

Management of cardiac hemochromatosis

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Abstract

Iron-overload syndromes may be hereditary or acquired. Patients may be asymptomatic early in the disease. Once heart failure develops, there is rapid deterioration. Cardiac hemochromatosis is characterized by a dilated cardiomyopathy with dilated ventricles, reduced ejection fraction, and reduced fractional shortening. Deposition of iron may occur in the entire cardiac conduction system, especially the atrioventricular node. Cardiac hemochromatosis should be considered in any patient with unexplained heart failure. Screening for systemic iron overload with serum ferritin and transferrin saturation should be performed. If these tests are consistent with iron overload, further noninvasive and histologic confirmation is indicated to confirm organ involvement with iron overload. Cardiac magnetic resonance imaging is superior to other diagnostic tests since it can quantitatively assess myocardial iron load. Therapeutic phlebotomy is the therapy of choice in nonanemic patients with cardiac hemochromatosis. Therapeutic phlebotomy should be started in men with serum ferritin levels of 300 µg/l or more and in women with serum ferritin levels of 200 µg/l or more. Therapeutic phlebotomy consists of removing 1 unit of blood (450 to 500 ml) weekly until the serum ferritin level is 10 to 20 µg/l and maintenance of the serum ferritin level at 50 µg/l or lower thereafter by periodic removal of blood. Phlebotomy is not a treatment option in patients with anemia (secondary iron-overload disorders) nor in patients with severe congestive heart failure. In these patients, the treatment of choice is iron chelation therapy.

Key words: hemochromatosis, cardiomyopathy, iron overload.

Introduction

Hemochromatosis is caused by abnormal deposition of iron in parenchymal organs causing organ toxicity and dysfunction. Cardiac hemochromatosis or primary iron-overload cardiomyopathy is an important and potentially preventable cause of heart failure. Iron-overload syndromes may be hereditary or acquired. There are 4 subtypes of hereditary hemochromatosis resulting from increased gastrointestinal absorption of iron into the bloodstream. Reduced activity or reduced synthesis of hepcidin cause most cases of hemochromatosis. The 4 subtypes are type 1 caused by the high iron (HFE) gene which accounts for more than 80% of hemochromatosis cases, type 2 caused by the hemojuvelin gene, type 3 caused by the transferrin receptor-2 gene, and type 4 caused by the ferroportin gene. Iron overload cardiomyopathy is defined as systolic or diastolic cardiac dysfunction caused by increased deposition of iron and emerging as an important cause of congestive heart failure because

of the increased incidence of this disorder seen in thalassemic patients and in patients with hereditary hemochromatosis [1]. Cardiomyocyte ferroportin regulates cellular iron homeostasis, and the site of myocardial iron deposition determines the severity with which cardiac function is affected [2]. The prevalence of hemochromatosis in the United States of America is 0.37%. Thalassemia is an example of a hereditary anemia requiring frequent blood transfusions. Thalassemia occurs in 4.4 of every 10,000 live births throughout the world. Alpha-thalassemia is most common among persons of Southeast Asian descent. Beta-thalassemia is most common among populations of Mediterranean, African, and South Asian ancestry.

Clinical features

Patients may be asymptomatic early in the disease. Once heart failure develops, there is rapid deterioration. Cardiac hemochromatosis causes a dilated cardiomyopathy with dilated ventricles, low left ventricular ejection fraction (LVEF), and decreased fractional shortening [3, 4]. Patients may have exertional dyspnea caused by left ventricular diastolic dysfunction with restrictive hemodynamics and increased filling pressures. Dilated cardiomyopathy with a low LVEF develops as the disease progresses. Biventricular failure causes pulmonary congestion, peripheral edema, and hepatic congestion [5]. Pericardial constriction or tamponade caused by pericardial iron deposition may result in rapid clinical deterioration [6]. Angina pectoris without coronary artery disease responding to venesection may also occur [7].

Deposition of iron may occur in the entire cardiac conduction system, especially the atrioventricular node. Complete atrioventricular block caused by iron deposition may need placement of a permanent pacemaker [8]. Iron deposition in the cardiac tissue causes nonhomogenous electrical conduction and repolarization with atrial and ventricular tachyarrhythmias [9]. Chronic iron overload reduces CaV1.3-dependent L-type Ca²⁺ currents, resulting in bradycardia, altered electrical conduction, and atrial fibrillation [10]. Paroxysmal atrial fibrillation is the most common arrhythmia observed in patients with cardiac hemochromatosis. The prevalence of ventricular arrhythmias increases with left ventricular dilation and low LVEF. Sudden cardiac death may develop [11]. Cardiac hemochromatosis is not associated with ischemic heart disease or myocardial infarction [12, 13].

Diagnosis

Biochemical measures

Cardiac hemochromatosis should be considered in any patient who has unexplained heart

failure. Screening for systemic iron overload with serum ferritin and transferrin saturation should be performed. If the results of these tests are consistent with iron overload, further noninvasive and histologic confirmation is indicated to confirm organ involvement with iron overload.

Guidelines recommend that a plasma transferrin saturation exceeding 55% and a serum ferritin exceeding 200 ng/ml in women or exceeding 300 ng/ml in men identify patients with iron overload [14, 15]. Since serum ferritin is an acute phase reactant, it is unreliable in disorders with active inflammation [16]. Serum iron studies are useful for screening for total body iron overload but are unreliable for diagnosing organ-specific overload such as cardiac iron. Serum ferritin levels do not correlate with the severity of myocardial iron overload. High myocardial iron deposition may occur despite low serum ferritin levels [17]. There is a strong association between plasma N-terminal pro-B-type natriuretic peptide levels and indices of iron overload [18].

Biopsy of tissues

Liver biopsy is the best biopsy to quantify iron overload. However, there is no correlation between liver and myocardial iron deposition. Myocardial iron deposition is slower than uptake of iron by the liver. Endomyocardial biopsy may have to be performed in patients with cardiac manifestations. Myocardial iron is consistently found in endomyocardial biopsy specimens in patients with left ventricular dysfunction resulting from cardiac hemochromatosis.

Electrocardiographic findings

The electrocardiogram (ECG) is usually nondiagnostic in early cardiac hemochromatosis. With advanced cardiac hemochromatosis, low QRS complex voltage and nonspecific ST and T wave abnormalities are present on the ECG. Atrial tachyarrhythmias, especially paroxysmal atrial fibrillation, are common. Ventricular arrhythmias occur if there is a reduced LVEF. Iron deposition in the conduction system may cause first-degree, second-degree, and complete atrioventricular block [8].

Echocardiographic findings

Left ventricular diastolic dysfunction secondary to a restrictive physiology is seen early in cardiac hemochromatosis and can be diagnosed by echocardiography. This will progress to a dilated cardiomyopathy with a reduced LVEF. Patients with cardiac hemochromatosis may have left and right cardiac chamber dilatation and a low LVEF or left atrial and right ventricular dilatation with increased pulmonary artery pressure and a normal LVEF [19].

Eccentric left ventricular hypertrophy may also occur [20]. Tissue Doppler echocardiography may be used to diagnose left ventricular diastolic dysfunction early in cardiac hemochromatosis [21].

Cardiac magnetic resonance imaging findings

Although echocardiography may be used to screen for myocardial iron overload, it does not accurately predict myocardial iron content. Cardiac magnetic resonance (CMR) imaging can quantitatively assess myocardial iron load. In patients with cardiac hemochromatosis, the iron overloaded myocardium shows changes in signal intensity and susceptibility with a shorter relaxation time and quicker darkening of the image caused by the paramagnetic effect of iron [22]. The relaxation time may be measured using the spin echo technique, where the signals are refocused using a special radiofrequency pulse, or by using the small magnetic fields called gradients (gradient echo) at specific time intervals called echo time. The time constant of decay for the relaxation time is inversely proportional to the myocardial iron content. The greater the iron content in the myocardium, the shorter are the T₂ and T₂^{*}, the time constant of decay for spin echo and gradient echo-induced relaxation time, respectively. Spin echo is less sensitive than gradient echo for assessing the iron content in the myocardium [23]. The T₂^{*} method is more sensitive and highly specific for quantitation and longitudinal tracking of myocardial iron deposition. There is good inverse correlation between the patient's myocardial T₂^{*} and LVEF and significant correlation between the patient's myocardial T₂^{*} and the need for therapy of the cardiac hemochromatosis [24].

T₂^{*} relaxation time is determined by iron in the form of hemosiderin and not by iron in the form of labile cellular iron or ferritin and accurately predicts myocardial iron content [25]. The clinical severity of myocardial iron overload in cardiac hemochromatosis is assessed by T₂^{*} values. Patients with a T₂^{*} relaxation time greater than 20 ms are at low risk for developing congestive heart failure. Patients with a T₂^{*} relaxation time between 10 and 20 ms probably have deposition of iron in their myocardium and are at intermediate risk for developing congestive heart failure. Patients with a T₂^{*} relaxation time of less than 10 ms are at high risk for developing congestive heart failure and need chelation therapy [26]. In a prospective study of 662 thalassemia major patients, congestive heart failure developed within 1 year in 47% of patients with a T₂^{*} relaxation time less than 6 ms, in 21% of patients with a T₂^{*} relaxation time of 6 to 10 ms, and in 0.2% of patients with a T₂^{*} relaxation time greater than 10 ms [25]. Cardiac arrhythmias developed within 1 year in 19% of

patients with a T₂^{*} relaxation time less than 6 ms, in 18% of patients with a T₂^{*} relaxation time of 6 to 10 ms, and in 4% of patients with a T₂^{*} relaxation time greater than 10 ms [27].

In addition to quantifying the myocardial iron load in patients with cardiac hemochromatosis, CMR imaging can assess stress-induced myocardial ischemia, myocardial viability, resting LVEF, left ventricular end-systolic and end-diastolic volumes, and left ventricular mass. A reduction in LVEF correlates with the myocardial iron content measured by T₂^{*} relaxation time [28]. When the T₂^{*} relaxation time is below 20 ms, left ventricular systolic function decreases progressively, accompanied by increased left ventricular end-systolic volume and increased left ventricular mass [29].

Approach to diagnosis of hemochromatosis

Hemochromatosis may be suspected by a positive family history, abnormal hepatic enzymes, endocrinopathies, or other organ systems involvement. A thorough history and physical examination should be obtained. Patients suspected of having hemochromatosis should have measurements of transferrin saturation and ferritin for diagnosis of iron overload and assessment of other organ involvement such as liver, pancreas, thyroid, and gonads. Genetic testing should be performed to diagnose hereditary hemochromatosis. An ECG and chest roentgenogram should be obtained [30].

Patients without cardiac symptoms suspected of having hemochromatosis should have a transthoracic echocardiogram with assessment of left ventricular diastolic function including tissue Doppler imaging measurements of the mitral annulus every 1 to 2 years [31]. If there is abnormal left ventricular diastolic function and/or reduced peak systolic tissue velocity of the mitral annulus detected by echocardiography, CMR with T₂^{*} relaxation time measurement should be obtained. Periodic evaluation of ventricular function may help up-titration of medical treatment for heart failure and decide if an implantable cardioverter-defibrillator is indicated. Echocardiography should be performed every 6 to 12 months if the T₂^{*} relaxation time measured by CMR is less than 20 ms and every 6 months or less if the patient becomes symptomatic. The CMR with measurement of T₂^{*} relaxation time should be performed in all patients with idiopathic cardiomyopathy. A normal serum iron measurement does not rule out myocardial iron overload in patients with hemochromatosis. Therapy of cardiac hemochromatosis should be guided by abnormal CMR results. The CMR is an excellent tool for early diagnosis of heart involvement, risk stratification, treatment evaluation, and long-term follow-up of patients with metabolic cardiomyopathies including cardi-

ac hemochromatosis [32]. Patients who have an endomyocardial biopsy for heart failure caused by a dilated cardiomyopathy of unknown etiology should have iron staining of the biopsy specimens since stainable iron is consistently observed in patients with cardiac hemochromatosis and reduced left ventricular systolic function [33, 34]. Patients suspected of having hemochromatosis should be investigated for evidence of myocardial iron deposition with treatment started immediately if cardiac hemochromatosis is diagnosed.

Therapy

Therapy of iron-overload states is important to prevent or reverse cardiac dysfunction [35–39]. Removal of excess iron from the tissues in these patients minimizes generation of free radicals, reducing organ damage [40, 41]. Therapy to remove excess iron stores includes therapeutic phlebotomy and iron-chelating agents. Therapy of the primary disease causing iron overload and dietary management are also important in managing cardiac hemochromatosis. Dietary management includes avoidance of medicinal iron, mineral supplements, excess vitamin C, and uncooked seafoods [39]. Congestive heart failure should be managed with standard medical therapy for heart failure [42].

Therapeutic phlebotomy for cardiac hemochromatosis

Therapeutic phlebotomy is the therapy of choice in nonanemic patients with cardiac hemochromatosis. Therapeutic phlebotomy should be started in men with serum ferritin levels of 300 $\mu\text{g/l}$ or more and in women with serum ferritin levels of 200 $\mu\text{g/l}$ or more, regardless of the presence or absence of symptoms [39]. Therapeutic phlebotomy consists of removing 1 unit of blood (450 to 500 ml) weekly until the serum ferritin level is 10 to 20 $\mu\text{g/l}$ and maintenance of the serum ferritin level at 50 $\mu\text{g/l}$ or lower thereafter by periodic removal of blood [39]. Each unit of blood removed depletes 200 to 250 mg of iron from the blood. This removal of iron from the blood mobilizes an equal amount of iron stored in the tissues to form hemoglobin [43]. Patients with ferroportin mutation-associated iron overload may not tolerate a more aggressive schedule [44]. Serum ferritin is measured every month until it reaches 200 ng/ml and once in 1 to 2 weeks after. Measurement of hemoglobin and hematocrit should be obtained before each phlebotomy. Phlebotomy should not be performed if the hematocrit falls below 80% of the previous value [45]. After reaching a target ferritin level below 50 ng/ml and transferrin saturation below 30%, the frequency of phlebotomy is reduced. The frequency of maintenance phlebotomy varies once every few months to few

years depending on the iron reaccumulation rate [46]. Adequate hydration is recommended before and after phlebotomy to prevent volume depletion. Phlebotomy lowers the myocardial iron content and improves left ventricular diameter, left ventricular fractional shortening, LVEF, left ventricular mass, and left atrial dimension in these patients [47–49].

Therapeutic phlebotomy performed before iron overload becomes severe prevents complications caused by iron overload such as hepatic cirrhosis, primary hepatic carcinoma, diabetes mellitus, hypogonadotropic hypogonadism, joint disease, and cardiomyopathy [39]. Patients with these complications often need additional specific management [39]. Medical therapy to treat congestive heart failure from cardiomyopathy and serious cardiac arrhythmias in patients with cardiac hemochromatosis must be used until therapeutic phlebotomy possibly combined with iron chelation therapy reduces the excess myocardial iron content [39].

Iron chelation treatment

Phlebotomy is not an option for therapy in patients with anemia (secondary iron-overload disorders) nor in patients with severe heart failure [50]. In these patients, the therapy of choice is iron chelation treatment [51]. Iron chelating agents increase the iron excretion rate by binding to the iron in plasma and tissues, depleting the body of excess iron [52]. Serum ferritin levels should be periodically obtained. When the serum ferritin level falls below 1000 ng/ml, iron chelation therapy should not be given [53]. Deferoxamine, deferiprone, and deferasirox are the 3 iron-chelating drugs approved by the United States Food and Drug administration for management of chronic secondary iron overload.

Deferoxamine is a hexadentate molecule which binds directly to labile iron in plasma and in tissues including the heart [54]. Deferoxamine has poor oral bioavailability and a short half-life. This drug is administered as a subcutaneous or intravenous infusion. The recommended dose in adults is 40 to 50 mg/kg/day infused over 8 to 12 h for 5 to 7 days per week. Treatment with deferoxamine therapy reduces myocardial iron content approximately 24%, delays onset of cardiac hemochromatosis, reverses early cardiac hemochromatosis, improves left ventricular function, and improves survival in transfusion-dependent patients who have thalassemia [55–58]. However, long-term compliance with deferoxamine is poor [59].

Deferiprone is an orally active bidentate iron chelator approved for management of iron overload in transfusion-dependent patients with thalassemia when current chelation treatment is

not adequate. The starting dose of deferiprone is 75 mg/kg/day administered in 3 divided doses. The maximum dose of deferiprone is 99 mg/kg/day. Some studies have found that deferiprone is better than deferoxamine in lowering myocardial iron content [60, 61]. Combination treatment with deferiprone plus deferoxamine has been found to rapidly lower iron overload and improve cardiac function in iron overload patients with heart failure and unstable hemodynamics [62–64].

Deferasirox is a tridentate iron chelating drug with good oral bioavailability approved to manage iron overload resulting from recurrent blood transfusions. The initial oral dose of deferasirox given once daily is 20 mg/kg/day which can be increased to a maximum dose of 40 mg/kg/day [65]. Deferasirox lowers the serum ferritin level and lowers iron overload of the heart and liver [66–70]. Newer iron-chelating agents being investigated for the therapy of chronic iron overload disorders include silybin [71], deferitricin [72], and starch conjugated deferoxamine [73]. Percutaneous excretion of iron and ferritin through Al-hijamah is a novel treatment for iron overload in β -thalassemia major, hemochromatosis, and sideroblastic anemia [74].

Dietary treatment

Iron supplements should not be ingested [39]. Eating large amounts of vitamin C rapidly mobilizes iron from the heart, increases free radicals production, and causes fatal cardiac arrhythmias [75, 76]. Therefore, supplemental vitamin C should not be ingested by these patients. However, vegetables and fruits rich in vitamin C may be eaten [77]. Alcohol increases iron absorption, and some red wines contain a high iron content [78, 79]. Patients with hereditary hemochromatosis should avoid eating raw shellfish [79]. Patients with cardiomyopathy and heart failure should be treated with a low sodium diet [42].

Erythrocytapheresis in hemochromatosis

Erythrocytapheresis is the technique of selective removal of red blood cells, with or without administering erythropoietin [80, 81]. This process removes excess iron stores from the tissues twice as rapidly as phlebotomy of whole blood [82]. In a study of patients with hereditary hemochromatosis, therapeutic erythrocytapheresis showed almost a 70% decrease in the total number and the duration of treatments compared with phlebotomy [83]. End-stage cardiomyopathy caused by hereditary hemochromatosis was successfully treated with erythrocytapheresis in combination with left ventricular assist device support [84].

Cardiac transplantation for cardiac hemochromatosis

Cardiac transplantation is a therapeutic option for patients with cardiac hemochromatosis with severe heart failure refractory to optimal medical therapy and cardiac resynchronization therapy [42, 48, 85]. Of 16 patients who had cardiac transplantation for iron overload cardiomyopathy, the etiology was primary hemochromatosis in 11 patients, thalassemia major in 4 patients, and Diamond-Blackfan anemia in 1 patient [86]. The 30-day mortality was 12%, with the 3 deaths due to infectious complications [86]. The actuarial Kaplan-Meier survival rates at 1, 3, and 5 years were 81%, 81%, and 81%, respectively [86]. The actuarial survival at 10 years was 41% [86].

Congestive heart failure after liver transplantation may require a biventricular assist device [87]. Combined heart-liver transplantation is indicated in patients with severe iron overload cardiomyopathy and cirrhosis [88]. All of these patients should continue to have therapy to decrease iron overload to prevent hemochromatosis of the transplanted heart [89]. In patients with secondary iron overload such as the myelodysplastic syndrome [90], sickle cell anemia [91], β -thalassemia [92], and the Diamond-Blackfan syndrome [93], hematopoietic stem cell transplantation can reduce requirements for blood transfusion and slow the rate of iron overload in these patients.

Therapies under investigation for hemochromatosis

Calcium channel blockers

L-type Ca^{2+} channels and T-type calcium channels provide a major pathway for iron entry into cardiomyocytes in iron overload cardiomyopathy [94–96]. Amlodipine has been demonstrated to reduce iron uptake and oxygen free radical production in the heart of chronically iron overloaded mice [97]. Therapy with calcium channel blockers (nifedipine, verapamil, and efonidipine) and a divalent metal transporter1 (ebselen) have shown a decrease in cardiac iron deposition, cardiac malondialdehyde, and plasma non-transferrin-bound iron and an improvement in heart rate variability and in left ventricular function in thalassemic mice with iron overload [98]. Efonidipine and ebselen reduced mortality in these mice [98]. Further investigation is needed to determine whether calcium channel blockers can be efficacious in the prevention and treatment of iron overload cardiomyopathy.

Hepcidin therapy

Deficiency of hepcidin, the hormone that controls iron absorption and its distribution in tissues,

is the cause of iron overload in nearly all forms of hereditary hemochromatosis and in untransfused iron loading anemias [99–104]. Hepcidin analogs have been demonstrated to reduce iron overload and excess iron-induced tissue toxicity in mouse models [99, 101]. Minihepcidins are smaller hepcidin-like peptides which have been shown to reduce myocardial iron content in hepcidin knockout mice [104]. Minihepcidins prevented iron overload in a hepcidin-deficient mouse model of severe hemochromatosis [104]. Minihepcidins could possibly be beneficial in iron overload disorders either used alone for prevention or as adjunctive therapy with phlebotomy or chelation [104]. Natural hepcidin and hepcidin analogs are under investigation to treat iron overload in hemochromatosis.

Apotransferrin treatment reduced erythroid *Fam132b* gene (erythroferrone) expression, increased hepatic hepcidin gene expression and plasma hepcidin-25 levels, and reduced intestinal ferroportin-1 in apotransferrin-treated thalassemic mice [105]. Apotransferrin treatment needs further investigation for normalizing iron content in the myocardium and other organs.

Gene therapy

Management of underlying disorders such as β -thalassemia and sickle cell disease by gene therapy may prevent need for blood transfusions and prevent iron overload in tissues [106, 107]. Targets for gene therapy have been recommended for patients with hereditary hemochromatosis including inhibition of divalent metal transporter1 and ferroportin gene expression in enterocytes [108]. Overexpression of the wild-type HFE gene in enterocytes and overexpression of the iron regulatory peptide hepcidin in the liver are other therapeutic approaches that could be investigated. The HFE genotype may affect the survival of patients with myelodysplastic syndrome, and studies need to be performed if these patients should be treated with potent iron chelation therapy [109].

Conflict of interest

The author declares no conflict of interest.

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