During this time frame, 52 cardiac events, including 15 deaths, occurred in the DFO-treated patients; thus, cardiac events occurred in 14.5% of the DFO-treated patients but did not occur in any of the L1-treated patients. The authors concluded that there was a significant difference in cardiac morbidity and mortality between thalassemia patients treated with L1 and those treated with DFO. A study by Esposito revealed that the levels of LPI species were suppressed by DFO treatment but increased once again within a few hours after the treatment was discontinued (51). It appears that in addition to the dose administered, the duration of infusion per day is also critical in DFO therapy. The use of oral chelators such as L1 can prevent problems associated with rebounding levels of LPI. Due to iron mobilization, the plasma NTBI levels increase to some extent in L1 patients; however, L1 treatment does not increase the LPI levels, suggesting that L1-chelated iron is not redox active. In fact, oral L1 treatment can completely clear LPI in patients (51). Our first prospective report (12) compared the cardiac iron levels and the LVEF over 3 years between 13 patients receiving DFO (50 mg·kg⁻¹·d⁻¹) for at least 5 d/wk and 11 patients receiving L1 (75 mg·kg⁻¹·d⁻¹ orally every 8 h. The cardiac iron levels improved greatly in 5 L1-treated patients and slightly in 2 DFO-treated patients, as reflected by the signal intensity (SI) obtained in T2-weighted MRI. The mean LVEF increased dramatically with L1 treatment (58.6% ± 6.8% to 65.2% ± 7.1%) but exhibited no appreciable change with DFO treatment (63.3% ± 6.3% to 64.6% ± 7.0%). Both drugs had similar effects on the serum ferritin and hepatic iron levels, indicating that these parameters do not reflect the cardiac iron loading. In 2003, we reported the successful treatment of severe heart failure in 2 beta-TM patients by using combined DFO and L1 therapy (13). T2-weighted MRI revealed distinct recovery of the SI yielded by the heart, indicating a drastic reduction in the iron load. Thus, combined therapy may be recommended for beta-TM patients with cardiac complications.

7. CONCLUSIONS

In the past, heart failure could occur at any time after the age of 10 years in TM patients undergoing transfusions. Today, heart failure usually occurs in the third or fourth decade of life in patients who adhere to the suggested transfusion and chelation regimens. Due to extensive improvements in chelation therapy, the saying “It is never too late” now appears to apply to all beta-TM patients (11,69,85). However, heart failure is responsible for mortality in most of these patients. Patients receiving regular and long-term transfusion therapy develop chronic anemia (14), and therefore, normal cardiac data do not apply to them. The mechanisms and kinetics of iron entry and clearance through cell membranes differ markedly between the heart and liver (45,46,48). Increased iron loading in the heart is harmful to myocardial function and can be detected by performing MRI (19,66). L1, an oral iron chelator, has been recognized to play a key role in cardioprotection. However, even before large-scale studies were conducted, many physicians observed that combination therapy involving both DFO and L1 exhibited superior effects in rescuing TM patients with decompensated heart failure. Both serum ferritin and LPI levels can be appreciably lowered by such combination therapy. Combination therapy is considerably more effective for thalassemic iron loading-mediated cardiomyopathy than for cardiomyopathy stemming from other pathophysiologies (104). CHF is reversible in most patients (4), and currently, many modalities are being developed for the rescue of these patients. Further, it is extremely important to accurately estimate the extent of iron loading and the risk of failure of each vital organ by using reliable evaluation tools such as MRI and TDE. Hippocrates stated that “It is better to prevent than to cure”; optimal chelation, if initiated at the appropriate time, can prevent cardiomyopathy (104). While heart MRI T2* measurement lower than 10 ms proves effective in identifying significant ventricular dysfunction, it is not clear which limit above 10 ms is best for MRI T2*.
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Anderson has reported the lower normal limit to be 20 ms (66), while Wood has reported it to be 25 ms (19). However, these settings (10–25 ms) do not usually reveal impaired heart function in the steady state, as indicated by MRI (19,66,104). The manner in which they behave under stress conditions such as infection or whether they risk cardiac functional abnormalities remains unclear.

8. FUTURE PERSPECTIVE

Oral chelators such as L1 improve adherence in chelation therapy and can probably improve the prognosis of the condition. In nonrandomized trials, L1 treatment alone or in combination with DFO appears to be at least as effective as DFO treatment for reducing the incidence of cardiac disease and for clearing myocardial iron (103,107,108). Combination therapy comprising DFO and L1 treatment in adequate doses produces a cumulative effect and induces a negative iron balance in the patients (109,110). Combined therapy is now currently well accepted for patients with CHF and those in whom heart MRI reveals a T2* value of less than 10 ms (12,13,96,103). The efficiency of monotherapy with L1 and deferasirox for these specific patients is currently under investigation; however, many studies have demonstrated that L1 is more effective than DFO in clearing cardiac iron in standard regimens (12,13,103,104,106), while deferasirox appears to be as effective as DFO in this regard (111). In the case of T2* values of more than 25 ms, treatment with an oral chelator appears to be as appropriate as treatment with DFO. The current treatment options selected based on cardiac iron measurements performed by MRI are promising for preventing heart injury and prolonging life expectancy. Thalassemia patients are prime candidates for genetic therapy. Allogeneic stem-cell transplantation reverses the beta-thalassemia phenotype via stem-cell replacement; however, this system is associated with toxicity and presents problems related to inadequate donor availability. The discovery of a beta-globin locus control region along with progress in the field of vector construction and the development of effective gene transfer systems may pave the way for the long-awaited eradication of beta-thalassemia (112).

9. REFERENCES


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Abbreviations: TM: thalassemia major; CHF: congestive heart failure; ECG: electrocardiogram; LV: left ventricular; TDE: tissue Doppler echocardiography; EF: ejection fraction; MRI: magnetic resonance imaging; DFO: deferoxamine; L1: deferiprone; CO: cardiac output; RV: right ventricle; Hb: hemoglobin; NTBI: non-transferrin-bound iron; SI: signal intensity; RBC: red blood cell; NO: nitric oxide; DMT1: dimethyl transferase 1; LVDCs: L-type voltage-dependent channels; LPI: labile plasma iron; IV: intravenous

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