European Heart Journal (2001) **22,** 2140–2141
doi:10.1053/euhj.2001.2951, available online at http://www.idealibrary.com on IDEAL®

Diagnosing myocardial iron overload

See page 2171, doi:10.1053/euhj.2001.2822 for the article to which this Editorial refers

Cardiac failure or arrhythmia are the dominant causes of death in patients with thalassaemia major and other transfusion-dependent refractory anaemias. Each unit of blood contains 200–250 mg of iron and body iron stores are normally only 0·5–1·5 g. Since the body has no physiological mechanism for excreting iron, repeated blood transfusions result in iron accumulation in the reticuloendothelial system and parenchymal cells. The principal damage occurs to the heart, liver and endocrine organs. The rate of iron accumulation is on average 0·5 mg . kg^{-1} body weight per day and iron chelation therapy must be given to cause excretion of this amount of iron and so prevent early mortality from an iron-induced cardiomyopathy.

The most widely used iron chelating drug, and the only one licensed worldwide, is desferrioxamine. With the introduction of self-administered slow subcutaneous daily infusions of this drug in 1976–7[1,2] the life expectancy of patients with thalassaemia major improved dramatically[3,4]. Desferrioxamine is, however, expensive and has toxic or allergic side effects in a number of patients. Compliance with the arduous daily infusion regime is often poor, especially in teenagers and this results in reduced patient survival[5,6].

The mechanisms by which iron damages myocardial cells has been extensively studied in vitro by Link, Hershko and co-workers[7]. Clinically it has proved difficult to predict at an early stage which patients are particularly at risk of dying from an iron-induced cardiomyopathy. Various indirect tests that have been investigated include measurement of serum ferritin, of liver iron, of non-transferrin bound iron in plasma[8], as well as direct tests of cardiac function including electro- and echocardiography and multigated angiography (MUGA) scanning. Some studies have suggested that maintenance of serum ferritin below 2500 µg . l^{-1} is essential[9] but many patients with ferritin levels below this level have died from a cardiomyopathy. Based on data on genetic haemochromatosis, liver iron measured chemically after biopsy has been proposed as the 'gold standard'. A level over 15 mg . g^{-1} dry weight (80 µmol . g^{-1} liver wet weight) predicted short survival[10]. This particular dividing line has not been validated for patients with thalassaemia major, although clearly, the greater the body iron burden, the greater the risk of cardiac and other complications of iron overload[10].

In the present study, Anderson and colleagues[11] have developed a new reproducible non-invasive method for measuring cardiac (or liver) iron. As the authors explain, previous attempts to measure cardiac iron using spin-ECHO techniques have failed because of lack of sensitivity, motion artefacts and poor signal-to-background noise ratios. Electrocardiography and stress echoradiography have not detected early damage. They use a cardiac T2-star (T2*) technique, a relaxation parameter which depends mainly on heterogeneity in the local magnetic field. The result is increased iron overload. They found a good inverse correlation between the patients' myocardial T2* and left ventricular ejection fraction but no significant correlation between myocardial T2* and serum ferritin or liver iron. There was also a significant correlation between myocardial T2* and the need for cardiac medication.

The principal value of this new non-invasive technique is in the early detection of cardiomyopathy while it is still reversible. Although in some cases even severe cardiomyopathy induced by iron can be reversed[12], this is often not possible. Myocardial T2* provides the earliest, and probably the most sensitive and reproducible test yet available of cardiac iron and consequent cardiac damage. Protocols are being explored for the removal of this cardiac iron by the use of more intensive desferrioxamine treatment[13] or with deferiprone, an orally active iron chelating drug[14] or with a combination of the two drugs[15]. Deferiprone is now licensed in the European Union, India and other countries. It has a much lower molecular weight (139) than desferrioxamine. There is evidence that it is able to penetrate cells, including myocardial cells, and remove iron directly[16]. A combination of the drug with desferrioxamine has been postulated to have a 'shuttle' effect, in which deferiprone removes iron from cells and then passes it to desferrioxamine which results in its rapid excretion in urine and faeces[16]. The combined therapy is additive in increasing urine iron excretion[15] and may result in increased compliance by reducing the number of days each week desferrioxamine must be infused and the number of capsules of deferiprone (which can cause nausea) to be swallowed each day. It may also help to avoid toxic effects of both drugs since lower doses may be satisfactory when the drugs are used in combination, rather than alone.

Published online 4 October 2001.

It will be important to use the T2* technique to see how well the drugs alone or in combination prevent myocardial iron accumulation or remove myocardial iron and reverse cardiac damage in the face of continuing blood transfusions. It is hoped that other groups will adopt this new technique and provide confirmatory data on its value for assessing myocardial iron. Since it is a sophisticated and expensive technique, however, it is not practicable for introduction into many poor countries where thalassaemia major is most common. It is hoped, however, that with the T2* technique it may be possible to reassess the value of simpler tests of iron overload and cardiac dysfunction which may be feasible to perform in poor countries.

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European Heart Journal (2001) **22,** 2141–2143
doi:10.1053/euhj.2001.2831, available online at http://www.idealibrary.com on IDEAL®

Dofetilide: what role in the treatment of ventricular tachyarrhythmias?

See page 2180, doi: 10.1053/euhj.2001.2679 for the article to which this Editorial refers

In the present issue Boriani *et al.*[1] report the results of a prospective double-blind randomized crossover study, in which the short- and long-term efficacy and safety of oral dofetilide or oral sotalol were compared in 135 patients with ischaemic heart disease and inducible sustained ventricular tachycardia. Dofetilide was as efficacious as sotalol in preventing the induction of sustained ventricular tachycardia, which was achieved in one third of the patients. There was no concordance in the response to the two drugs. During the acute phase dofetilide was significantly better tolerated than sotalol. However, during long-term treatment, which was not randomized, both drugs were well tolerated.

This study is based on the use of electrophysiological testing as a guide for selecting antiarrhythmic drug therapy in ventricular tachyarrhythmias, a

Published online 2 October 2001.