Iron Overload Cardiomyopathy in Clinical Practice

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The cardiomyopathies are heart muscle diseases of primary or secondary origin. Primary cardiomyopathies are often of unknown cause, hence their treatment is limited to general heart failure management. In secondary cardiomyopathies, in contrast, the identification of the underlying cause allows for a more specific, hence effective, approach that, when applied early, may prevent the development of heart failure.

The term iron overload cardiomyopathy (IOC) recently has been introduced to describe a secondary form of cardiomyopathy resulting from the accumulation of iron in the myocardium mainly because of genetically determined disorders of iron metabolism or multiple transfusions. This condition, although previously overlooked, has lately attracted the attention of investigators because iron overload is, on one hand, a frequently encountered condition, especially in association with certain hematologic conditions, and on the other hand, its accurate identification and effective management have now become possible.

IOC has been recently described as a dilated cardiomyopathy, characterized by left ventricular (LV) remodeling with chamber dilatation and reduced LV ejection fraction (LVEF). However, primary hemochromatosis, a genetically determined condition leading to iron overload, is classically categorized as an infiltrative cause of restrictive cardiomyopathy. Moreover, secondary hemochromatosis may lead to severe diastolic LV dysfunction in the early stages of the disease, before LVEF is affected. In the present review, we describe the forms, pathophysiology, and phenotypic expression of IOC, focusing on ventricular geometry and function and describing the early diastolic abnormalities that lead ultimately to heart muscle dysfunction and heart failure. The clinical implications of the condition are also discussed.

Iron Overload
Iron overload is the accumulation of excess body iron in different organs as a result of increased intestinal absorption, parenteral administration, or increased dietary intake. Besides being a crucial component of hemoglobin with a key role in erythropoiesis, oxygen transportation and storage, iron also has further important functions as part of several enzymatic systems and metabolic processes. Thus, iron deficiency results in impairment of functional status even in the absence of anemia, whereas iron repletion therapy is beneficial regardless of the presence of anemia. Iron homeostasis is therefore essential, and is regulated by a complex system that involves iron absorption, transportation, and storage with the participation of several regulatory proteins. Those proteins include ferritin, which serves for the intracellular iron storage; ferroportin, which is responsible for the release of stored iron from duodenal epithelial cells and macrophages in the form of ferrous iron (Fe\(^{2+}\)); hepcidin, which regulates the release of ferrous iron from duodenal cells and macrophages by acting on ferroportin; ceruloplasmin, which oxidizes ferrous iron to ferric iron (Fe\(^{3+}\)) before its transportation; transferrin, the transporter of ferric iron in the circulation; and other less understood ones (Figure 1).

However, iron is a double-facet element, and a derangement of iron homeostasis leading to excessive iron intake and storage is deleterious to several tissues. The heart, along with the liver and the endocrine glands, is the main organ affected by excess iron accumulation, and thus iron-loading conditions are primarily manifested as cardiac dysfunction and failure, liver dysfunction and cirrhosis, and endocrine abnormalities including hypothyroidism, hypogonadism, and diabetes mellitus, as well.

The term iron overload cardiomyopathy describes the different forms of cardiac dysfunction secondary to myocardial iron deposition. Besides being a major cause of morbidity, IOC accounts for one third of deaths in hereditary hemochromatosis, especially in young male patients; it is the leading cause of mortality in thalassemia major; and it is also a major cause of death in other conditions associated with secondary iron overload.

Pathogenesis and Forms
Iron overload may be either primary or secondary (Table 1). The primary form of iron overload is termed hereditary or primary hemochromatosis, an autosomal disorder resulting from mutations in genes encoding proteins involved in iron metabolism. Iron overload in this condition results from the increased intestinal iron absorption and a further derangement of iron metabolism. Four types are currently identified according to the implicated gene mutation. Type 1 results from mutations of the HFE gene on chromosome 6, and it corresponds to classical hereditary hemochromatosis. Type 2 is associated with mutations of the HJV gene on chromosome 1 that encodes heomojuvelin (subtype 1A) or in the HAMP...
gene on chromosome 19 that encodes hepcidin (subtype 2B). Type 3 results from mutations of the TFR2 gene on chromosome 7 encoding transferrin receptor 2. Finally, type 4 is caused by mutations of the SLC40A1 gene on chromosome 2 that encodes ferroportin. All mutations are inherited by the autosomal recessive type, with the exception of type 4, which is inherited as an autosomal dominant condition. Types 1, 3, and 4 are manifested in adulthood and usually during the fourth or fifth decade of life, whereas type 2, also called juvenile hemochromatosis, is clinically expressed much earlier, in the second or third decade, and its phenotype is much more severe.12 The typical clinical triad of hereditary hemochromatosis, is clinically expressed much earlier, in the second or third decade, and its phenotype is much more severe. The typical clinical triad of hereditary hemochromatosis is cirrhosis, bronze skin, and diabetes mellitus, but the phenotype of the disorder is extremely variable and depends on several interfering genetic and other factors, particularly in HFE-related hemochromatosis (type 1). In types 1 and 3, hepatic involvement predominates, whereas in type 2, endocrine and cardiac complications are more pronounced, and heart failure is a frequent cause of death before the age of 30 years.12

Secondary iron overload is mainly caused by the considerably high parenteral iron administration, and is primarily observed in association with transfusion-dependent hereditary or acquired anemias, such as inherited hemoglobinopathies, myelodysplastic syndromes (MDS), myelofibrosis, aplastic anemia, sideroblastic anemia, and Blackfan-Diamond anemia.11 Regarding inherited hemoglobinopathies, which are the most common single-gene disorders in humans, all thalassemia major patients and ≈20% of those with sickle cell disease are transfusion-dependent.13,14 On the other hand, the effective management of MDS and other acquired hematologic conditions with novel agents has improved patients’ survival, increasing at the same time the need for supportive care with blood transfusions.15 Thus, the majority of MDS patients are currently chronically transfused, and it has been calculated that about half of patients who receive 75 to 100 U of transfused blood develop clinically significant myocardial iron overload.13,16 Other conditions associated with secondary iron overload include chronic liver diseases such as alcoholic cirrhosis, Friedreich ataxia, porphyria cutanea tarda, intravenous iron therapy in end-stage renal disease, extreme dietary intake, and some rare disorders affecting iron metabolism, such as congenital transferrinemia or aceruloplasminemia.1,2

Pathogenetic Mechanisms
In hereditary hemochromatosis, mutations of genes encoding crucial proteins involved in iron metabolism lead to an inappropriately high duodenal iron absorption compared with the total body iron content.12 In secondary hemochromatosis, iron overload results primarily from repetitive blood transfusions that saturate the reticuloendothelial system cells with iron, which then spills out to other parenchymal cells.17,18 During iron overload, transferrin, the carrier of iron in the circulation, which is normally ≈30% saturated, becomes fully saturated, and the toxic non–transferrin-bound iron species appear in the circulation.14 It should be stressed that the cellular uptake of non–transferrin-bound iron is not controlled by the negative feedback mechanism that regulates transferring bound iron uptake. This, in combination with the lack of an iron excretory mechanism, leads to intracellular iron accumulation. Uptake of iron from non–transferrin-bound iron species in hepatocytes, cardiac myocytes, and endocrine gland cells leads to tissue iron accumulation and, ultimately, the deleterious effects of iron overload.13 In thalassemia major patients, besides repetitive transfusions, there is also an increase in intestinal iron absorption because of inappropriate hepcidin suppression caused by the ineffective erythropoiesis.

In the presence of iron overload, iron, in the form of ferrous iron (Fe$^{2+}$), enters the myocytes through the voltage-
excitation-contraction coupling, which may in turn be in-
the L-type calcium channels also results in derangement of
membrane lipids, cellular proteins, and nucleic acids. At
antioxidant properties are exceeded, resulting to peroxidation
via the Fenton reaction, which converts ferrous to ferric iron
labile iron leads to the formation of reactive oxygen species
the myocytes in the form of ferritin, hemosiderin, and labile
Secondary iron overload
Hereditary anemias
Hemoglobinopathies
Thalassemia
Sickle cell disease
Diamond–Blackfan anemia
Congenital dyserythropoiesis anemia
Sideroblastic anemia
Acquired anemias
Myelodysplastic syndromes
Myelofibrosis
Aplastic anemia
Leukemias
Myeloproliferative disorders
Stem cell transplantation
Chronic kidney disease
Other conditions
Chronic liver disease
Friedreich ataxia
Aceruloplasminemia
Congenital atransferrinemia
Increased dietary intake

Table 1. Main Conditions Leading to Iron Overload

<table>
<thead>
<tr>
<th>Primary iron overload</th>
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<tbody>
<tr>
<td>Hereditary hemochromatosis</td>
</tr>
<tr>
<td>Type I: HFE-related</td>
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<tr>
<td>Type II: Juvenile</td>
</tr>
<tr>
<td>Subtype A: HJV-related</td>
</tr>
<tr>
<td>Subtype B: HAMP-related</td>
</tr>
<tr>
<td>Type III: TfR2-related</td>
</tr>
<tr>
<td>Type IV: Ferroportin-related</td>
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<tr>
<td>Secondary iron overload</td>
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<td>Hereditary anemias</td>
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<td>Increased dietary intake</td>
</tr>
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dependent L-type calcium channels. Myocardial iron uptake
is much slower in comparison with hepatic uptake, and thus
myocardial iron overload develops at a later stage in com-
parison with hepatic iron overload. Iron deposition occurs
initially in the ventricular myocardium and subsequently in
the atrial myocardium and also affects the conducting system,
but to a lesser extent compared with the working myocar-
dium. The epicardial iron concentration is generally higher
than the subendocardial one, but it was recently shown that
there was no variation in iron deposition among the different
LV segments in patients with severe IOC. Iron is stored in
the myocytes in the form of ferritin, hemosiderin, and labile
cellular iron (free iron), the latter being the most active one.
Labile iron leads to the formation of reactive oxygen species
via the Fenton reaction, which converts ferrous to ferric iron
with the generation of the toxic hydroxyl radical. The cellular
antioxidant properties are exceeded, resulting to peroxidation
of membrane lipids, cellular proteins, and nucleic acids. At
the same time, increased ferrous iron transportation through
the L-type calcium channels also results in derangement of
cardiomyocyte calcium transportation and impaired
excitation-contraction coupling, which may in turn be in-
volved in the development of the diastolic and systolic
ventricular dysfunction seen in association with iron
overload.

The end result of this process is the development of a
cardiomyopathy characterized mainly by LV dysfunction. It
should be noted that myocardial iron overload, although it
holds a key role as a triggering factor in the development of
IOC, is not the only mechanism involved. Early studies in
thalassemia major showed that several indices of LV function
had a poor correlation with the total number of blood units
transfused. Those preliminary findings implied that IOC was
rather a particular type of cardiomyopathy with complex
pathophysiology and not a direct effect simply of iron
infiltration. This concept was later confirmed, because a
number of studies showed that, apart from iron, additional
immunoinflammatory and genetic factors seemed to interfere
in the pathogenesis of IOC, such as myocarditis, the HLA
genotype, and the apolipoprotein E genotype. More
specifically, myocarditis was identified as a cause of LV
failure, whereas the HLA-DQA1*0501 allele and the apo-
lipoprotein E e4 allele were both associated with an increased
prevalence of adverse LV remodeling and reduced LVEF in
patients with thalassemia major.

Besides direct myocardial injury, iron overload may also
affect the heart indirectly through its effects on other organs.
Thus, hepatic dysfunction, endocrinopathies (diabetes melli-
tus, hypothyroidism, hypoparathyroidism), and immune defi-
ciency resulting from iron overload may contribute to the
pathophysiology of IOC.26,27 The pathophysiology of IOC is
summarized in Figure 2.

Phenotypic Expression

In general, IOC is far more frequent in the secondary forms of
iron overload than in primary hemochromatosis. Two pheno-
types of IOC have been identified: the dilated phenotype,
characterized by a process of LV remodeling leading to
chamber dilatation and reduced LVEF, and the restrictive
phenotype, characterized by diastolic LV dysfunction with
restrictive filling, preserved LVEF, pulmonary hypertension,
and subsequent right ventricular dilatation. Those 2 pheno-
types are followed by several other manifestations including
conduction system abnormalities, tachyarrhythmias, and
perimyocarditis.1,23,28

In the early stages of the disease, myocardial iron overload
is expressed as diastolic LV dysfunction. Spirito et al studied
32 young thalassemia major patients with preserved LVEF;
transmitral Doppler flow velocities revealed a restrictive LV
filling pattern in 50% of those patients. To overcome the
potential confounding effects of age, a larger trial in 88
thalassemia major patients with preserved LVEF recruited
both adolescents and adults and evaluated both transmitral
and pulmonary vein diastolic Doppler indices.5 Restrictive
LV filling was also encountered in this cohort, but with a
much lower prevalence (8%). Moreover, all patients with
restrictive LV filling had advanced age and highly elevated
serum ferritin concentration. Similar findings were subse-
sequently reported by other investigators. More recent trials
using natriuretic peptides revealed the presence of elevated
LV filling pressures and diastolic LV dysfunction in the early stages of the disease.\textsuperscript{30,31}

If the cause of iron overload persists and no proper iron chelation therapy is initiated, the majority of patients with IOC develop LV remodeling that ultimately leads to LV dilatation and reduced LVEF, the so-called dilated phenotype of IOC.\textsuperscript{10,32} In a minority of cases (<10%) characterized by severe iron overload, restrictive LV dysfunction leads, in advanced age, to the development of pulmonary hypertension, right ventricular dilatation, and right-sided heart failure without LV anatomic remodeling and with preserved LVEF, even at the final stages, the so-called restrictive phenotype.\textsuperscript{5,32} Whether a patient follows the dilated or the restrictive pathway seems to be crucially dependent on the interaction between the main disease and the additional immunoinflammatory and molecular factors discussed above.\textsuperscript{23–25} The interference of some of those factors, such as myocarditis, leads to the dilated phenotype, which is believed to be multifactorial in pathophysiology.\textsuperscript{10,32}

Cardiovascular magnetic resonance imaging (CMR) with T2* relaxometry made possible the quantitative assessment of iron load and confirmed the close correlation between LVEF and myocardial iron deposition. In the seminal study by Anderson et al,\textsuperscript{33} in 106 thalassemia major patients, LVEF declined progressively as iron burden increased, whereas it remained within normal range in the absence of detectable myocardial iron. Those findings were subsequently confirmed in larger patient populations.\textsuperscript{34,35} Moreover, CMR also revealed evidence of myocardial fibrosis and scars in thalassemia major patients with iron overload,\textsuperscript{36} although the finding was later questioned by other investigators.\textsuperscript{37}

It should be noted that LV diastolic dysfunction and reduced LVEF may both be masked by an anemia-induced high-output state in patients with hemoglobinopathies and other hematologic conditions.\textsuperscript{38} Thus, a pseudonormalized pattern is frequently encountered in transmitral inflow,\textsuperscript{10} which may be unmasked by studying pulmonary vein flow pattern or mitral annulus motion by tissue Doppler imaging. On the other hand, it has been proposed that a higher cutoff value for LVEF should be applied in those patients.\textsuperscript{39}

Right ventricular function may be impaired by LV dysfunction and pulmonary hypertension.\textsuperscript{10} In addition, a form of right ventricular cardiomyopathy was previously reported in a small group of thalassemia major patients with congestive heart failure.\textsuperscript{40} More recently, a retrospective analysis of CMR data in 319 thalassemia major patients showed that right ventricular ejection fraction declined progressively with the increase of myocardial iron load, following a pattern similar to that of LVEF.\textsuperscript{41}

**Clinical Implications**

**Current Impact and Physicians’ Awareness**

The mutations leading to hereditary hemochromatosis are not rare, especially among white populations.\textsuperscript{11} However, the clinical impact of hereditary hemochromatosis on the cardiovascular system is generally limited, and, although IOC may account for a significant percentage of deaths in patients with the juvenile-onset forms, noncardiac complications and mor-
tality usually predominate in the adult-onset forms. In contrast, secondary iron overload has a much greater clinical impact, because it is related to a significantly higher iron-loading rate, and its prevalence has a tendency to rise. On one hand, the growing usage of bone marrow transplantation and stem cell therapies and the improved survival of patients with hematologic malignancies or MDS increase the need for repetitive blood transfusions. On the other hand, the hemoglobinopathies are the most common monogenic disorders in humans, and, although traditionally confined to specific geographical regions, they have currently expanded to a global distribution because of financial immigration and ethnic globalization. Moreover, the survival of patients with hemoglobinopathy currently tends to reach that of the healthy population by virtue of modern therapy. However, IOC has generally been overlooked both by physicians and the medical literature. Given that IOC has a rising clinical impact, bears some distinct clinical features, and requires a particular diagnostic and therapeutic approach, cardiovascular care providers should be aware of this entity.

**Diagnosis and Screening**

The initial evaluation and follow-up plan for patients with IOC or at risk for IOC is presented in Figure 3. History taking, physical examination, standard ECG, and chest x-ray should all be part of patients’ initial evaluation and of their regular cardiac follow-up and screening. The latter is generally performed annually unless cardiac abnormalities or cardiac siderosis are present. History taking may reveal a known or suspected condition causing iron overload, such as hemoglobinopathies, MDS, or other transfusion-dependent hereditary or acquired anemias or hereditary hemochromatosis or other rare disorders of iron metabolism. A wide spectrum of cardiac symptoms, indicative of left- or right-sided heart failure or rhythm disorders, may be present, along with other symptoms related to the underlying disease or iron-induced extracardiac organ damage (hepatic dysfunction, diabetes mellitus, hypogonadism, other endocrine disorders, arthritis). Physical examination may reveal signs of left- or right-sided heart failure, along with findings related to the underlying cause of iron overload or iron-induced injury. Typical skin pigmentation is seen usually in association with moderate to severe iron overload and is practically the only specific sign of iron overload.

**Basic laboratory investigation** includes serum ferritin and transferrin saturation for the diagnosis of iron overload, along with a full blood count, hemoglobin electrophoresis, liver function tests, endocrine tests (diabetes mellitus, thyroid, gonads, etc) to assess the underlying disorder causing iron overload and the potential consequences of iron on organ function. Genetic testing may be needed for the diagnosis or confirmation of hereditary disorders and mainly of hemoglobinopathies (mutations mainly of the β-globin gene cluster) or hereditary hemochromatosis (mutations of HFE, HJV, HAMP, TFR2, or SLC40A1 genes).

Standard resting ECG allows the identification of supraventricular and ventricular arrhythmias and conduction system abnormalities, which are part of IOC clinical phenotype, although serious arrhythmias are usually prevented in patients following modern therapy. Nonspecific repolarization abnormalities may also be seen in association with intensive chelation therapy. Chest x-ray may reveal cardiomegaly due to LV enlargement in patients with the dilated phenotype of IOC, signs of pulmonary congestion in cases
with left-sided heart failure, or left atrial or right ventricular enlargement with or without signs of pulmonary hypertension in those with the restrictive phenotype.

Echocardiography is the main modality used in screening patients with iron-loading conditions for heart disease as part of their initial and regular follow-up evaluation.10 Left and right ventricular systolic and diastolic function abnormalities, and pericardial and valvular involvement, as well, may easily be detected. Impaired diastolic LV function featuring pseudo-normalized or restrictive filling pattern, with or without left atrial enlargement constitute early findings.4,5,22,29,38,47,48 Advanced-stage disease is characterized by left and right cardiac chamber dilatation and reduced LVEF (the dilated phenotype) or, alternatively, by restrictive LV filling with left atrial and right ventricular dilatation, increased pulmonary artery pressure, and preserved LVEF (the restrictive phenotype).23,40,47,48 High cardiac output with chamber dilatation, eccentric LV hypertrophy, and normal or increased LVEF may also be seen.47,48 Although echocardiography identifies the consequences of iron on myocardial structure and function, it does not accurately predict myocardial iron content. However, it provides a simple means for the screening of asymptomatic patients and the follow-up of patients with known pathology.10

Although sophisticated imaging methods such as strain and strain rate may identify subtle LV dysfunction,49 this may not be possible for the imaging techniques used in the everyday clinical practice. The amino-terminal pro-B-type natriuretic peptide may serve as an early index of diastolic LV dysfunction in patients with iron overload.10 Indeed, it was shown that amino-terminal pro-B-type natriuretic peptide might be elevated in thalassemia major patients with preserved LVEF before conventional Doppler indices of diastolic function became abnormal10 or when Doppler and tissue Doppler values were inconclusive.31

CMR-derived T2* relaxation time is currently the mainstay for the quantitative assessment of cardiac iron deposition.11 Introduced a decade ago,33 this modality has revolutionized the clinical management of patients with hemoglobinopathies and other iron overload conditions, because it allows the accurate diagnosis and quantification of myocardial and hepatic iron deposition and hence the tailoring and monitoring of iron chelation therapy. Actually, it is postulated that the currently observed survival improvement in thalassemia major is partly attributable to the introduction of CMR-T2* imaging into clinical practice.32 The T2* relaxation time is mainly affected by iron in the form of hemosiderin and not by ferritin or labile cellular iron, but because there is a continuous reflux between the 3 forms of stored iron, the technique accurately predicts tissue iron content.11 Measured in a full-thickness area of interest in the interventricular septum, T2* is highly representative of global myocardial iron.20 A value of 20 ms is considered to be the threshold for myocardial iron content.11

Figure 4. Schematic presentation of the relationship between cardiac T2* values, cardiac tissue iron concentration, and risk for heart failure (data extracted from Kirk et al50).
the technique is still limited by its restricted availability in several developing countries.

The traditional predictor of iron overload, serum ferritin, increases linearly with the number of blood transfusions and is closely correlated with liver iron content. However, it is also an acute-phase protein that increases in several other conditions and is poorly correlated with myocardial iron load. Nevertheless, serum ferritin provides a simple means for the monitoring of iron chelation therapy. Liver iron concentration, on the other hand, requires an invasive procedure (liver biopsy) and is also poorly correlated with myocardial iron content.

The diagnosis of IOC is made when evidence of heart disease, particularly diastolic LV dysfunction with restrictive filling or LV remodeling and reduced LVEF, coexists with iron overload (serum ferritin >300 ng/mL, transferrin saturation >55%) and cardiac siderosis (cardiac T2* <20 ms; Figure 5). Despite the poor correlation of serum ferritin with cardiac iron or the presence of IOC, a concentration >2500 ng/mL still indicates the presence of significant total body iron content with a high risk of heart disease. Besides identifying patients with established IOC, it is of utmost importance to also identify those at risk for developing IOC, namely patients with iron overload with or without cardiac siderosis, and those with conditions potentially causing iron overload, as well, because proper and timely therapy prevents the development of IOC.

**Prevention and Therapy**

All 4 types of hereditary hemochromatosis respond to therapeutic phlebotomy. Phlebotomy is an easily applicable, safe, and inexpensive procedure that prevents the development of iron-induced organ damage and prolongs survival when initiated early, but it cannot reverse the established severe complications, including liver cirrhosis, insulin-dependent diabetes mellitus, hypogonadism, and destructive arthritis. It is generally applied in patients with hereditary hemochromatosis when serum ferritin exceeds 1000 ng/mL or in the presence of symptoms and consists of an induction phase with weekly removal of 1 to 2 blood units to reduce serum ferritin <50 ng/mL and transferrin saturation <30%, followed by a life-long maintenance phase aiming at serum ferritin <100 ng/mL and transferrin saturation <50% (Figure 6). Since the introduction of the potent iron chelator deferoxamine in the 1970s, the management of secondary iron overload also became possible. The subsequent advances in the field of chelators have rendered iron overload efficiently treatable and IOC almost completely preventable. Three chelators are currently available: the parenteral deferoxamine and the oral deferiprone and deferasirox. A vast clinical and research experience on their use has been accumulated in patients with hemoglobinopathies and mainly thalassemia major. In those patients, proper iron chelation regimens, guided by CMR-T2*, have dramatically improved the prognosis and survival, preventing the development of LV dysfunction and heart failure among other complications. Moreover, dual chelation regimens combining deferoxamine and deferiprone have proved considerably effective in improving LVEF in patients with severe myocardial siderosis and/or heart failure. The available evidence on the comparative efficacy of the 3 available chelators in patients with...
Thalassemia major in the CMR era is outlined in Table 2. Furthermore, recent trials have also documented the efficacy of chelation therapy in reducing iron burden and improving survival in transfusion-dependent patients with MDS.65–67 Finally, a novel oral chelator with the code name FBS0701 is currently under clinical testing.68

In patients with thalassemia major, chelation therapy is usually started 2 to 3 years after the initiation of transfusions.44 The applied dosing scheme depends on the presence and severity of heart and liver siderosis, the estimated total body iron burden, the presence of iron-induced organ dysfunction, and the rate of transfusion therapy.17 In this context, the role of T2* relaxometry is important for the tailoring of therapy. More specifically, patients with severe cardiac siderosis (T2* <10 ms) or established IOC, particularly LV remodeling and reduced LVEF or clinically manifested heart failure, require intensive therapy, usually with a combination of deferoxamine and deferiprone or, in clinically unstable cases, continuous deferoxamine infusion to increase T2* >20 ms and improve cardiac performance.10,17,26,40,41,44 Patients with low to moderate cardiac iron burden (T2* 10–19 ms) and without evidence of IOC are generally treated with a single-drug chelation regimen to increase T2* ≥20 ms along with careful and close follow-up, whereas combination ther-

![Figure 6. Management of iron chelation in patients with or at risk of iron overload cardiomyopathy. ACEi indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.](image)

### Table 2. Clinical Trials on the Efficacy of Iron Chelation Regimens for the Management of Iron Overload Cardiomyopathy in Thalassemia Major Patients in the Era of Cardiovascular Magnetic Resonance and T2* Relaxometry

<table>
<thead>
<tr>
<th>Chelation Regimen</th>
<th>Study Population (n)</th>
<th>Cardiac Findings</th>
<th>Reference</th>
</tr>
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<tr>
<td>DFP vs DF0</td>
<td>45</td>
<td>T2* and LVEF: DFP&gt;DFO</td>
<td>Anderson et al53</td>
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<tr>
<td>DFP vs DF0</td>
<td>129</td>
<td>DFP: lower occurrence of heart disease (4% vs 21%)</td>
<td>Piga et al54</td>
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<tr>
<td>DFP vs DF0</td>
<td>72</td>
<td>No difference in HSIR</td>
<td>Galia et al55</td>
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<tr>
<td>DFP vs DF0</td>
<td>61</td>
<td>DFP: greater improvement in T2* and LVEF</td>
<td>Pennel et al56</td>
</tr>
<tr>
<td>DFR vs DF0</td>
<td>36</td>
<td>T2*: DFP&gt;DFO</td>
<td>Pepe et al57</td>
</tr>
<tr>
<td>DFR vs DF0</td>
<td>50</td>
<td>T2* improvement only with DFP+DFO</td>
<td>Christoforidis et al58</td>
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<td>DFP+DFP vs DFO</td>
<td>65, T2* 8–20 ms</td>
<td>T2* and LVEF improvement: DFP+DFP&gt;DFO</td>
<td>Tanner et al59</td>
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<tr>
<td>DFO+DFP</td>
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<td>T2* and LVEF improvement</td>
<td>Tanner et al60</td>
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<td>DFO vs DFP vs sequential DFO-DFP vs DFP+DFP</td>
<td>265</td>
<td>DFO monotherapy: worse survival</td>
<td>Maggio et al61</td>
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<td>DFO vs DFP vs DFX</td>
<td>232</td>
<td>T2* improvement with DFO+DFP and DFP, not with DFO</td>
<td>Berdoukas et al62</td>
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<td>DFX</td>
<td>114, T2* 5–20 ms</td>
<td>T2* improved, LVEF unchanged</td>
<td>Pennell et al62</td>
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<td>DFX</td>
<td>78, T2* ≥20 ms</td>
<td>T2* unchanged, LVEF improved</td>
<td>Pennell et al63</td>
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<td>Pepe et al64</td>
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<td>DFX</td>
<td>155</td>
<td>LVEF: DFP or DFO&gt;DFX</td>
<td>Pennell et al66</td>
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</table>

DFP indicates deferiprone; DFO, deferoxamine; DFX, deferasirox; LVEF, left ventricular ejection fraction; and HSIR, heart to muscle signal intensity ratio.
apy may also be considered for those at the lower end of this spectrum (T2* 10–15 ms). Finally, patients without cardiac siderosis (T2* ≥20 ms) and no evidence of IOC are generally treated with a single-drug regimen to maintain T2* ≥20 ms. In the latter patients, oral agents are usually preferred for convenience.

In transfusion-dependent patients with MDS or other acquired hematologic conditions, iron chelation therapy is generally initiated after 10 to 20 transfusions to prevent clinically significant tissue iron accumulation. Patients with MDS are usually managed with a single-agent chelation regimen, and deferasirox tends to be the mainstay in these patients because of its simple dosing scheme (oral administration, once daily).

Besides the better management of iron overload by iron chelators, the more efficient control of blood-borne infections due to the enhanced safety of blood transfusions has also contributed to the lower rates of pericarditis and myocarditis. However, the effects of iron chelators on diastolic LV function have not yet been clarified, and LVEF may still be affected in a small number of cases despite proper chelation therapy. The efficacy of iron chelators is partly limited by the fact that only a portion of total body iron content is directly chelatable. More specifically, from the 3 forms of stored iron, labile cellular iron is the most accessible to chelation, and hemosiderin is the least accessible one. Moreover, the rate of iron clearance during chelation therapy is much slower in the heart than in the liver.

In the presence of symptoms and signs of heart failure and/or objective evidence of functional or structural cardiac dysfunction, patients should be treated with intensification of iron chelation therapy and conventional heart failure medication, including renin-angiotensin-aldosterone system inhibitors and β-blockers, according to the current recommendations that apply to the general heart failure population. It should be stressed that in a group of thalassemia major patients with heart failure, the combination of regular transfusion–chelation therapy with the conventional heart failure therapy was followed by a 5-year survival rate similar to that of the regular heart failure population. Other cardioactive drugs may be used as appropriate in individual cases, including diuretics for the symptomatic relief in cases with congestion, warfarin in the presence of atrial fibrillation, thromboembolic complications, or central line in situ, and digitalis or amiodarone, as well.

Some patients with thalassemia or other hemoglobinopathies may require slow uptitration and have low maximum tolerated doses of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers because of low arterial blood pressure resulting from peripheral vasodilatation in the context of chronic anemia. Finally, in cases presenting with acute heart failure, intravenous loop diuretics, inotropes, renal replacement therapy, and mechanical circulatory support are used according to clinical needs.

Patients with IOC and particularly those with hemoglobinopathies and other secondary causes of iron overload are not good candidates for heart transplantation, in general, because of the multigorgan injury caused by iron overload and the chronic blood-borne infections, including hepatitis B and C. As a result, heart transplantation has only been performed in a limited number of selected patients. According to a report in 2005, heart transplantation had been performed in 16 patients with IOC, including 11 with primary hemochromatosis, 4 with thalassemia major, and 1 with Diamond-Blackfan anemia, with an overall 10-year survival rate of 41%. A successful combined liver and heart transplantation has also been reported in a patient with thalassemia major.

In conclusion, iron overload, resulting mostly from transfusion-dependent anemias and primary hemochromatosis, is a more frequently encountered condition than generally is believed. Iron-induced heart disease is mainly caused by secondary iron overload and involves a particular type of cardiomyopathy with 2 main LV phenotypes, a more frequent dilated one and a less frequent restrictive one. The management of iron overload with proper iron chelation therapy guided by CMR T2* relaxometry is the key for the prevention and treatment of IOC, in addition to other disease-specific modalities and the conventional heart failure therapy.

Disclosures

None.

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