# Iron overload thalassemic cardiomyopathy: Iron status assessment and mechanisms of mechanical and electrical disturbance due to iron toxicity

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Patients with thalassemia major have inevitably suffered from complications of the disease, due to iron overload. Among such complications, cardiomyopathy is the leading cause of morbidity and mortality (63.6% to 71%). The major causes of death in this group of patients are congestive heart failure and fatal cardiac tachyarrhythmias leading to sudden cardiac death. The free radical-mediated pathway is the principal mechanism of iron toxicity. The consequent series of events caused by iron overload lead to catastrophic cardiac effects. The authors review the electrophysiological and molecular mechanisms, pathophysiology and correlated clinical insight of heart failure and arrhythmias in iron overload thalassemic cardiomyopathy.

**Key Words:** *Cardiomyopathy; Cardiovascular death; Iron overload; Thalassemia*

## La myocardiopathie thalassémique par surcharge en fer : L'évaluation de la quantité de fer et des mécanismes de perturbation mécanique et électrique causés par la toxicité ferreuse

Les patients atteints de thalassémie majeure ont inévitablement souffert de complications de la maladie en raison d'une surcharge en fer. Parmi ces complications, la myocardiopathie est la principale cause de morbidité et de mortalité (63,6 % à 71 %). Les principales causes de décès au sein de ce groupe de patients sont l'insuffisance cardiaque congestive et les tachyarythmies cardiaques fatales. La voie à médiation par radicaux libres est le principal mécanisme de toxicité ferreuse. La série d'événements causés par la surcharge en fer a des effets cardiaques catastrophiques. Les auteurs ont examiné les mécanismes électrophysiologiques et moléculaires, la physiopathologie et les aperçus cliniques connexes d'insuffisance cardiaque et d'arythmie en cas de myocardiopathie thalassémique par surcharge en fer.

Thalassemia is the most common monogenic disorder causing decreased globin, a protein composition of hemoglobin synthesis. By clinical manifestation, beta-thalassemia major (TM) is the most severe form apart from hemoglobin Bart's disease, which is always fatal. TM patients require intensive blood transfusions due to severe anemia from ineffective erythropoiesis. Generally, an increase in body iron burden occurs in patients who are not receiving transfusions, ranging from 2 g to 5 g/year, compared with 0.0015 g/year in healthy individuals (1). Regular transfusions may double this rate of iron accumulation (2). Hence, the inevitably pursuant complications are from iron excess in various organs such as the heart, liver and pancreas. Although the heart is not the first target organ, cardiac iron overload or iron overload cardiomyopathy is regarded as the most serious condition (3,4). In the present review, clinical manifestation of iron overload thalassemic cardiomyopathy and the tools used for its detection and monitoring are presented. Mechanisms by which iron toxicity causes alterations in cardiomyocytes and cardiac electrophysiology are also reviewed and discussed.

## CLINICAL INSIGHT

The incidence of iron overload cardiomyopathy ranges from 11.4% to 15.1% in TM (3,5). Usually it begins at an accumulation of 20 g of iron (6). In the early stage, patients are usually asymptomatic. Restrictive cardiomyopathy usually occurs before dilated cardiomyopathy (7), in accordance with diastolic dysfunction, which normally happens before systolic dysfunction and overt heart failure (8-12). Generally, once the onset of a failing heart occurs, the survival time is usually less than three months if left untreated (13). Autopsy examinations have found dilated cardiomegaly in patients who died from late-stage iron overload cardiomyopathy (7). Although systolic dysfunction becomes obvious during the late stage, decreased contractile function has been demonstrated during the early stage of the disease (14-16). Left-sided heart failure is clinically more common than right-sided heart failure (12). However, it has been shown that right ventricular dysfunction develops earlier in asymptomatic TM patients (9,17).

In addition to congestive heart failure, another major cause of death in this group of patients is cardiac tachyarrhythmias, which may occur simultaneously with a failing heart, leading to sudden cardiac death (12). Kremastinos et al (12) reported that the incidence of sudden death was approximately 11.6% in TM patients with left ventricular failure, which accounted for approximately 18.5% of total cardiac deaths. Similar to mechanical dysfunction, electrophysiological dysfunction varies with the stage of disease. Findings in the early stage are usually accidental, including bradycardia, ST-T changes, infrequent premature atrial or ventricular contractions, first-degree atrioventricular block and evidence of left ventricular hypertrophy (18,19). In the late stage, frequent premature atrial or ventricular contractions, short runs of supraventricular tachycardia, atrial flutter and fibrillation, ventricular tachycardia and second-degree or complete heart block (including intraventricular block) have been demonstrated (7,12,19). Among these late electrocardiogram (ECG)

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changes, frequent premature ventricular contraction is most commonly found, while sustained ventricular tachycardia is predominantly related to cardiac death (12). Iron levels in the myocardium seem to be associated more with arrhythmias and conduction disturbance than with the conduction system itself (20,21). It has been shown that patients with supraventricular arrhythmias have extensive iron deposition in the atria, and not in the sinoatrial node (20). In addition, patients with atrioventricular block did not have iron deposition in the ventricular conduction system (20).

## ASSESSMENT AND MARKERS OF CARDIAC IRON STATUS

Because chelation therapy is an effective way of preventing iron overload cardiomyopathy, the methods and/or markers that can accurately assess cardiac iron status and predict the development of cardiac complications are essential (8,9,11,12,15,16,22-26). Many methods and parameters, both direct and indirect, have been investigated. Some have been proven to be nonreproducible, some controversial but still used, and others are undergoing investigations or being used for research work.

Among serum iron markers, serum ferritin is most commonly used as an indirect estimate of body iron store. However, reliance on ferritin alone can lead to an inaccurate assessment (24). Certain conditions, such as inflammation, infection and chronic liver disease from the hepatitis C virus, which are common complications of thalassemia, may cause an elevation of serum ferritin (27). In view of cardiac complications, serum ferritin concentrations have been shown to correlate poorly with all stages of cardiac dysfunction (diastolic, systolic and overt heart failure) (15). Non-transferrin-bound iron (NTBI) seems to be the best parameter among serum iron markers. Currently, however, it is commonly used only in research studies. Various methods and protocols used in the determination of NTBI have been proposed, but no consensus has been established (28-32).

Transfusional iron load or the number of blood transfusions is usually unreliable in predicting cardiac iron status (25). However, in the case of accurate data collection, an increased ratio of the transfusional iron load to deferoxamine use (not transfusional iron load alone) has been shown to correlate with cardiac dysfunction and death (25).

Hepatic iron concentration provides the most quantitative means of assessing the body iron burden in TM patients (33). However, no relationships between hepatic iron concentration and cardiac iron status or cardiac dysfunction, have been found (16,26,34). Despite being a direct estimation, endomyocardial biopsy has not been correlated with cardiac iron status and function, possibly due to the pattern of iron deposition and the large sampling variation (35). Iron usually deposits primarily in the subepicardial layer toward the subendocardial layer and is often patchy (20,36). It tends to accumulate in myocardium (especially interventricular septum and ventricular free wall) more often than in the conduction system. Moreover, clinically, antemortem arrhythmias and conduction disturbance have shown no correlation with iron density in the conduction system (21). Other assessments, such as antioxidant levels – particularly vitamin E, which combats oxidative stress from iron toxicity – have been proposed as being indicative of iron overload cardiomyopathy in TM patients (37).

## ASSESSMENT FOR THE DEVELOPMENT OF IRON OVERLOAD CARDIOMYOPATHY

Accurate assessments of cardiac dysfunction and/or cardiac iron status are currently based on imaging techniques. The T2-star magnetic resonance (MR-T2*), a novel tool, has been demonstrated to evaluate cardiac iron status accurately and detect an early global ventricular dysfunction (16). In addition, it can be used for monitoring myocardial iron levels during iron chelation therapy (22). While conventional standard echocardiographic measurements usually demonstrate positive findings at the late stage (38), low-dose dobutamine stress echocardiography may be useful for early detection of cardiac dysfunction in patients at risk for cardiac hemosiderosis (11). Recently, tissue Doppler echocardiography (8) and radionuclide angiography (with exercise or low-dose dobutamine stimulation) (9) have been shown to detect regional wall motion abnormality, even in early-stage thalassemic patients. This finding may also reflect patchy, nonhomogeneous deposition of iron in cardiac muscle. However, stress echocardiography, tissue Doppler echocardiography and radionuclide angiography cannot estimate cardiac iron content. MR-T2* seems to be superlative (but costly) in terms of noninvasiveness, earliness (sensitivity) and accuracy (specificity), due to its ability to simultaneously assess both cardiac iron and structure, as well as cardiac function.

Although cardiac dysfunction is more clinically obvious than conduction disturbance or arrhythmias in iron-overloaded patients, the pathogenesis of arrhythmias may start at the same time, with, or even earlier, than contractile dysfunction (39). It has been shown that when patients have symptoms of arrhythmias, the mortality rate is potentially high (12). Thus, any method or parameter that can determine arrhythmogenic risk would be a very useful tool as a guide for future therapeutic strategies. Although ECG findings, including 24 h Holter monitoring, during the early stage of the disease may trigger awareness, they are not specific to iron overload cardiomyopathy. Another ECG parameter, QT dispersion, has been proposed to be a relevant parameter for the heterogeneity of iron deposition and duration of cardiac action potential (23). Kuryshev et al (23) found that 14 of 24 TM patients with iron overload had increased QT dispersion (longer than 60 ms) in their preliminary study.

Abnormal neurohormonal regulation has been investigated and proposed to be a potential contributor to cardiac disease in TM patients. Altered sympathovagal balance in TM patients was first demonstrated by Veglio et al (18). They investigated heart rate variability (HRV) and blood pressure variability in nine asymptomatic TM patients and found diminished sympathetic activity. This was characterized by the lack of a circadian rhythm of blood pressure and heart rate; decreased short-term variability of blood pressure and heart rate, particularly at a low frequency range; reduced low to high frequency ratio of HRV, suggesting an impaired sympathovagal balance; impaired baroreflex gain during a head tilt; and significantly decreased plasma norepinephrine. A recent study in iron-overloaded rats (40) demonstrated similar findings on baroreflex function. Moreover, Franzoni et al (41) demonstrated a significant reduction of HRV parameters and increased incidence of ventricular late potential (VLP) in asymptomatic TM patients (n=19). In this study, TM patients with VLP showed a higher incidence of premature ventricular contraction, with episodes of nonsustained ventricular tachycardia. Recently, De Chiara et al (9) reported that decreased HRV parameters can be detected as early as ventricular regional wall motion in asymptomatic TM patients (n=20). However, no long-term follow-up study has been reported to confirm the validity of HRV parameters for predicting cardiac dysfunction and mortality in iron overload thalassemic patients.

In TM patients, renin-angiotensin activity has been shown to increase (40). An increased atrial natriuretic peptide level has also been proposed as a predictor in asymptomatic TM patients, because it was found to be in close correlation with left ventricular diastolic dysfunction (42). Taken together, impaired sympathovagal balance and altered hormonal regulation may be responsible for the pathophysiology of TM patients, who are at risk for iron overload cardiomyopathy.

## MECHANISMS OF IRON TOXICITY

**Free radical-mediated iron toxicity**

Tissue toxicity by iron occurs via the free radical-mediated pathway. Iron has the capacity to accept and donate electrons, switching between $Fe^{2+}$ and $Fe^{3+}$, which is known as redox activity. In general, it is physiologically essential and present in the plasma in a transferrin-bound form. In chronic iron overload, when transferrin is completely

saturated, NTBI is found in the plasma (43), which is the form of iron that causes toxicity. Iron excess in various conditions is harmful by engaging in the Fenton-catalyzed Haber-Weiss reaction to yield hydroxyl radicals from hydrogen peroxide and superoxide (44). They are all called oxygen free radicals. Highly reactive hydroxyl radical production, previously demonstrated in an in vivo model of iron-overloaded rats (45), is capable of widespread damage to cellular lipids, proteins, sugar and DNA (46).

**Pathways of iron entry into cardiomyocytes**

In in vitro studies using iron-treated, cultured neonatal rat ventricular myocytes (NRVMs), NTBI had more than a 300-fold higher rate of uptake than transferrin-bound iron (47). The enhancing rate of NTBI uptake occurs in a dose- and time-dependent pattern (34), suggesting a carrier- or channel-mediated pathway.

The exact iron uptake pathway is still unclear. The redox form of iron uptake is most likely specific to the reduced $Fe^{2+}$ form, but not $Fe^{3+}$ (48,49). Using the isolated adult rat heart to study iron uptake, Tsushima et al (49) demonstrated that iron uptake was diminished when cardiac electrical activity was arrested by potassium chloride. This finding suggests that iron uptake partly depends on membrane potential, indicating that iron enters the cell via voltage-gated channels. Many studies have indicated that the sarcolemmal L-type $Ca^{2+}$ channel is a major pathway of iron uptake into cardiomyocytes (49-51). Using the patch clamp technique, it has been shown that the iron current competes with the calcium current, and is inhibited by a calcium channel blocker (49). Other in vivo (chronically iron-loaded adult mice) studies have demonstrated the inhibitory effect of L-type $Ca^{2+}$ channel blockers on cardiac iron uptake, indicated by decreased tissue iron content (50,51), preserved cardiac function and improved survival (51). However, using iron-loaded cultured NRVMs, Parkes et al (48) demonstrated contradictory results. They reported that iron uptake did not occur via the L-type $Ca^{2+}$ channel, but was preferably dependent on the altered redox ($Fe^{2+}$ to $Fe^{3+}$) pathway situated on the plasma membrane. The discrepancy in these findings may be due to differences in the age of animal models. Neonatal myocytes have fewer L-type $Ca^{2+}$ channels with a smaller L-type $Ca^{2+}$ current than adult myocytes (52). It has been proposed that the $Ca^{2+}$ current investigated in cultured neonatal myocytes may be underestimated due to less density in beating cells and more myocyte death (52).

## EVIDENCE OF IRON-MEDIATED CARDIOMYOCYTE DAMAGE

In chronic iron overload, iron toxicity is dose-dependent (53). The highly toxic hydroxyl radicals, produced via the Fenton-catalyzed Haber-Weiss reaction in the setting of iron excess, is well known to damage the lipid-rich cell membrane, which is called lipid peroxidation, or lipoperoxidation. Lipid peroxidation in the presence of adequate lipids (substrate) and iron (catalyst) seems to be perpetual. This reaction is not only restricted to cell membrane phospholipids, but also to other membrane-bound cellular organelles. By studying iron overload in cultured NRVMs, Link et al (54) demonstrated evidence of lipid peroxidation, reduction in polyunsaturated fatty acids (PUFAs) and increased products from cellular lipid peroxidation, particularly toxic aldehydes (47,53,55,56). The aldehyde products such as malondialdehyde and 4-hydroxynonenal can form a covalent link to proteins (aldehyde-protein adducts), rendering the loss of cellular protein function (57).

Loss of cell membrane integrity from lipid peroxidation was evidenced by lactate dehydrogenase release (58). As a result, structures located on the cell membrane, such as $Na^+$-$K^+$ ATPase and 5′-nucleotidase, were affected thereafter (59). Oxidative stress-mediated iron tocixity also affects other cellular organelles and their functions, such as increased lysosomal fragility (60), decreased mitochondrial inner membrane respiratory enzyme activity and ATP (61), decreased protective antioxidant enzyme (ie, glutathione peroxidase) activity, decreased myofibrile elements and a decreased number of mitochondria (36).

## MECHANISMS OF MECHANICAL DISTURBANCE IN IRON OVERLOAD CARDIOMYOPATHY

Cardiac effects following iron-induced membrane lipid peroxidation can be divided into two parts – changes following altered membrane lipid components and their metabolites, and changes following altered embedding enzymes, ion channels, receptors and other membrane proteins. Arachidonic acid (AA) is a 20-carbon PUFA normally esterified in membrane phospholipids. It is released through the action of cellular phospholipases, which may be activated by chemical stimuli or other mediators. AA metabolites, also called eicosanoids, are lipid mediators involved in the signal transduction pathway. Both AA and eicosanoids have been shown to play a role in iron overload cardiomyopathy (62). In cultured NRVMs treated with iron, Mattera et al (62) have shown that the rate of AA release is increased, particularly after the angiotensin II type I receptor has been activated. AA has been shown to activate mitogen-activated protein kinase (63) and apoptosis (64). Because the activated angiotensin II type I receptor is associated with cardiomyocyte growth and hypertrophy (65,66), the outweighing increment of AA release may be a possible mechanism in the progression of cardiac hypertrophy to heart failure in iron overload cardiomyopathy (62). In addition, cyclooxygenase-2 (COX-2) activity also increased and may be responsible for heart failure development in iron overload; it is associated with an increased apoptotic rate and symptomatic heart failure (67,68).

Other than the effects of membrane lipid peroxidation causing cellular environmental changes, the membrane-embedding enzymes, such as $Na^+$-$K^+$ ATPase, $Ca^{2+}$ ATPase and 5′-nucleotidase, may be attacked directly by oxygen radicals (59,69,70). It has been shown that modification of the sulfhydryl groups of these enzymes by an oxygen radical reduces their activity (70). Alteration of sarcolemmal $Na^+$-$K^+$ ATPase activity in an iron-overloaded heart may be one of the important mechanisms in the pathophysiology of the disease. A decrease in $Na^+$-$K^+$ ATPase activity was shown in both an iron-loading NRVMs (59) and a hydroxyl radical-exposed heart (69). Impaired $Na^+$-$K^+$ ATPase activity renders an increased resting membrane potential (membrane depolarization) and changes in ion conductance. Altered $Na^+$-$Ca^{2+}$ exchange can occur following impaired $Na^+$-$K^+$ ATPase activity. An increase in intracellular $Na^+$, due to an impaired $Na^+$-$K^+$ ATPase pump, shifts the $Na^+$ efflux via $Na^+$-$Ca^{2+}$ exchange, resulting in $Ca^{2+}$ influx. This $Ca^{2+}$ influx may persist due to impaired $Ca^{2+}$ extrusion caused by iron-inhibited sarcolemmal $Ca^{2+}$ pump activity and may lead to cardiac arrhythmias (70). Furthermore, $Ca^{2+}$ influx normally causes a release of $Ca^{2+}$ from the sarcoplasmic reticulum (SR), leading to myocardial contraction. However, iron ($Fe^{2+}$) itself has a direct inhibitory action on ryanodine-sensitive $Ca^{2+}$ channels on the SR by competing with $Ca^{2+}$, thus contributing to a reduction in $Ca^{2+}$-induced $Ca^{2+}$ release from the SR (71) results in impaired contractility. Oxygen free radicals also have a direct effect on decreased cardiac SR $Ca^{2+}$ ATPase activity (72), which may be responsible for diastolic failure. In the in vitro study by Zeitz et al (69), hydroxyl radical-exposed rabbit heart muscle was demonstrated to have calcium overload (via $Na^+$-$Ca^{2+}$ exchange), with an acute diastolic dysfunction. These mechanisms may explain the pathophysiology of early cardiac dysfunction in iron overload cardiomyopathy.

Persistently high iron and free radicals from iron overload also affect other cellular constituents, such as altered function (73), structure and number of mitochondria (36,74), altered SR function and structure, and decreased myofibril elements (36). Mitochondrial dysfunction results in decreased phospholipid synthesis of all cellular membranes, including the mitochondria themselves (75). SR membrane destruction from lipid peroxidation, together with impaired phospholipid synthesis, leads to calcium leakage into the cytoplasm.

Further increaseses in intracellular calcium can cause degradation of membrane phospholipids by activating endogenous phospholipase and the degradation of myofibril elements by activating proteases (76). The net effect is toward the end stage of cellular declination, eventually leading to systolic dysfunction.

## MECHANISMS OF ELECTRICAL DISTURBANCE IN IRON OVERLOAD CARDIOMYOPATHY

In ex vivo guinea pig hearts, delayed and blocked electrical conduction has been demonstrated to occur earlier in iron-loaded cardiac toxicity than impaired contractility (39). An optical mapping study of iron-loaded Mongolian gerbils (77) also exhibited pertinent results of slow conduction and impulse block, with evidence of re-entry, which may lead to cardiac arrhythmias. Iron-overloaded cardiomyocytes have been shown to have a smaller overshoot potential and a shorter action potential duration than iron-free cardiomyocytes in the same heart (23,58). An alteration of ion currents characterized by reduced $Na^+$ currents may be an underlying mechanism (23). The severity of $Na^+$ current reduction is also associated with higher dose and longer duration of iron exposure (23). Reduced overshoot potential ensues as a result of decreased rapid phase 0 depolarization (fast sodium current). A reduction in the late fast sodium current during the plateau phase may result in the rapid shortening of the action potential duration due to the disturbance of a delicate balance of small currents. Abnormal sodium currents may also explain the delayed impulse conduction causing widening of the QRS complex, as demonstrated in the intact gerbil heart model (77). These electrophysiological heterogeneities, including the patchy nature of cardiac iron deposition, may provide substrates for re-entry and risk of developing fatal arrhythmias (77). Other arrhythmias include PR and QRS interval prolongation (65) and bradycardia in the early stage (34,66), and premature ventricular contraction (40), ST-T changes (66), QT prolongation (66), second- and third-degree atrioventricular block (65), and arrhythmias in the late stage (59). These changes are similar to those reported in iron overload patients (7,19). Further investigations on alterations of ion channels, both quantitatively and structurally, are required to explain the association of molecular and electrophysiological changes at the cellular level.

Changes in calcium homeostasis, as described in the 'Mechanisms of Mechanical Disturbance in Iron Overload Cardiomyopathy' section, may also lead to cardiac arrhythmias, such as triggered activity and sudden cardiac death (78). In addition, increased COX-2 activity, due to iron overload, results in enhanced eicosanoid production and an altered ratio of eicosanoid products (62). An increased ratio of prostaglandin E2 to prostacyclin found in an iron overload condition can trigger tachyarrhythmias (79,80). This phenomenon can also occur when being stimulated by interleukin-1 alpha, an inflammatory cytokine (62). Interleukin-1 alpha-related eicosanoid production causing fatal arrhythmias may be a hidden mechanism responsible for sudden cardiac death in iron overload thalassemic patients, who die suddenly from overwhelming infection (7).

## POSSIBLE FUTURE THERAPEUTIC MODALITIES

Iron chelation therapy is accepted worldwide as the most effective treatment for iron overload cardiomyopathy. In some cases, iron chelation therapy is not suitable due to its high cost, poor compliance (because of the route of drug administration) and some adverse effects. Calcium channel blockers may be useful in preventing NTBI from entering cardiomyocytes via the L-type $Ca^{2+}$ channel (49-51). Oudit et al (51) demonstrated that amlodipine and verapamil reduced intracellular iron accumulation and oxidative stress without disturbing diastolic and systolic function. L-type $Ca^{2+}$ channel blockers affect not only cardiomyocytes, but also pancreatic beta cells and anterior pituitary cells, which are important target cells for iron toxicity (52). On the other hand, because the pathophysiology of iron overload cardiomyopathy depends mainly on oxidative injury, antioxidant therapy is possibly one of the best alternative choices. Vitamin E has been demonstrated to be effective for this therapeutic purpose (37,54,55). However, vitamin C is not useful because it can promote iron toxicity by reducing iron redox status ($Fe^{3+}$ to $Fe^{2+}$) and enhancing cellular uptake, which may worsen cardiac dysfunction in patients at risk for iron overload cardiomyopathy (55).

Omega-3 PUFAs, abundant in fish oil, have been known for their cardioprotective effects (81). Although they are substrates in lipid peroxidation, the by-products of lipid peroxidation were not increased after omega-3 PUFA supplement (82). However, in intensive oxidative stress due to iron overload, omega-3 fatty acid dietary supplement should be used with caution, unless the antioxidant level is adequate (83). Using selective COX-2 inhibitors when an anti-inflammatory drug is required in these patients may be beneficial in reducing the proarrhythmic effect of the eicosanoid product (prostaglandin E2) (62). Further studies of COX-2 inhibitor treatment in iron overload cardiomyopathy may be worthwhile.

Natural products have played a role as alternative therapeutic modalities in many diseases, including iron overload thalassemia. Curcumin, a constitutent of a type of spice, has been demonstrated to have antioxidative (84,85), anti-inflammatory (84) and iron-chelating effects (86). These beneficial effects may provide vast benefits to iron overload TM patients. However, more interventional studies in animal models and humans are needed to confirm their beneficial role in iron-overload thalassemic cardiomyopathy.

## CONCLUSION

The most common cause of morbidity and mortality in TM patients is iron overload cardiomyopathy, in which the exact pathophysiology is crucial for proper management. NTBI has been accepted as the key culprit. Recently, the L-type calcium channel was strongly proposed as the pathway of intracellular NTBI uptake in cardiomyocytes. Subsequent cellular damage occurs mainly via the free radical-mediated mechanism, in which iron acts as a catalytic agent. Lipid peroxidation seems to play the most important role for both heart failure and arrhythmias, particularly by destroying membrane-embedding enzymes (such as ATPase) and being the source of AA metabolites.

For clinical management, early detection is the goal in asymptomatic patients. Cardiac MR-T2*, tissue Doppler echocardiography, radionuclide angiography and stress echocardiography are useful imaging studies for detecting early cardiac dysfunction. Similarly, many electrophysiological parameters, such as decreased HRV, presence of VLP and impaired baroreflex function, seem to be excellent predictors, especially for arrhythmias. In addition, several electrophysiological parameters that have been documented as risk stratifiers of other cardiovascular diseases (ie, heart rate turbulence) may be applied to iron overload cardiomyopathy. Future investigations of large populations with long-term follow-up are needed to warrant the clinical benefits in iron overload cardiomyopathy.

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