

Assessment of Cardiac Iron Overload and Function

The thalassaemias are the commonest inherited single-gene disorders worldwide, resulting in reduced or absent output of either the alpha or the beta chains of haemoglobin. The absence of beta globin chains (beta-0 thalassaemia) or a reduction in their output (beta+ thalassaemias) leads to an excess of alpha chains, which then precipitate causing red cell destruction. The resulting severe anaemia stimulates further ineffective erythropoiesis with secondary bone marrow expansion and bony deformities. Inheritance is recessive and asymptomatic heterozygotes have a 25% chance of having an affected child. Beta thalassaemia major requires regular blood transfusions from birth to prolong life.

Thalassaemia occurs widely in a broad belt ranging from the Mediterranean and parts of north and West Africa through the Middle East and Indian subcontinent to Southeast Asia, with the heterozygous carrier frequency ranging from 3% to 30%. The beta thalassaemia gene is not present in Northern Europeans, but through migration it is now present in every industrialised nation in the world. Worldwide, there are approximately 94 million heterozygotes for beta thalassaemia and up to 60,000 affected homozygote infants are born each year. Beta thalassaemia can also occur sporadically in every racial group. With improving social conditions and medical care worldwide, children with thalassaemia now survive long enough to require treatment for longer term complications. This makes the management of the disease increasingly important, not only where the disease is particularly common, but also for any country which has an immigrant population from these regions.

Patients with thalassaemia major die of anaemia in infancy unless they are regularly transfused. However, in treated patients the combination of transfusional iron (200-250mg per unit of blood), and an inappropriate increase in intestinal absorption, leads to an inexorable accumulation of iron in the body tissues. Eventually, extensive iron-induced injury develops in the heart, liver, pancreas and endocrine organs. Around the age of 10 years, the heart size increases and left ventricular hypertrophy develops on the ECG. Congestive cardiac failure eventually develops at a mean age of 16 years, and patients rarely survive over the age of 20 years, due to cardiac iron overload leading to cardiomyopathy. Iron deposition in the heart follows a characteristic pattern, with the left ventricular wall containing the most iron. The right ventricle, atria, and conduction system contain lesser amounts. Iron deposition in the ventricular wall is non uniform, with the epicardial layer containing the most, the endocardium containing a moderate and the intermediate layer containing the least amount of iron. The degree of cardiac dysfunction depends on the quantity of iron deposited in individual myocardial fibres and the number of fibres affected. The iron deposition in the myocyte is intracellular, being stored as ferritin or haemosiderin, preventing free radical production. In the myocyte, once a critical concentration is reached the iron appears in a free toxic form, leading to the release of free hydroxyl radicals. Little has changed in recent years once cardiac complications occur, despite advances in transfusion therapy, chelation therapy, and

diagnostic cardiology. Despite this, the relatively mild degree of fibrosis in most autopsy studies suggests that even when advanced, the cardiomyopathy may be potentially reversible.

Due to the variability in iron deposition between and within different organs, no single measurement of body iron is satisfactory. In normals, serum ferritin correlates with iron stores, and with liver iron measured directly by liver biopsy. In beta thalassaemia major this relationship is distorted by several factors: First, liver fibrosis and transfusion transmitted viral hepatitis reduce the effect of iron status on serum ferritin by about 50%; Second, ferritin is an acute-phase reactant and can appear falsely elevated in the presence of inflammation; Third, vitamin C deficiency is common in these patients and leads to falsely low elevations in serum ferritin despite extensive iron loading. Serum ferritin does also not correlate with myocardial iron load., The current gold standard for determining the liver iron burden is by direct measurement from a liver biopsy. However, this is an invasive technique with a low but recognised complication rate and iron is unevenly distributed even in the non-cirrhotic stage. Therefore a single liver biopsy cannot be assumed to reliably represent the mean hepatic iron concentration. Although some initial reports suggested a correlation between myocardial and hepatic iron burden” it seems that this is now not the case (see figure 1).²²”, Endomyocardial biopsy has been used to evaluate iron deposition in the heart in thalassaemia., As well as the complications of this technique there is even greater chance of sampling error, as the iron is preferentially distributed in the epicardium, and the right ventricle is relatively spared., MR scanning is currently the only method shown to be reliable and accurate to assess both hepatic and myocardial iron loading.

The MR signal intensity reflects differences among tissues of their magnetic relaxation properties. These properties are disturbed by the presence of iron, which increases signal decay. Much of the early work for the assessment of iron using MR was in the liver. Initial studies using magnetic susceptometry demonstrated that MR may be capable of measuring tissue iron. Studies then used spin echo techniques to determine the transverse relaxation times (T2) of tissues. Although gross iron overload could be detected, the method was insensitive to mild iron overload. One of the main advantages of having such a technique available is early detection of iron overload, so that treatment is started before irreversible damage occurs. Newer techniques have been developed that can extend the range over which iron overload can be detected.