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Diagnosis of iron overload and heart disease by magnetic resonance imaging

J.C. Wood, L. Noetzli

Division of Cardiology, Children's Hospital Los Angeles, CA, USA

Abstract

The use of Magnetic resonance imaging (MRI) to estimate tissue iron was initiated nearly three decades ago but has only become a practical reality in the last ten years. MRI is most often used to estimate hepatic and cardiac iron in patients with thalassemia or sickle cell disease and has largely replaced liver biopsy for liver iron quantification. The ability of MRI to image extra hepatic organs has really transformed our understanding of iron mediated toxicity in transfusional siderosis. For decades, iron cardiomyopathy was the leading cause of death in thalassemia major, but it is now relatively rare in centers with regular MRI screening. Early recognition of cardiac iron loading allows more gentle modifications of iron chelation therapy prior to life threatening organ dysfunction. Serial MRI evaluations have demonstrated differential kinetics of uptake and clearance among the difference organs of the body. Although elevated serum ferritin and liver iron concentration increase the risk of cardiac and endocrine toxicities, extra hepatic iron deposition and toxicity occurs in many patients despite having low total body iron stores; there is no *safe* liver iron level in chronically transfused patients. Instead, the type, dose, and pattern of iron chelation therapy all contribute to whether cardiac iron accumulation will occur. These observations, coupled with the advent of increasing options for iron chelation therapy, are allowing clinicians to more appropriately tailor chelation therapy to individual patient needs, producing greater efficacy with fewer toxicities. With the decline in cardiac mortality, future frontiers in MRI monitoring including better prevention of endocrine toxicities, particularly hypogonadotropic hypogonadism and diabetes. These organs also serve as early warning signals for inadequate control of non-transferrin bound iron, a risk factor for cardiac iron loading. Thus MRI assessment of extra hepatic iron stores is a critical monitoring tool for chronically transfused patients. Further prospective work is necessary to determine whether markers of endocrine and exocrine pancreatic function can be used as surrogates of cardiac risk in regions where MRI is not available.

Correspondence: J.C. Wood, Division of Cardiology, Children's Hospital Los Angeles, CA, USA.

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Introduction

Morbidity and mortality from transfusional siderosis is still disturbingly common, despite the availability of effective iron chelation therapy since the mid 1970's. Poor compliance with iron chelation therapy remains the single greatest contributor to iron-mediated endocrine and cardiac complications, but some patients develop iron cardiomyopathy despite apparently adequate adherence to iron chelation therapies.

The introduction of Magnetic resonance imaging (MRI) to detect iron in the heart and endocrine tissues in the early 2000's provided insight into this paradox. MRI was able to recognize preclinical iron deposition and was used to study the relative interplay between iron pools in different organs.

This review recapitulates how MRI has clarified the mechanisms of iron cardiomyopathy, therapy of established disease, and strategies for disease prevention.

Iron recycling and storage in non-transfused and transfused subjects

Typically, the gut is the only source for iron uptake, consisting of around 1 mg per day of heme and non-heme iron. Free ferrous iron ions are exported through ferroportin channels located in the apical enterocyte membrane. These ions are oxidized to the ferric state and loaded onto transferrin molecule for transport to all tissues. Excess transferrin-bound iron is taken up in the liver for long –term storage. In non-transfused subjects, there is a 3-fold excess of non-iron containing transferrin (apotransferrin) and circulating non-transferrin bound iron (NTBI) is undetectable. Iron is most heavily utilized by the bone-marrow for red blood cell synthesis. Senescent red blood cells are scavenged by reticuloendothelial macrophages in the liver and spleen; ferrous iron derived from hemoglobin degradation is exported via macrophage ferroportin, creating a highly-efficient recycling mechanism for iron. The only source of iron-loss is normal sloughing of intestinal epithelia, constituting approximately 1 mg per day, balancing intake.

Regular transfusion therapy delivers iron to the transferrin-cycle at

a rate 15-20 fold greater than via normal absorption. Transferrin becomes progressively saturated, leading to the appearance of various forms of circulating NTBI. NTBI enters endocrine, cardiac and hepatic tissues through unregulated mechanisms, possibly divalent metal channels such as L and T type calcium channels, but details of these transport processes remain elusive.

Importance of NTBI

The NTBI-centric concept of cardiac iron deposition is important for understanding and minimizing cardiac risk in patients with transfusional iron overload. NTBI levels rebound within thirty minutes of ceasing deferoxamine therapy, leaving the heart unprotected for most of the day. Thus it is possible for patients to insidiously develop cardiac iron overload despite excellent iron balance and perfect adherence to chelation therapy.[1] More typically, patients skip a few days per week of chelation therapy; in fact, five doses per week was standard therapy at many institutions. Now it is clear that the heart health depends as much on the hours/day and days/week of chelation as it does about the grams per week of drug taken.[2] Newer oral iron chelators that control NTBI over longer periods should prevent cardiac iron accumulation if taken every day, however adherence continues to represent a significant challenge.[3] Long *chelator holidays*, whether initiated as a reward for good behavior, difficulties associated with patient travel or insurance, or because of ferritins below 500, are potentially dangerous and ill-advised because high circulating NTBI can rapidly load the heart and endocrine tissues.

Modulators of circulating NTBI levels

A number of physiologic processes influence circulating NTBI levels and cardiac risk. Liver iron overload, chelator requirements, transferrin saturation, and cardiac risk all appear to increase with transfusion rate.[4, 5] Increased liver iron concentration also increases NTBI levels and hepatic toxicity.[6-8] The mechanisms of this process are poorly understood but probably account for the liver iron *threshold* for cardiac risk describe in several prior studies.[3, 7, 9]

In contrast, cardiac risk appears to decrease proportionally to effective erythropoeisis; iron utilization by bone-marrow lowers circulating NTBI levels. In fact, bone-marrow suppression by radiation or chemotherapy dramatically raises transferrin saturation and NTBI levels even in non iron-overloaded subjects.[10] Chronic inflammation also lowers NTBI levels by limiting iron release from gut and reticuloendotheial system.[11]

Iron storage in the heart

Once NTBI species enter the heart, the labile and potentially dangerous iron is either used by metabolic processes or is bound to cytoplasmic ferritin. Iron-laden ferritin, in turn, is shuttled off to lysosomes for degradation to hemosiderin and long-term storage. Buffering is robust and most patients with cardiac iron overload (even severe cardiac iron overload) have no symptoms or detectable cardiac functional abnormalities because labile iron species are maintained at physiologic levels in the myocyte. Symptoms only develop once buffering capacity is overwhelmed, though a combination of high iron stores, chronicity of cardiac iron exposure, and the type/pattern of iron chelation therapy.

MRI of cardiac iron stores

MRI does cannot directly detect labile cardiac iron stores, although MRI estimates of systolic and diastolic performance represent good surrogates for cardiac performance. Instead, MRI predominantly detects hemosiderin deposits because its larger particle size produces magnetic disturbances that profoundly shorten the T2 and T2* of iron-laden tissue.[12] Since the overwhelming majority of tissue iron is stored as hemosiderin, both T2 and T2* parameters have been calibrated to tissue iron levels in the heart and liver.[13-15]

The principles of cardiac T2 and T2* imaging are straightforward. A single short-axis image of the heart is collected at multiple recall or *echo* times. Iron laden tissue darkens more rapidly with echo time, with a half-life known as T2 or T2* depending on the MRI technique employed. T2* imaging is most widely used for the heart because of its availability, robustness to motion artifact, speed of image collection, and transferability among different imaging centers. Inter-institution and inter-study variability are on the order of 5-7%.[16, 17]

Relationship between cardiac T2* and cardiac function

Normal cardiac T2* values are around 37 ± 6 ms, but 20 ms is typically considered the lower limit of normal to improve specificity.[18] Patients with cardiac T2* > 20 ms typically have normal cardiac function and a low risk of developing arrhythmias or congestive heart failure over a one year period.[19] As cardiac T2* declines, the cross-sectional and prospective risk of cardiac dysfunction rise. Since cardiac T2* primarily reflects the stored cardiac iron, many patients with low cardiac T2* initially have normal cardiac function and are clinically asymptomatic. But since the stored iron pool is in dynamic equilibrium with labile myocyte iron, low T2* predicts subsequent cardiac dysfunction if chelation therapy is unmodified. In fact, a natural history study demonstrated that patients having a cardiac T2* less than 6 ms had greater than a 50% chance of developing symptomatic congestive heart failure in one year's time.[19]

Relationship between cardiac and liver iron

When cardiac MRI emerged, it became abundantly clear that the relationship between cardiac and liver iron stores was quite complicated. Liver iron level is a superb marker of total body iron balance[20] and high levels are associated with increased cardiac risk but is completely uncorrelated with cardiac T2* in cross-sectional studies.[18] Longitudinal studies demonstrated that the kinetics of cardiac iron uptake and elimination are significantly slower in the heart compared with the liver.[1, 21] The half-life of cardiac iron elimination to intensive intravenous deferoximine is more than five-fold longer than for liver iron clearance (16 months versus 3 months).[21] Thus patients who have high cardiac and liver iron loads will generally transition to a state of high cardiac and low liver iron before clearing their cardiac iron.[1]

The apparent sluggishness of cardiac iron loading is a bit misleading. Significant hepatic iron loading may occur with no detectable cardiac iron, particularly in children and adolescents.[22] However cardiac iron accumulation can progress rapidly, once it is initiated.[1] The events *triggering* cardiac iron accumulation are poorly understood but include all of the modulators of circulating NTBI levels and chelator type, dose, and adherance.

Relationship between cardiac and endocrine iron stores

The marked temporal disconnect between hepatic and cardiac iron loading weakens the utility of liver iron measurements in predicting cardiac risk. Furthermore, more than half of our patients who have prospectively developed cardiac iron have never developed liver iron levels above 10 mg/g[1]. The pancreas, which solely takes up NTBI like the heart, appears to have a much closer iron transport dynamics to the heart.[23] Furthermore, all patients with cardiac iron appear to have pancreas R2* values > 100 Hz (T2* < 10 ms) regardless of their liver iron burden. This relationship is sufficiently strong that we *triage* the need for cardiac T2* analysis based upon pancreas R2* values.[23] Furthermore, there is a broad temporal window where pancreas iron is increased but the heart remains clear. This window allows more gentle

modifications to chelation therapy (including reinforcing compliance) than if one waited for cardiac T2* to fall. Furthermore, the long half-life of cardiac iron clearance reinforces the importance of primary prevention of cardiac iron overload.

Pancreas iron measurements are more technically challenging than for liver or heart, hence larger, multicenter studies are necessary to validate their utility in routine clinical practice. Further work is also ongoing to understand the functional significance of pancreas iron on glucose dysregulation. Pituitary iron overload also has intermediate kinetics between liver and heart loading and may represent a target for primary cardiac prevention as well.[24]

Conclusion

In summary, liver and extrahepatic organs have unique mechanisms and kinetics of iron loading. High liver iron loads increase cardiac risk but low liver iron levels do not guarantee cardiac protection. Compliance is the single greatest predictor of cardioprotection, by limiting the duration of cardiac exposure to circulating NTBI. Similarly, drug holidays are dangerous unless there is overt toxicity. MRI assessment of hepatic and extrahepatic iron is essential for management of transfusional siderosis. Pancreas and pituitary iron appear to be early markers of poor NTBI control.

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