European Journal of Haematology ISSN 0902-4441

REVIEW ARTICLE

The heart in transfusion dependent homozygous thalassaemia today – prediction, prevention and management

Athanassios Aessopos, Vasilios Berdoukas, Maria Tsironi

First Department of Medicine, University of Athens, 'Laiko' Hospital, Goudi, Athens, Greece

Abstract

Cardiac disease remains the major cause of death in thalassaemia major. This review deals with the mechanisms involved in heart failure development, the peculiar clinical presentation of congestive heart failure and provides guidelines for diagnosis and management of the acute phase of cardiac failure. It emphasizes the need for intensive medical – cardiac care and aggressive iron chelating management as, with such approaches, today, the patients outcomes can be favourable in the long term. It covers advances in the assessment of cardiac iron overload with the use of magnetic resonance imaging and makes recommendations for preventing the onset of cardiac problems by tailoring iron chelation therapy appropriate to the degree of cardiac iron loading found.

Key words thalassaemia major; cardiomyopathy; cardiac failure; transfusion therapy; iron chelation therapy

Correspondence Athanassios Aessopos, MD, PhD, First Department of Medicine, University of Athens, 'Laiko' Hospital, Goudi, Athens TK: 11527, Greece. Tel: +30 (210) 7771161; Fax: +30 (210) 7788830; e-mail: aaisopos@cc.uoa.gr

Accepted for publication 24 June 2007 doi:10.1111/j.1600-0609.2007.01018.x

In beta thalassaemia major transfusions and iron chelation therapy have significantly improved the survival and reduced the morbidity (1, 2). In the 1960's 80% of patients had died by the age of 16 (3) and now at least 80% survive beyond the age of 40 yrs (4). This improvement is unique, as no other formerly fatal genetic defect has shown such a benefit. However, heart complications still represent significant morbidity and remain the leading cause of mortality in transfusion dependent thalassaemia (TM) patients (2). Cardiac dysfunction with congestive cardiac failure (CCF), arrhythmias and ultimately, premature deaths continue to present. In some cases this was because of the difficulty in accepting the chelation treatment, which was cumbersome (5), but also occurred even in some patients who accepted the chelation therapy well (6, 7).

In this review, we present some aspects of the existing knowledge including our view, acquired of our 30 yrs experience in following the cardiac course of the disease in more than 1000 thalassaemic patients. Pathophysiology of the heart injury, clinical findings, diagnosis of CCF and the global strategies regarding therapeutic interventions for CCF in TM patients, as well as for prevention of its onset are herein presented.

Mechanisms of heart injury

Cardiac structure and function in TM are mainly affected by two competing factors: iron load and increased cardiac output (CO). The cardiac iron deposition results in a decrease of left ventricular function. The anaemia together with marrow expansion leads to volume overload and increased CO that then demands increased contractility adding additional stress to the heart. (Starling's Law).

The cardiac iron load

Direct iron related injury

Iron overload results principally from the regular blood transfusions. Patients receive between 0.3 and 0.5 mg/kg/d of iron through transfusions. The average daily losses are less than 1 mg in males and 2 mg in

females. There are no other physiological mechanisms for effecting body iron reduction. In addition to the transfused iron, TM patients absorb more iron than normal individuals. The mechanism of increased absorption is thought to be related to paradoxical Hepcidin suppression from the dyserythropoiesis (8–10). In the presence of excess iron Hepcidin should be elevated to inhibit iron absorption but the dyserythropoiesis overrides that effect. Among the different mechanisms in the cellular pathways of ferrous iron (Fe^{2+}) membrane L-type calcium channels are significantly involved (11). L-type Ca^{2+} channels are high-capacity pathways for ferrous iron (Fe^{2+}) uptake into cardiomyocytes in conditions of iron overload.

Iron is stored in cells, including myocytes, in the form of ferritin, haemosiderin and free iron. The latter is referred as the labile cellular iron (LCI) (12). There is a significant flux between the three forms, with haemosiderin being the least accessible. The LCI is thought to be the most accessible to chelation, but it is also the most toxic form as it stimulates the formation of free radicals. These result in peroxidative damage of membrane lipids and proteins provoking cellular injury. In the heart, this leads to impaired function of the mitochondrial respiratory chain and is clinically manifested by reduction of cardiac muscular contractility and CCF development (13). Furthermore, in the presence of increased intracellular ferrous iron, the ryanodine sensitive calcium channels of sarcoplasmic reticulum (SR), are inhibited. This modulates SR calcium release, resulting in further reduction of cardiac function and arrhythmia development. The new knowledge on calcium channels may offer new potential therapeutic interventions for cellular iron reduction and treatment of arrhythmia and cardiac dysfunction (11, 14, 15).

To date, at least 90 genes that control iron metabolism have been identified (16). Due to the possible gene variations the handling of iron in each individual is expected to be different. Similarly the action of iron chelators could be affected and act differently in the individual patient. It has been shown that TM patients who express the apo-lipoprotein E4 allele were at greater risk for left ventricular (LV) dysfunction. Apo E4 is less efficient at handling oxidative stress (17, 18) when compared to Apo E2 and Apo E3. Additionally the genetic variations of the GSTM1 enzyme (Glutathione S-Transferase M1) are associated with increased cardiac iron deposition in patients with TM (19). These concepts fit in well with the wide range of reported different clinical cardiac courses seen in TM patients who have followed similar life-time, well accepted treatment (6).

Knowledge derived by recent magnetic resonance imaging (MRI) studies which also assessed cardiac function, showed that all patients with reduced LV function had cardiac iron overload and in many cases this was severe (20–23). This strongly suggests that in addition to the damage caused by the accumulated iron, excessive iron in the myocytes results in greater amounts of LCI leading to free radical formation that overwhelms the antioxidant mechanisms and ultimately precipitates cardiac dysfunction. In the above MRI studies, despite heavy iron load, many TM patients maintained normal cardiac function, albeit perhaps temporarily, and this may be related to their different, intracellular iron metabolism, in particular their neutralisation of oxidants as discussed above.

Indirect iron related injury

Infections

Any significant infection may precipitate cardiac failure particularly in the presence of other underlying cardiac pathology. Immune competence in beta-thalassemia is impaired (24–27) and patients are more vulnerable to infections. Furthermore, siderophore bacteria, such as yersinia and klebsiella, rely on iron for multiplication and grow well in the microenvironment of TM patients (26, 27).

Iron overload is considered to be the main etiologic factor that can disturb the immune balance in favour of the growth of infectious organisms (25). This may also be affected by differences in the existing immunogenetic profile in TM (28) especially with respect to viral infections. Two severe cardiac complications, pericarditis and myocarditis, are linked to iron load induced viral infection susceptibility.

Pericarditis, frequently seen (50%) in TM patients with poor or no chelation in the past (3), is very rare today (5%), with the use of chelation therapy (6). Similarly, the reported myocarditis in TM patient with decreased LV function (29), seems most likely to be related to iron load. Even though there may be histological evidence of infections, as demonstrated by lymphocytic infiltration, recent evidence shows that LV failure only occurs in the presence of excessive iron (20–23). Viral myocarditis without iron in the heart may be rare and may follow similar outcomes to those of the normal population. Elevated plasma cardiac enzymes or troponine may be indicative of concomitant viral myocarditis.

Vascular involvement (afterload)

Systemic arterial involvement in TM, as observed recently through clinical, functional (30) and anatomical (31) studies, plays a role in the development of cardiac dysfunction by affecting heart afterload. Vascular involvement starts early in life and becomes obvious in

the older patients (32). The anatomical component including elastic tissue abnormalities is expressed in arteries by thickening and disruption of the elastic laminae and adventitia, followed by calcium deposition. The injury is suggested to be mediated by the chronic haemolytic state along with the increased labile plasma iron (LPI). Erythrocyte membrane fragments, haem and free haemoglobin in addition to free iron, provoke a strong oxidative stress on endothelium (32). A component of the vascular dysfunction is due to the reduction of nitric oxide (NO). There are at least three mechanisms responsible for that effect related to haemolysis; a) Red cell destruction releases arginase which reduces arginine levels and its supplementation to the endothelium. b) Oxyhaemoglobin is transformed to methhaemoglobin after reacting with NO and converts it to inactive NO^3 i.e. neutralising it and c) Oxidative stress inactivates endothelial cell enzymes and reduces formation of NO from the precursor arginine (33).

Similar mechanisms apply also to the pulmonary artery bed, where vascular contribution together with coexisting hypercoaguability is considered to be responsible for increased pulmonary artery resistance (34, 35).

Arrhythmias

The iron induced cardiac toxicity is often complicated by arrhythmias such as extra atrial and ventricular beats, paroxysmal atrial tachycardia, flutter or fibrillation. Life threatening ventricular tachycardia is rare and often associated with reduced LV function. Short runs of non-specific ventricular tachycardia are quite common and are more common with elevated cardiac iron. Atrial arrhythmias occur more frequently. These are more clinically relevant and difficult to treat, but less specific for iron toxicity. Some of these arrhythmias can also be triggering factors for CCF or reduced cardiac function in TM patients without previous obvious LV dysfunction.

Endocrine abnormalities

Iron toxicity may also indirectly affect heart function by damaging other organs in varying degrees. The endocrine abnormalities hypothyroidism and diabetes mellitus can have a significant impact on cardiac function (36). Hypothyroidism can precipitate pericardial effusion, decreased LV function, bradycardia and increased peripheral vascular resistance. The onset of diabetes is often associated with the presentation of cardiac dysfunction. Chronic hyperglycaemia is an oxidative stress on many organs, particularly the heart. Hypocalcaemia associated with occult or overt hypoparathyroidism can precipitate heart dysfunction.

Medications

Vitamin C has been given to patients in order to enhance their iron excretion when they are on chelation therapy. There have been case reports of patients who developed sudden acute cardiac failure with a fatal outcome that had been precipitated by the administration of Vitamin C possibly by releasing free iron that is toxic (37).

Increased CO effect (preload)

Disease related increased CO, resulting in increased workload on the heart, contributes to the development of cardiac dysfunction in TM patients. In other chronic anemias, resting CO increases when Hb levels decline below 9 g/dL (38–41). TM patients, however, even those well transfused (mean pre transfusion Hb level > 9.5 g/dL) with excellent suppression of marrow activity and with mean Hb level between transfusions of 11.3 g/dL, still demonstrate some degree of high CO (Cardiac Index 4.3 ± 0.9 L/m^2 in TM cf. 3.8 ± 0.8 $P < .01$ in normal individuals) (6). It is more obvious in cases were low Hb levels and tissue hypoxia stimulate compensatory reactions leading to development of peripheral shunts (42). Liver iron load or viral induced hepatic injury can also contribute, as cirrhosis can increase CO significantly (43). Furthermore, the presence of elastic fibre degeneration, affecting elastic lamina and adventitia, which render vessels more susceptible to dilatation by pulse pressure increase in the context of a hyperkinetic state also increases the total blood volume (31).

Summary of the mechanisms of heart injury

In TM, the impaired heart from iron overload, is obliged to maintain a high output through a rigid vascular bed that results from the abovementioned vascular damage and is therefore subjected to a continuous state of both volume and pressure overload rendering the LV more susceptible to decompensation. Similarly, in TM patients the coexistence of high CO state and gradually increasing pulmonary vascular resistance seems to lead to the development of pulmonary hypertension (PHT), which readily precipitates right ventricular (RV) failure (34). Infections, with a direct or indirect effect also have an impact on heart function. In well-treated TM patients, the inhibition of the above mechanisms, result in a considerable reduction of LV dysfunction incidence, vascular damage, PHT development and RV failure (44, 45).

Heart pathology

Iron is thought to saturate liver firstly, and then to accumulate in other organs. In the heart, it accumulates

in all four chambers, papillary muscles and the electrical conduction system, including the sinoatrial and atrioventricular nodes (46). In the free wall of the left ventricle there is more iron concentrated in the epicardial layers than in the endocardial and middle third (47). From the epicardium, it encroaches upon the pericardium. Such iron deposition raises a possibility that pericarditis may also have an iron induced chemical inflammatory component and also may cause fibrosis of the pericardium with or without a history of viral pericarditis (Fig. 1). Histology has shown individual myocyte hypertrophy with multiple deposits of brown granular material within the cytoplasm of the myocytes (Fig. 2). These granules stain positive with Prussian blue, confirming heavy myocardial iron deposition. Interstitial macrophages containing iron are also present (48). Moreover, the study of cardiac biopsies from TM patients with light and electron microscopy, as well as with X-ray microanalysis has revealed the presence of disrupted myocytes showing loss of myofibers, dense nuclei, and a variable number of pleomorphic electron dense granules. These cytoplasmic granules or siderosomes consist of iron-containing particles as confirmed by X-ray microanalysis.

Clinical presentation of cardiac involvement in TM

Cardiac involvement includes heart failure, arrhythmias and pericarditis. The presentation of pericarditis is similar to that which occurs in the general population. This is also the case with arrhythmias.

Heart failure can present at any time after the age of 10 yrs but with optimal treatment, heart failure usually occurs in the third or fourth decade of life (6). The presentation can be abrupt, sometimes associated with an infection or with a slow relentless onset.

Although some patients can present with symptoms of left-sided heart failure including exertional dyspnoea, cough and fatigue, followed by râles and gallop rhythm on chest auscultation, it is worth noting that the majority presents with symptoms and signs of right ventricular dysfunction. The patients often present to an outpatient clinic with severe fatigability and abdominal pain, the latter due to liver distention. The patient may be lying on the examination couch without dyspnoea. These signs can easily be misinterpreted as not being symptoms of cardiac origin (49, 50). The clinical course in this young population, has often been associated with a gradual reduction in physical activity, which obscures and delays the presentation.

However, clinical examination with the patient in a correct position, will reveal a positive hepatojugular reflex with neck vein distention and a third and fourth heart sounds. In more severe cases, peripheral oedema

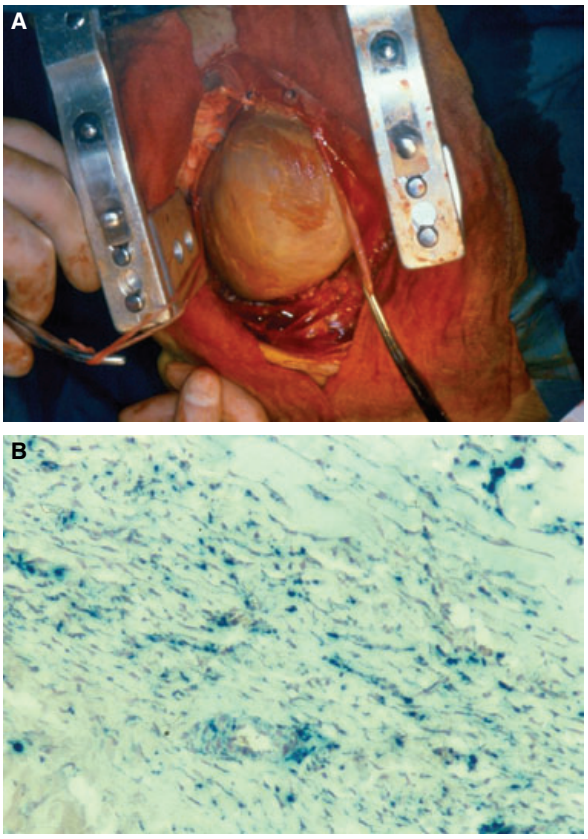

Figure 1 (A) Operative field in a 27 yr old male thalassaemia patient with a history of recurrent pericarditis and effusive constrictive pericarditis at the time of surgery (B) with biopsy from the same patient demonstrating significant pericardial thickening with severe iron deposition and a small amount of muscle in the left hand corner which contains iron (Prussian Blue Stain).

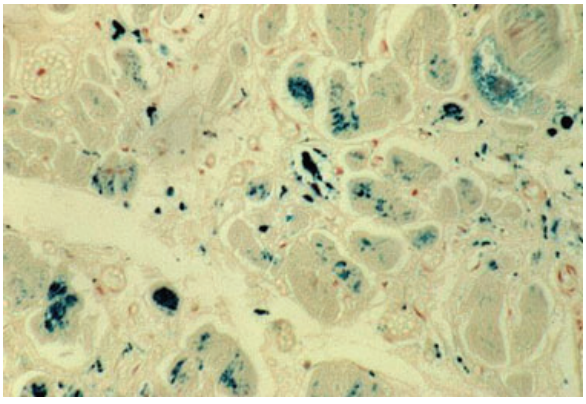

Figure 2 Histological features from an autopsy from a 29 yr old male thalassaemia patient who died of congestive cardiac failure. Histology shows individual myocyte hypertrophy with multiple deposits of brown granular material within the cytoplasm of the myocytes. These granules stain positive with Prussian blue, confirming heavy myocardial iron deposition.

and ascites may be found. This peculiar clinical appearance in TM patients should be kept in mind. It results from the thin iron loaded right ventricle decompensating earlier (51). Râles may be found in cases where there is also left sided heart failure.

Investigation findings for CCF

Chest X-ray, shows cardiomegaly but frequently there are no features of pulmonary congestion. Lung congestion and pleural effusion may be present as well as a prominent pulmonary artery in cases with coexisting PHT.

It is unusual for the electrocardiogram (ECG) to be normal. Wide QRS complex with low voltage, inverted T waves, non-specific ST-T changes, Left Ventricular Hypertrophy, prolonged A-V conduction and arrhythmias are frequently seen.

Doppler echocardiographic study usually shows biventricular dilatation and systolic and diastolic dysfunction. The variety, however, of the different abovementioned pathogenetic factors and their degree of contribution to the cardiac damage, including the different treatment regimes (lower transfusion schemes, inadequate chelation) lead TM patients, who present with CCF not always to show uniform cardiac injury. Restrictive cardiomyopathy-constrictive pericarditis or high cardiac state Doppler echocardiographic findings could present either alone or in combination. The development of significant PHT may accompany the CCF in almost all the above forms, contributing to the precipitation of right-sided heart failure. In cases with impaired LV function, thrombus formation in the apex of the heart may be present and can lead to the development of stroke (52) (Fig. 3).

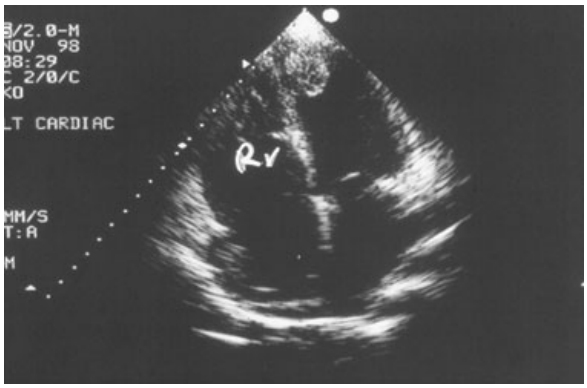

Figure 3 A 30 yr old female thalassaemia patient 2-D four chamber view with the presence of an apical thrombus.

Therapeutic approach to TM patients with CCF

Thalassaemia patients with signs and symptoms of CCF should be hospitalised and closely monitored. Extensive laboratory tests should be performed and include:

arterial blood gas,
endocrine profile,
liver and renal function tests,
chest X-ray,
ECG and
Doppler echocardiographic study.

As stated above recent MRI studies have confirmed that almost all patients with decreased left ventricular function have severe iron load (20–23). In the acute failure patients the values of MRI measurements are only important to determine the degree of iron overload for future follow-up and can be postponed till after the patient has improved clinically.

Triggering factors for CCF development such as arrhythmias, blood volume overload after transfusion, infections, severe anaemia, should be identified and treated. In cases where *Yersinia enterocolitica* or *Klebsiella pneumoniae* infection is suspected (53), patients should be treated even before immunological or bacterial culture test results are available. If arrhythmias are present, the least negative inotropic antiarrhythmic agent, amiodarone should be infused intravenously (54). In general, implantable defibrillators are not recommended for the management of ventricular arrhythmias in TM and the essential intervention is intensification of chelation therapy. However, in rare case of sustained ventricular tachycardia, later in the clinical progress, an implantable defibrillator may be necessary.

Daily measurements of body weight, blood pressure and 24-hrs urine secretion are of paramount importance in these patients. Frequent monitoring of Hct, Hb, blood electrolytes, urea, creatinine, glucose, AST, ALT, uric acid, is also mandatory.

Chelation therapy

Combination of the two iron chelators (deferrioxamine and deferiprone) seems to maximise the efficacy producing additive and synergistic effects in iron excretion (55, 56). It seems that each of those two agents chelates iron from different pools and there is at least an additive effect when combined treatment is administered (57). Available evidence now suggests that combined therapy should be the treatment of choice for patients with established cardiac failure. We have reported two cases with severe CCF who reversed with intensive combination therapy (58, 59) and we have at least eight more patients with similar outcome. Two other studies show similar responses (56, 60). In a recent study with combined

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.