Disorders in hemoglobin synthesis, or hemoglobinopathies, represent the most common genetic diseases in the world. Thalassemia syndromes represent one subtype and patients with severe thalassemia syndromes (thalassemia major) require lifelong regimens of blood transfusions every three weeks. Each transfusion provides three times the body's annual iron requirements. Unfortunately, excess iron cannot be eliminated without arduous chemical chelation therapies. Excess iron first accumulates in the liver but then accumulates in the endocrine glands[1-3] and heart[4,5]. Until the early 2000's, iron-mediated cardiac toxicity was the leading cause of death in thalassemia major[6,7]. Cardiac iron deposition is clinically silent for decades but typically presented acutely in the second and third decade of life with malignant arrhythmias and biventricular failure. Median survival was only 35 years.

Although the feasibility of using MRI to detect liver iron was first demonstrated in the 1980's [8] and in the heart in 1989[9], it wasn't until 2001 when a team from the Royal Brompton demonstrated that low T2* was clearly associated with abnormal function in thalassemia major patients[10]. This manuscript was followed one year later suggesting that a particular iron chelator, deferiprone, was cardioprotective compared with the more widely prescribed chelator deferoxamine[11].

These two papers set off a firestorm of controversy[12]. Cardiac T2* and liver iron concentration were uncorrelated with one another, shaking a fundamental dogma of iron chelation management[13]. Many patients with heavy cardiac iron were completely asymptomatic. Deferiprone was unpopular with some prominent physicians and scientists.

As a result, many questioned the source of the T2* changes, attributing them to susceptibility artifacts and increased deoxygenated hemoglobin in diseased myocardium[14]. However, our laboratory was able to demonstrate by computer modeling[15], animal models[16] and autopsy studies[17], that R2* was linearly proportional to tissue iron concentration over a broad range. Furthermore, we demonstrated transverse relaxivity in overloaded tissues result primary from diffusion in a magnetically heterogeneous environment rather dipole-dipole interactions[15,18,19]. In the liver and the heart, these magnetic inhomogeneities are

produced by aggregates of the storage forms of iron, known as ferritin and hemosiderin. This storage pool was not directly toxic, but increased the risk of developing dangerous labile forms of cardiac iron over time[20].

We were also able to explain the dissociation between cardiac and liver iron levels[21]. The heart and endocrine glands have and have different uptake mechanisms than the liver, taking up exclusively iron that is not bound to the transferrin transport protein[22]. As a result, the kinetics of iron loading and unloading are organ specific, disrupting the correlation between heart and liver iron levels at any single point in time. Furthermore, we demonstrated that it is possible to administer iron chelation that balanced total body iron burden but inadequately protected the heart and endocrine system[21]. This affirmed that liver iron, alone, was an inadequate surrogate for iron toxicity risk.

Proof that cardiac T2* was predictive of poor outcome was definitively addressed by registry cohort of 652 thalassemia patients from 21 centers in the United Kingdom[23]. Only one patient with a T2* > 10 ms developed congestive heart failure in one year, while more than 50% of patients having a T2* less than 6 ms developed symptomatic congestive heart failure.

Since the publication of these findings, annual assessments of liver and heart iron have become routine clinical practice at major thalassemia centers[24]. Disease history has changed dramatically, as clinicians now escalate iron chelation therapy before the patient develops clinical symptoms. Randomized clinical trials, using MRI T2* and ejection fractions as endpoints, confirmed earlier reports of deferiprone cardioprotection[25,26]. Consequently, deferiprone (alone or in combination therapy) has become the standard of care for thalassemia patients having a cardiac T2* less than 10 ms. Newer oral iron chelators have also improved overall patient outcomes by improving drug compliance and preventing cardiac iron accumulation in younger patients[27].

While many important clinical questions have been answered, additional challenges remain. Thalassemia patients in some regions are demonstrating myocardial fibrosis, arrhythmias, and scarring that are independent of current iron accumulation[28-30]; these findings may represent chronic myocarditis exacerbated by

hepatitis C, previous cardiac iron overload, and ongoing microvascular damage through diabetes and vascular inflammation. While premature death from iron cardiomyopathy is clearly preventable, thalassemia patients still suffer from accelerated vascular aging[31-34]. MRI will play a large role in unraveling the mechanisms of chronic vasculopathy in the hemoglobinopathies.

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