group. It may be that significant problems were picked up earlier in the patients who were more intensively followed-up. The authors suggest that because patients did not receive advice while they were still on the ward, but often up to 7 days after discharge, there may have been a time lag before the benefits of home-based interventions were seen. It is interesting that most studies of this sort follow-up patients for only 6 to 12 months. There may well be long-term benefits of intensive management and it is certainly feasible that mortality may be reduced, albeit modestly, by careful attention to optimal medical management, patient compliance, and managing co-morbidities effectively. This study suggests a trend in that direction.

It is notable that only a third of re-admissions were due to worsening heart failure. This serves to illustrate the other problems faced by these patients, who often have co-existing ischaemic heart disease, diabetes, and COAD. It also highlights the fact that they are elderly and often admitted for falls and social reasons. One of the benefits of more intensive management of heart failure is that circumstances potentially precipitating a prolonged admission can be identified and managed promptly. This trial confirms the findings of others of its sort in showing that structured intervention, whether it be by nurse-led home-based intervention or specialist clinic, is beneficial in heart failure patients, at least in reducing the frequency of re-admissions and improving quality of life. It is an important trial in that the study patients were typical of the average heart failure patient. It also confirms the importance of the role of the GP in managing these patients and shows that a sensible model of shared care between the primary and secondary sectors is both feasible and useful.

We now have both pharmacological and non-pharmacological heart failure management strategies that can improve patients’ wellbeing. The challenge is to implement these systematically, doing the educating as well as the medicating.

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The heart in thalassaemia

See page 147, doi:10.1053/euhj.2001.2709 for the article to which this Editorial refers

Thalassaemia is a monogenetic disorder affecting globin chain synthesis[1] with a heterozygote frequency varying from 3 to 30% in high-risk populations. In the U.K. there are approximately 800 transfusion dependent patients with homozygote \(\beta\)-thalassaemia and it is estimated that there are 30 000 to 60 000 births per year worldwide with the condition[2]. Adoption of transfusion regimes, followed in the 1970s by the use of chelation with desferrioxamine[3], has meant that survival into adulthood can now be expected for the majority of affected individuals.

Nevertheless, even in countries, such as the U.K., where treatment with desferrioxamine has been available, there remains a dramatic rate of accelerated mortality and morbidity beginning in the teenage years and leading to a 50% mortality before the age of 35[4]. Acute iron overload is toxic to the heart[5] and in the syndromes of chronic iron overload
majority of deaths are due to cardiac failure[6–9] and sudden death, the latter probably due to arrhythmia. Clinically apparent, although symptomatically silent the cardiac effects of iron overload begin with the accumulation of 20 g of iron, usually after the age of 10 years, in a regularly transfused child maintained with a pre-transfusion haemoglobin of 9 to 10 g . dl−1, unless adequate chelation has been prescribed and taken. A cardiomyopathy develops by 16 years and mean survival falls to 3 months once this complication has arisen[7].

Iron accumulates in the ventricular septum as well as the free wall of the ventricles[10], with a tendency to be more concentrated in the epicardial layers[11,12]. Successful reversal of the cardiomyopathy of iron overload was reported soon after the adoption of desferrioxamine chelation treatment[13], and improvements in cardiac function following desferrioxamine confirmed by others[14–17]. Improved outcomes, with prevention of the development of cardiac complications, follows effective chelation treatment[18–20]. In animal studies, a dose relationship between iron load and the development of cardiac impairment is seen[21–26]. This wealth of evidence supports the hypothesis that cardiac complications in thalassaemia and other iron-overload has a direct relationship with the amount of iron in the heart. This content is in proportion to the iron burden faced by the individual and responds to treatment known to be able to decrease the accumulation of iron in tissues.

The mainstay of treatment for thalassaemia iron overload remains the parenteral administration of desferrioxamine, using prolonged subcutaneous or intravenous infusions. The treatment is difficult to administer, expensive and hard to comply with, particularly by adolescents and young adults[41,47]. Focusing the most intensive regimes on those at greatest risk, is an important clinical aim. Establishing individual cardiovascular risk, however, can be problematical. There is no single parameter able to establish with precision the iron burden. Indirect assessments from the levels of serum ferritin over time can be useful[20], but ferritin, being an acute phase protein is influenced by many other factors including inflammation and vitamin status[28,29]. Liver biopsy to quantify iron content, despite some sampling errors, gives an accurate assessment of body iron burden[30]. However, there is dissociation between liver and heart iron accumulation, so that prediction of cardiac iron load from liver iron content is not reliable in an individual.

Quantifying myocardial iron content is difficult. Biopsy is invasive and suffers from sampling errors, particularly due to the tendency for iron to accumulate in the subepicardial layers[11,12]. Magnetic resonance imaging has been used non-invasively to measure myocardial iron[31–36]. Gradient echo magnetic resonance imaging imaging images were developed for hepatic iron measurement, having the advantage of increased sensitivity for lower levels of iron content[37]. Modifications of these magnetic resonance imaging protocols to measure a T2* parameter has allowed the measurement of intra-cardiac iron in a large cohort of thalassaemia patients. Preliminary results confirm a poor correlation between magnetic resonance imaging T2* and serum ferritin and biopsy measurements of liver iron[38]. Impaired left ventricular function was only seen in individuals with high iron content, but importantly, a group with preserved function and high iron content was identified, who, if hypothesized, are at high risk of developing cardiac complications. It is this group which should attract the intensified treatment regimes known to improve cardiac outcomes[39]. Unfortunately, the capital cost and lack of availability of magnetic resonance imaging scanners in many nations will rule out magnetic resonance imaging for many of the potential patients who would benefit from this technology. Other, more readily available methods of assessing the heart, such as nuclear ventriculography[40] and echocardiography, have been used, but often pick up abnormalities at a late stage in the disease[41–43]. Once systolic function of the left ventricle becomes impaired, survival is reduced, suggesting this is a very late stage in the disease process[44,45]. Diastolic abnormalities may occur earlier[46,47], or dynamic studies highlight abnormalities of function not evident at rest[48,49].

Dilatation of the ventricles, to a mild degree, is a frequent finding in thalassaemia patients and, when associated with normal systolic and diastolic function, is likely to be due to the associated moderate anaemia rather than to myocardial failure[50]. Increases in ventricular mass index occur[51] and changes in the reflectivity of ventricular myocardium have been attributed to iron overload[52]. The difficulty in correlating the findings on echocardiography with indirect indices of body iron load, such as the number of blood transfusions received and serum ferritin, has led some to suggest that iron loading is not the cause of left ventricular failure[52,53]. These authors have demonstrated that myocarditis occurred in about 4% of a thalassaemic cohort observed over 5 years, and had severe implications for ventricular function[54]. However myocarditis is unlikely to account for many patients who develop severe left ventricular impairment as a consequence of iron overload. Pre-disposition of tissues to viral infection in iron overload, and a susceptibility to increased damage by infection is a feature of these patients, as illustrated by the liver response to hepatitis C infection[55].
Newer echo modalities, such as tissue Doppler imaging may improve the diagnostic capabilities in thalassaemia, but it is only when echocardiographic measurements are able to be reliably correlated with tissue iron content that predictive indices will be available. The magnetic resonance imaging T2* measurement may hold this key. In this, issue Hahalis and colleagues[56] clarify an issue regarding the role of the right ventricle in the clinical picture of cardiac failure in thalassaemia. They have shown, in a group of suboptimally chelated patients, that severe right ventricular impairment accounts for the clinical manifestation of heart failure. As ventricular myocytes throughout the heart face an iron load it is perhaps not surprising that the right ventricle might fail first, with proportionately fewer cells to generate normal right ventricular function. Importantly right ventricular impairment appears to be primary rather than secondary to pulmonary hypertension, contrary to previous assumptions[47,57,58]. A restrictive defect seen in pulmonary function tests in thalassaemia has been reported and remains unexplained[59,60].

The mechanism by which iron excess interferes with myocyte function involves the capacity to catalyse the formation of damaging oxidative free radicals[61,62]. Many intracellular processes and organelles are affected[63]. The capacity for hearts to recover from states of very poor function to virtual normality is one of the most striking and rewarding aspects of dealing with the disease. The analogies to myocardial stunning are therefore striking. For most cardiologists, the cardiomyopathy of iron overload remains an infrequently observed clinical curiosity. However, worldwide it is an important cause of morbidity and mortality in young people.

Thalassaemic heart disease also affords an opportunity to understand myocardial adaptive processes. This is a unique group of patients with a single cause for cardiac failure, which develops with an incidence of 3–5% per year even in those well-chelated adults with thalassaemia. Many of the mutations causing β-thalassaemia have been identified, and some of the reasons behind the very variable phenotypic expression of this monogenic disorder are being unravelled[64,65]. More uncertainties exist than answers, serving as a caution to the over-optimistic view that knowing the gene defect can easily predict phenotype and then translate into clinical practice. Managing these patients optimally will still require careful clinical observation, measurements and well-planned trials of new therapies.

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