CARDIOLOGY Rounds®

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Iron-overload Cardiomyopathy Associated with Iron-overload Conditions: Incidence, Pathophysiology, and Treatment

By GAVIN Y. OUDIT, MD, PHD, FRCPC, and GORDON MOE, MD, FRCPC

The prevalence of primary (hereditary) hemochromatosis and secondary iron-overload (hemosiderosis) is reaching epidemic levels worldwide. Iron-overload leads to excessive iron deposition in a wide variety of tissues, including the heart and endocrine tissues. Chronically elevated cardiac iron concentrations impair diastolic function, increase the propensity for arrhythmias and, ultimately, cause end-stage dilated cardiomyopathy. The presence of iron-overload cardiomyopathy – while being a leading cause of morbidity and mortality in patients with primary hemochromatosis – is the primary determinant of survival in patients with secondary iron overload. Iron-induced cardiovascular (CV) injury also plays a role in acute iron toxicosis (iron poisoning), myocardial ischemia-reperfusion injury, cardiomyopathy associated with Friedreich's ataxia, pulmonary hypertension, and vascular dysfunction. The mainstay therapies for iron-overload associated with primary hemochromatosis and secondary iron-overload are phlebotomy and iron chelation therapy, respectively. Recent studies have established that L-type Ca^{2+} channels (LTCC) provide a high capacity pathway for ferrous (Fe^{2+}) uptake into cardiomyocytes in iron-overload conditions and that LTCC blockers may represent a new therapeutic tool to reduce the toxic effects of excess iron on the cardiovascular system. This issue of *Cardiology Rounds* provides an overview of primary and secondary iron overload and describes evolving treatment modalities for this increasingly common condition.

Ferrous (Fe^{2+}) and ferric (Fe^{3+}) iron are essential for cell metabolism and the function of many cellular enzymes. Consequently, iron levels are precisely regulated under normal physiological conditions.[1,2] The biological importance of iron is largely attributable to its chemical properties as a transition metal, wherein it readily undergoes oxidation-reduction reactions between its ferric (Fe^{3+}) and ferrous (Fe^{2+}) states. Iron is an essential constituent of hemoproteins such as hemoglobin, myoglobin, the cytochrome p450 system, iron-sulfur (Fe-S) proteins, and many other proteins essential for cellular metabolism.[1,2] Under physiological conditions, iron transport is highly conserved and controlled via negative feedback regulatory mechanisms involving transferrin and its receptors, as well as other iron transporters.[2] In several clinical conditions, including primary hemochromatosis and secondary iron-overload, iron metabolism is perturbed and, in combination with modified environmental factors, leads to chronic iron-overload and its associated morbidity and mortality.[3-6] The prevalence of iron-overload conditions are rapidly increasing worldwide owing, in part, to a reduction in childhood mortality and increased use of blood transfusions.[3-6]

In iron-overload conditions, iron in the circulation typically exceeds the serum transferrin iron-binding capacity, leading to the appearance of non-transferrin-bound iron (NTBI), which is highly reactive.[7,8] NTBI uptake into cells bypasses the normal negative feedback regulatory mechanisms that control cellular iron uptake and metabolism.[2,7] Excess uptake of NTBI, combined with the lack of an effective iron excretory pathway, leads to the expansion

St. Michael's Hospital
30 Bond St.,
Suite 7049, Queen Wing
Toronto, Ont. M5B 1W8
Fax: (416) 864-5941

of the labile intracellular iron pool (LIP), as well as the formation of highly-reactive oxygen free radicals causing peroxidation of membrane lipids and oxidative damage to cellular proteins.[1,2] Iron-mediated cellular damage plays a key pathophysiological role in multiple disorders, including acute iron toxicosis, iron-overload cardiomyopathy, Friedreich's ataxia associated cardiomyopathy, and myocardial ischemia-reperfusion injury.[9]

Iron-overload conditions

Primary hemochromatosis (hereditary or idiopathic) is a common inherited disorder and presents as 4 distinct subtypes.[1,6] In this condition, excessive iron accumulation results primarily from increased gastrointestinal (GI) absorption of iron, coupled with abnormal iron metabolism in other tissues and cell types.[1,2,6]

- Type 1 primary hemochromatosis (classic hereditary hemochromatosis) is an autosomal recessive disorder linked to mutations in the *HFE* gene, which is involved in the control of GI absorption of iron. Mutations in the *HFE* gene involve either a single-base change, resulting in a tyrosine for cysteine substitution at position 282 (C282Y),[1,6] or a substitution of aspartate for histidine at position 63 (H63D).[1,6] The distribution of the 2 mutations differs, with the C282Y mutation limited to people of northern European ancestry and an allele frequency of about 10%, while the H63D mutation occurs at allele frequencies of >5% in Mediterranean and Middle Eastern regions, as well as the Indian subcontinent.[10]
- In addition to classical (type 1) hemochromatosis, there are several other types of primary hemochromatosis (types 2, 3, and 4) that have been linked to mutations in various proteins involved with iron metabolism.[6,11]

Unlike primary hemochromatosis, secondary iron-overload occurs primarily in patients with hereditary anemias, including alpha-thalassemia,[12] beta-thalassemia,[4] and sickle cell anemia.[13] In these patients, excessive iron exposure and secondary iron-overload ensues mainly because of repeated blood transfusions, as well as increased GI iron absorption in the setting of ineffective erythropoiesis.[1,2,4] A reduction in childhood mortality due to infection and malnutrition, coupled with increased use of chronic blood transfusions, have led to a growing incidence of iron-overload in patients with thalassemia and sickle cell disease (SCD).[3,5,13,14]

Thalassemia originates mainly from the Mediterranean region, Africa, the Middle East, the Indian subcontinent, and Southeast Asia, where estimates of gene frequencies range from 3% to 10% in some areas, but can reach frequencies as high as 30%-40% in certain subpopulations.[4,5,12] Sickle cell anemia is the most common and most severe form of SCD caused by the homozygous presence of sickle hemoglobin (Hgb S) and occurs most commonly in individuals of African ancestry. In the United States, 9% of African Americans carry the sickle cell trait and 1 in 600 has sickle cell anemia.[15,16] In addition to thalassemia and SCD, several other clinical disorders are associated with secondary iron-overload, including sideroblastic anemia, myelodysplastic syndrome, acute myeloid leukemia, congenital dyserythropoietic anemia, and chronic renal failure.[9]

Iron-overload induced cardiac disease

Iron-overload cardiomyopathy

Iron-overload cardiomyopathy is a common cause of CV death worldwide in subjects in their second and third decades of life.[3-5, 9,17,18] Indeed, iron-overload cardiomyopathy is the most important determinant of survival in European,[19] North American,[17,18] and Chinese[20] patients with thalassemia major. Although iron chelation therapy is widely used for treating iron-overload, recent data have shown that iron-overload cardiomyopathy and associated high mortality are still common in these patients.[20,21] Long-term follow-up studies in beta-thalassemia patients have established that the level of cardiac iron accumulation correlates directly with both the occurrence of heart disease and mortality,[4,17,18] while in patients with primary hemochromatosis, CV disease also contributes significantly to their mortality and morbidity.[22-25]

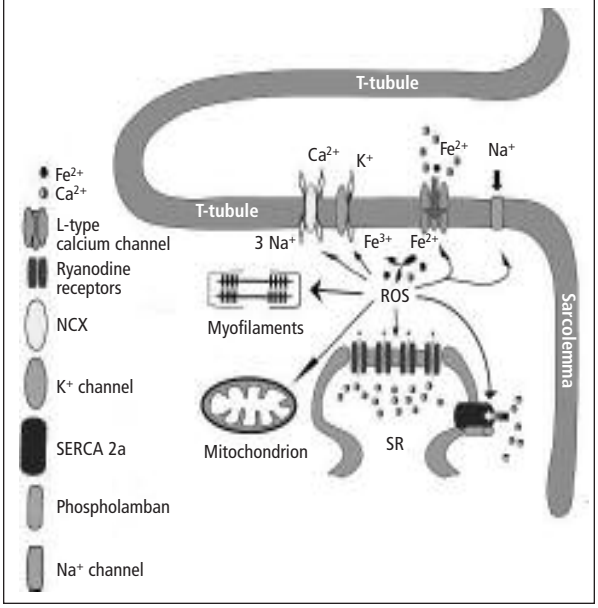
Iron-overload cardiomyopathy, regardless of its origin, is characterized by a restrictive cardiomyopathy with prominent early diastolic dysfunction that invariably progresses to end-stage dilated cardiomyopathy (Figure 1).[9,12,24,26,27] Diastolic dysfunction has been shown to be an independent prognostic marker of mortality.[28] Additional risk factors such as myocardial inflammation,[29,30] apoE polymorphism (indicator of low intrinsic antioxidant status),[31] and the manganese-superoxide dismutase (MnSOD) genotype (indicator of antioxidant potential),[32] may also modify and contribute to the early onset of heart failure in patients with iron-overload. Primary hemochromatosis mutations may also predispose cancer patients to doxorubicin-induced cardiomyopathy.[33] Chronic iron-overload can lead to a variety of arrhythmias, including atrioventricular (AV) block, conduction defects, bradyarrhythmias, tachyarrhythmias, and sudden cardiac death.[17,18,24,34,35] Iron-overload may also aggravate myocardial ischemia-reperfusion injury due to increased formation of reactive oxygen species (ROS) and reduced antioxidant reserve.[9]

The pathophysiology of iron-overload is clearly mediated by ROS, whereby the cytoplasmic labile iron pool becomes available for Fenton-type reactions. This leads to the conversion of reduced iron (Fe^{2+}) into

oxidized iron (Fe^{3+}) and generation of free radicals, including the highly reactive hydroxyl radical ($OH\cdot$).[9] When iron levels are elevated, excessive free radical generation leads to increased peroxidation and damage to lipids, proteins, and nucleic acids, triggering cellular damage and depletion of antioxidants.[36] The effects of free radical production and oxidative stress in conditions of acute iron toxicosis and iron-overload cardiomyopathy have been well documented in patients with primary hemochromatosis, beta-thalassemia major, and end-stage kidney disease.[37-39] In patients with primary hemochromatosis, the MnSOD genotype affects the risk of developing iron-overload cardiomyopathy and could represent a modifier gene of iron-mediated toxicity.[32] In patients with iron-overload, there is antioxidant depletion with increased lipid peroxidation, which is strongly inversely associated with NTBI.[37-39]

The permeation of reduced iron (Fe^{2+}) through cardiac LTCCs may be particularly relevant because this directly delivers reactive ferrous iron to the major regulators of excitation-contraction coupling in cardiomyocytes.[9] The Fe^{2+}-induced slowing of Ca^{2+} current inactivation by 0.5 mM µM Fe^{2+} results in a 50% increase in the time integral of the Ca^{2+} current and net Ca^{2+} influx,[40] which may possibly contribute to the impaired diastolic function observed during the early stages of iron overload.[12,24,26,27] With higher concentrations of ferrous iron (2-4 mM), there is a reduction in native *Ica* due to competition with ferrous iron.[40] This may contribute to the systolic dysfunction that is characteristic of more advanced iron-overload cardiomyopathy.[41] Cardiac excitation-contraction couplings are highly sensitive to changes in the cellular redox state, leading to reduced systolic and elevated diastolic Ca^{2+} levels, thereby causing impaired systolic and diastolic function that is characteristic of iron-overload cardiomyopathy (Figure 1).[9,36,42] Sinoatrial and atrioventricular conduction disease likely results from a combination of chronic iron deposition in the node tissue (and its subsequent electrophysiological effects), coupled with increased interstitial fibrosis.[34,42,43] Action potential shortening and abnormal impulse conduction,[35,44] in the setting of myocardial fibrosis[36,42] and a heterogeneous pattern of iron deposition,[34,44,45] increases the propensity for unidirectional conduction block, wavefront breakup, and creation of arrhythmic ventricular re-entry circuits. Iron-induced oxidative damage has also been linked to increased cardiomyocyte loss due to apoptosis,[36] altered cellular metabolism as seen in Friedreich's ataxia,[46] and/or iron-mediated stimulation of cardiac fibroblasts that may contribute to increased myocardial fibrosis.[7,9]

Figure 1: Interaction between iron-mediated oxidative stress and the excitation-contraction coupling in a cardiomyocyte

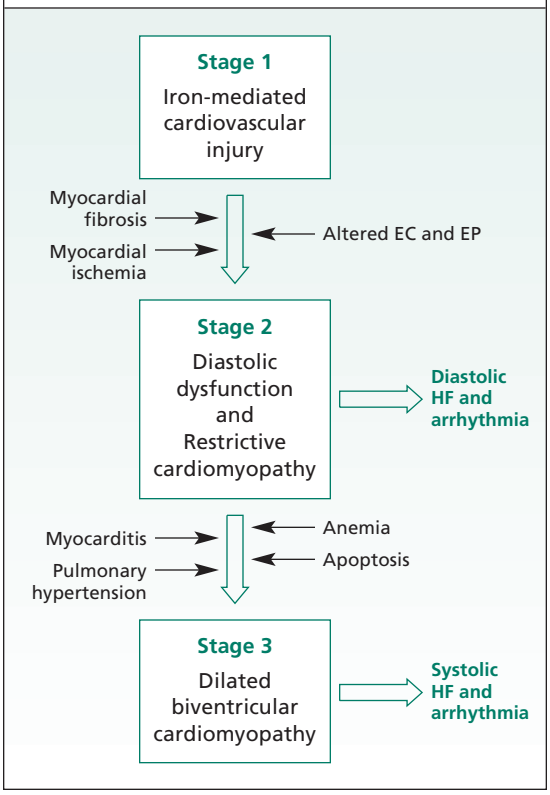


ROS=Reactive oxygen species; SERCA2a=Sarcoplasmic reticulum Ca^{2+}ATPase isoform 2; NCX=Sodium-calcium exchanger; SR=Sarcoplasmic reticulum.

Hemolysis, pulmonary hypertension, and right ventricular dysfunction

Sickle cell disease and thalassemic syndromes are characterized by a state of nitric oxide resistance due to chronic hemolysis, which reduces nitric oxide bioavailability, leading to endothelial dysfunction.[47] Hemolysis releases erythrocyte arginase that limits L-arginine bioavailability and erythrocyte hemoglobin, which scavenges nitric oxide. This results in endothelial dysfunction, vasoconstriction, and increased thrombosis, pulmonary hypertension, and mortality.[47,48] Chronic thromboembolic disease may also contribute to pulmonary hypertension in these patients.[41] Both pulmonary hypertension (tricuspid regurgitation velocity ≥2.5 m/s) and diastolic dysfunction (mitral E/A ratio <1) are independent predictors of increased mortality in patients with sickle cell disease.[28,49] Elevated plasma levels of N-terminal proß-type natriuretic peptide (NT-proBNP) are an important marker of pulmonary hypertension and increased mortality in these patients.[50] While pulmonary hypertension clearly contributes to right heart dysfunction in these patients, the majority of patients with beta-thalassaemia major and severe congestive heart failure have a unique hemodynamic pattern similar to that described in predominant right ventricular infarction, indicating severe right ventricular cardiomyopathy, in addition to left ventricular dysfunction (Figure 2).[41,51]

Figure 2: Pathophysiology of iron-mediated cardiovascular diseases



EC=Excitation-contraction coupling, EP=Electrophysiology; HF=Heart failure; PH=Pulmonary hypertension.

Diagnosis and assessment of iron-overload cardiomyopathy

The diagnosis of iron-overload is based on a careful history and physical examination. There are several well-recognized clinical conditions associated with iron-overload (Table 1). The cardiologist often functions as a consultant and should ascertain whether the patient has iron-overload cardiomyopathy. Iron-overload is a systemic process and is associated with multi-system manifestations of disease, including liver disease and endocrinopathies (eg, diabetes mellitus and pituitary dysfunction). In patients suspected of having secondary iron-overload, an important aspect of the clinical assessment includes determining the cumulative units of blood transfusion and/or IV iron that the patient has received. Several biochemical tests, imaging modalities, genetic studies, and liver and/or heart biopsy are available to the clinician when assessing patients for the presence of iron-overload cardiomyopathy.

Iron studies: A serum transferrin saturation that is >45%, a serum ferritin level >200 µg/L in premenopausal women, and a serum ferritin level >300 µg/L in men and postmenopausal women are indicators for primary hemochromatosis.[1,6] Serum ferritin is also commonly elevated in patients with secondary iron-overload and, although it correlates poorly with myocardial iron deposition, it remains a useful screening test for secondary iron-overload. Clinicians need to recognize that elevated serum ferritin levels may result from other causes besides iron-overload, including inflammation, infection, cancer, and end-stage renal disease.

Transthoracic echocardiogram: Echocardiography can provide a basic assessment of ventricular size and function. Although overt systolic dysfunction develops late in the course of the illness, assessment of diastolic function and estimation of pulmonary artery systolic pressure are important. Transmitral E- and A-waves, tissue Doppler, strain-rate imaging, and tricuspid regurgitant jet velocity are important tools to provide a complete assessment of diastolic function and pulmonary hypertension, which are characteristic of iron-overload cardiac dysfunction.[28,41,49] The detection of diastolic dysfunction in patients with secondary iron-overload has important prognostic importance.[28]

Cardiac magnetic resonance imaging: The evaluation of the T2* relaxation time is an excellent non-invasive correlate of myocardial iron deposition and a useful technique following a response to iron-chelation therapy.[52]

Genetic studies: Genetic screening for the C252Y and H52D mutations for type 1 primary hemochromatosis is now widely available. Genetic testing also provides a basis for family counseling. Hemoglobin electrophoresis for the detection of congenital hemoglobinopathies is a routine test that is widely available.

Liver and/or heart biopsy: Liver and/or right ventricular biopsy are not routinely used, but can serve as definitive assessment of tissue iron stores while allowing a detailed histological assessment of end-organ damage.

Table 1: Conditions associated with iron-overload cardiomyopathy

Primary hemochromatosis
• Classical (type 1)
• Nonclassical (types 2, 3 and 4)
Secondary Iron-overload
• Alpha- and beta-thalassemia
• Sickle cell anemia
• Myelodysplastic syndrome
• IV iron supplementation in patients with ESRD
• Friedreich's ataxia (mitochondrial iron-overload)

ESRD = end-stage renal disease

Treatment of iron-overload cardiomyopathy

Iron-removal and heart failure management

Currently, the mainstay therapy for excessive iron deposition in patients with primary and secondary hemochromatosis is phlebotomy and iron-chelation, respectively, which are designed to facilitate whole-body iron removal. In patients with primary hemochromatosis, a maintenance phlebotomy schedule should be continued following primary iron depletion to prevent reaccumulation of iron. A reasonable goal is to keep the serum ferritin concentration at 50 ng/mL or less.[22,24,53] Phlebotomy therapy that is initiated early can be expected to result in a normal lifespan; however, in patients with LV dysfunction, it can be the reverse.[22,24,53] Unfortunately, patients with primary hemochromatosis are often diagnosed and treated only after iron-overload becomes advanced.[22,24,53]

In patients with secondary iron-overload, iron chelation therapy is the main therapy available. It utilizes the parenteral iron chelator, deferoxamine, or the oral iron chelator, deferiprone. Chelation has been shown to improve ventricular function, prevent ventricular arrhythmias, and reduce mortality in patients with secondary iron-overload.[4,17,18,21,41,52] In comparison to standard chelation monotherapy with deferoxamine, combination treatment with additional deferiprone reduces myocardial iron, and improves ejection fraction and endothelial function in thalassemia major patients with mild-to-moderate cardiac iron loading. While chelation therapy has been consistently shown to reduce the CV burden from secondary iron-overload, chelation therapy is cumbersome, associated with toxic side effects, and has only a limited impact on clinical outcome.[4,21,41] Patients with heart failure should be managed with the same basic principles as patients with dilated cardiomyopathy and systolic heart failure.[41] Clearly, early use of angiotensin-converting enzyme (ACE) inhibitors and beta-adrenergic blockers, together with device therapies such as pacemakers and automated internal defibrillators, should be routine therapy for patients with iron-overload systolic heart failure.[41]

Potential new therapies: antioxidants and calcium channel blockers

Given the high degree of oxidative damage in iron-overload conditions, the use of antioxidants is a potentially rational therapy in these patients. In a murine model of iron-overload, taurine supplementation reduced myocardial iron burden, prevented iron-overload oxidative damage, and preserved cardiac function.[36] The recognition that LTCCs are critical transporters of iron in conditions of iron-overload opens up the possibility of combining calcium channel blockers (CCBs) with standard chelation therapy for the treatment and/or prevention of iron-overload cardiomyopathy. Unlike iron chelators, which are most effective in removing excess iron accumulation in cells, the use of CCBs is expected to be particularly effective early in iron-overload by reducing tissue iron uptake and preventing disease progression. However, the negative inotropic and chronotropic effects of CCBs may limit their applicability in the setting of advanced dilated cardiomyopathy and/or conduction blocks. Blockade of the LTCC may also provide additional benefits beyond those of direct inhibition of Fe^{2+} entry into cardiomyocytes and endocrine tissues. These benefits include a potential reduction in Fe^{2+}-induced Ca^{2+} overload as a result of LTCC inactivation[40] and facilitation of diastolic ventricular filling.[54] Finally, CCBs may promote myocardial microvascular perfusion by vasodilating coronary arterioles, while improving coronary endothelial function.[55,56] Dihydropyridines, like amlodipine, also possess antioxidant properties.[56] Given the high degree of oxidative stress, diastolic dysfunction, and possibility for coronary endothelial dysfunction in iron-overload cardiomyopathy, these effects may increase the potential therapeutic benefits of CCBs in patients with iron-overload. Clearly, clinical trials are warranted to establish the potential clinical efficacy and safety of CCB treatment in patients with iron-overload.

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