**REVIEW**

**Heart failure in β-thalassemia syndromes: A decade of progress**

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**ABSTRACT:** The thalassemias are common monogenic disorders of hemoglobin synthesis. β-thalassemias are the most important among the thalassemia syndromes and have become a worldwide clinical problem due to an increasing immigrant population. In β-thalassemia major, regular blood transfusions are necessary early in life. Beta-thalassemia intermedia refers to a less severe phenotype, whereas β-thalassemia/hemoglobin E disease encompasses a broad phenotypic spectrum. Blood transfusions and increased gastrointestinal iron absorption result in iron overload and tissue damage. Among patients with β-thalassemia major, biventricular, dilated cardiomyopathy remains the leading cause of mortality. In some patients, a restrictive type of left ventricular cardiomyopathy or pulmonary hypertension is noted. The clinical course, although variable and occasionally fulminant, is more benign in recent than in older series. Myocarditis has been described as a cause of left-sided heart failure in younger patients. Pulmonary arterial hypertension is the principal cause of heart failure in β-thalassemia intermedia. Chelation therapy has improved prognosis in β-thalassemia major both by reducing the incidence of heart failure and by reversing cardiomyopathy. Estimation of the patient’s cardiac risk is mainly based on clinical criteria and serial echocardiography. A new cardiovascular magnetic resonance technique will probably fulfill the need for more precise risk stratification in β-thalassemia syndromes. By increasing the proportion of patients on optimal chelation, survival in β-thalassemia major may further improve. Recent advances in gene therapy are expected to result in the long-awaited cure of this disease.

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The thalassemias are anemias of variable severity, which result from mutations of the genes encoding the synthesis of α- and β-globin chains of hemoglobin.1-4 Serious thalassemia is associated with iron overload, tissue damage, and increased risk of cardiovascular complications. Thalassemias are prevalent in a belt ranging from the Mediterranean basin through the Middle East and Indian subcontinent up to Southeast Asia. Beta-thalassemias are the most important among the thalassemia syndromes with an average trait prevalence of 7% in Greece, 15% among Cypriots, and 4.8% in Thailand.1-4 Furthermore, the hemoglobin E gene, which can interact with β-thalassemic alleles and cause a broad phenotypic spectrum, reaches a frequency of up to 50% in Thailand.1

Within the first months of life, adult hemoglobin containing 2 pairs of α and β chains (HbA:α2β2) physiologically replaces fetal hemoglobin (HbF:α2γ2).2 In β-thalassemia, deficient production of structurally normal β-chains and the attending accumulation of unopposed α-chains lead to anemia, largely as a consequence of ineffective hemoipoiesis.2-4 In β-thalassemia major, severity of anemia requires initiation of blood transfusions during infancy. Patients with a less severe phenotype, ie, β-thalassemia
intermedia, will, if at all, become transfusion-dependent later in life. In β-thalassemia/hemoglobin E disease, interpatient hemoglobin levels range between 3 and 13 g/dL, blood transfusion requirements are variable and phenotype varies between mild and serious anemia (Figure 1).4 Morbidity due to cardiovascular, endocrinological, and hepatic disease is considerable in β-thalassemia syndromes,5-14 whereas heart failure still constitutes the leading cause of mortality in patients with β-thalassemia major. Thus, β-thalassemias not only affect a large number of people worldwide resulting in a tremendous health care and social problem, but they also require a multidisciplinary medical expertise.1,2,5,14 In particular, physicians should become familiar with thalassemia-related problems in countries where a growing immigrant population resulted in an increasing number of such patients, including the United States and Canada, as well as many European countries.15 Research achievements in the last decade elucidated both the natural history of β-thalassemia major, which is principally determined by the cardiac function, and the pleiomor-
The pathophysiological diversity of heart failure

β-thalassemia major

On the background of cardiac iron overload, multiple factors can detrimentally affect cardiac function, including volume overload, high cardiac output, neurohumoral activation, eccentric left ventricular hypertrophy, genetic predisposition, endocrinopathies, and increased elaboration of pro-inflammatory cytokines, as well as additional or unknown factors. Heart failure usually develops among patients with nonoptimal chelation therapy and multi-endocrinopathies. Dyspnea or fatigue is reliably reported by the patients, and even mildly symptomatic patients demonstrate a substantial reduction in exercise capacity. Right heart failure manifests either early or, more frequently, evolves and predominates during the course of left-sided heart failure. Occasionally, acute right-sided heart failure may mimic acute abdomen and result in diagnostic delay. Paroxysmal atrial fibrillation is common and almost invariably associated with myocardial dysfunction. Restoration of sinus rhythm per se usually does not reverse cardiomyopathy. Due to longer survival of thalassemic patients, the incidence of this arrhythmia may increase in the future and be rather age- and volume-overload- than cardiomyopathy-dependent. The clinical picture of the disease varies between a long-lasting course and, sometimes, complete remission to fulminant disease.

Biventricular dilated cardiomyopathy

This is the most common underlying pathophysiological abnormality among heart failure patients with β-thalassemia major. Contractile dysfunction is accompanied by low cardiac output and may demonstrate substantial long-term variations (Figure 2). This is more likely explained by the extent of cardiac iron deposition or the myocardial responsiveness to the intensified chelation therapy. In advanced disease, a distinct hemodynamic pattern of severe right ventricular cardiomyopathy is evident. Ischemic cardiomyopathy is notably very uncommon, due to the rare incidence of coronary artery disease both clinically and angiographically (Kremastinos DT: unpublished data).

Myocarditis/pericarditis

In our series of 1048 patients, 4.5% of them with a mean age of 15 years were diagnosed over a 9-year period to have left heart failure as a consequence of biopsy-proven myocarditis. Almost half of the cases had a complete recovery, whereas 44% of the patients died. In a subsequent study, an association of heart failure with the major histocompatibility in patients with β-thalassemia major was reported. This
suggests an autoimmune pathophysiology of left-sided heart failure in these patients. Similar to iron-induced cardiomyopathy, genetic factors may therefore modulate predisposition of thalassemic patients to myocarditis. Future studies on thalassemic inflammatory cardiomyopathy should determine the prevalence of both immune-competent infiltrates and viral genomic materials in the myocardium by biopsy-ascertained immune-histochemistry as well as modern molecular techniques.

Although very frequent in the past, pericarditis seems to have a decreasing incidence in the chelation era. The available data, however, are contradictory and do not unanimously support this common experience.

**Restrictive type of left ventricular cardiomyopathy**

True restrictive cardiomyopathy is characterized by restrictive hemodynamics, nondilated ventricles and, at least initially, near normal or normal contractility. Some thalassemic patients with congestive heart failure demonstrate a restrictive type of left ventricular cardiomyopathy, in that almost all of the aforementioned criteria are met with the exception of the left ventricular contractility, which is always impaired. Neither pure diastolic myocardial heart failure in the presence of preserved ventricular systolic function nor right ventricular restrictive cardiomyopathy have, in our experience, been encountered in β-thalassemia major. In some patients, an echo-Doppler pattern of “left restrictive-right dilated” cardiomyopathy in association with pulmonary hypertension has been observed. In other patients, this finding probably reflects a timely disparate myocardial behavior of the 2 ventricles in the absence of pulmonary hypertension (Figure 3).

**Pulmonary arterial hypertension**

Recent studies clearly demonstrated the absence of pulmonary arterial hypertension among asymptomatic patients as well as in the vast majority of those with heart failure.
Thus, previous reports were not confirmed, despite the attractive theoretical background. Exceptionally, some older patients with high ferritin values do develop pulmonary hypertension and figures will probably increase in the future due to the growing population of aging patients. Acute cor pulmonale, which is occasionally encountered, reflects the increased thromboembolic risk of these patients.

Normal ventricular systolic function among asymptomatic patients

In contrast to an older report, recent investigations indicate that left ventricular filling in asymptomatic patients with β-thalassemia major is not restrictive but rather undisturbed and compatible with increased preload. Moreover, the right-sided inflow features suggest impaired right ventricular relaxation and carry prognostic information.

β-thalassemia intermedia

Aessopos et al recently reported on 110 Greek patients, half of whom were splenectomized. In approximately 50% of the patients, at least mild pulmonary hypertension and pericardial thickening were evident on echocardiography. Pulmonary pressures correlated with age and cardiac output, whereas high-output pulmonary hypertension was found on catheterization in all 6 patients with heart failure. A higher
susceptibility for pulmonary hypertension in β-thalassemia intermedia appears plausible, although both thalassemia phenotypes share common predisposing factors including hemolysis-mediated pulmonary hypertension.

Compared with β-thalassemia major patients, those with less severe phenotype both are older and suffer from more serious anemia. As a result of sporadic only transfusion requirements, patients with β-thalassemia intermedia retain, in addition, almost 100% of their own erythrocytes, which are potentially more procoagulant and associated with a higher incidence of splenectomy.

β-thalassemia/hemoglobin E disease

Heart disease is the leading cause of mortality among transfusion-dependent patients. Therefore, the major phenotype probably carries a comparable, although poorly defined, cardiac risk with that of the general β-thalassemia major patients.

Patients with the intermedia phenotype may develop biventricular failure. Acute pericarditis is frequent, and chronic pericardial disease is found in some patients. Degenerative valve disturbances are analogous to those described in Greek patients, whereas rheumatic valve disease is the consequence of frequent streptococcal infections. Pulmonary hypertension is well documented, largely in splenectomized patients with thrombocytosis and right heart failure, whereas accompanying hypoxemia is partially reversed by aspirin administration. Pathophysiologically, the vascular perturbation in this disorder may reflect qualitative, but probably not quantitative, similarities with the general β-thalassemia intermedia patient, including hemolysis, high output, hypoxia, postsplenectomy thrombocytosis, activated endothelial cells, nucleated erythrocytes and cytokine elevation, in the context of hypercoagulable state and predisposition to thromboembolism.

Normal ventricular systolic function in asymptomatic patients

Chamber dilatation and eccentric hypertrophy follow the degree of anemia, whereas myocardial function appears normal similar to other β-thalassemia intermedia patients. Furthermore, paroxysmal atrial fibrillation is a relatively common cause of morbidity in these patients.

Screening for cardiac disease and risk stratification in heart failure

β-thalassemia major

Myocardial dysfunction, which might have been obscured by the altered loading conditions in anemia, could be represented

Figure 4  Beta-thalassemia major: recommendations for patient management in relation to the clinical cardiac risk category.
β-thalassemia intermedia and β-thalassemia/hemoglobin E disease

Age, high ferritin levels, severity of anemia, need of blood transfusions, and splenectomy pose even asymptomatic patients at increased, although as yet ill-defined, cardiovascular risk. Surveillance for heart disease is imperative, given the interpatient heterogeneity of iron loading, particularly in association with the splenectomy status. Clinical information and regular echocardiographic monitoring, including investigation of pulmonary artery pressures, are therefore important tools for cardiac risk stratification, whereas the role of magnetic resonance techniques has yet to be determined. Moreover, heart failure patients should undergo a thorough diagnostic workup for precise determination of the cause and severity of the underlying cardiopulmonary disease.

The role of chelation therapy in prevention and course of cardiac disease—therapeutic implications

β-thalassemia major

In recent series, the prevalence of heart failure has been more than halved but is still 2.5% among well-treated patients. Even more, the age of onset of heart failure could only modestly, by 1 decade, be prolonged, due to suboptimal chelation of many adolescents and possibly to other, as yet poorly characterized causes (eg, genetic susceptibility). Pump failure is the principal cause of mortality, while sudden death in β-thalassemia major is notably uncommon despite data revealing a proarrhythmic substrate.

Primary prevention

In the last 2 decades, nonrandomized studies assessed prognosis in β-thalassemia major. These investigations demonstrated a survival improvement, which was almost entirely due to cardiac disease prevention among patients on optimal chelation therapy. Zurlo et al reported that the 5-year survival probability after the first decade of life was 81% for subjects born in 1960-1964 versus 97% for those born in 1970-1974. Modell et al showed that about 50% of patients with β-thalassemia died before the age of 35 years. The survival probability of both the 1955-1964 and 1965-1974 birth cohorts was 50% at the age of 40 years and better than in earlier series. Such outcome improvement, albeit modest, confirmed observations made by the same investigators 2 decades earlier on the survival benefit conferred by desferrioxamine. Ehlers et al reported almost a doubling of survival for patients placed on chelation therapy. Brittenham et al demonstrated that for each unit increase in the natural logarithm of the ratio of transfused iron to total desferrioxamine use (equivalent to a quadrupling of serum ferritin), the relative risk for cardiac disease was 9.9 and for death 12.6. Probability of survival to at least the age of 25 years was 32% for patients on ineffective chelation versus 100% for those on good chelation therapy. Olivieri et al reported a survival probability without cardiac disease of 91% at 15 years among appropriately chelated patients. Even in high-risk patients, intensive intravenous chelation treatment resulted in an actuarial survival of 63% at 13 years.

Thus, the long-term outlook of patients on optimal chelation therapy is good. Furthermore, the dogma “it is never too late” seems to apply to every patient with β-thalassemia major, because prognosis is largely determined by the current quality of chelation treatment.

Course of heart failure

In advanced cardiac iron overload states, outcome of heart failure is dismal, with a reported 3-month mortality rate of 58% in the prechelation era. Recent findings from Kremastinos et al indicate an improved prognosis over older series. Five-year survival was 48% and positively associated with left ventricular systolic function. All deaths occurred among patients with biventricular cardiomyopathy, shortly after involvement of the nonfailing ventricle. Such improved survival is explained by the widespread use of chelation treatment and possibly also by better management of anemia and use of angiotensin-converting enzyme inhibitors. Thus, heart failure seems to have a milder course among patients on adequate chelation, similar to that of the general population of heart failure patients. Furthermore, a substantial minority of these patients experience reversal of cardiomyopathy after intensification of chelation. In contrast, insufficient chelation therapy may be associated with a fulminant course.

Therapeutic implications

Intensification of chelation therapy is of paramount importance in asymptomatic high-risk patients as well as in patients with heart failure, because of its additional and possibly also greater benefit as compared with current therapeutic modalities for systolic heart failure (Figure 1). By extrapolating current guidelines, such established treatment options should also be recommended for thalassemic patients. In face of the altered loading conditions in thalassemia, initiation of therapy with angiotensin-converting enzyme inhibitors should be implemented early, for example when the left ventricular ejection fraction approaches a value of 50%. Angiotensin II receptor blockers can alternatively or additionally be used. Diuretics, including spironolactone antagonists and digitalis glycosides, are necessary in
symptomatic patients, whereas beta-blocker therapy has to be considered in compensated patients.89 Patients with \( \beta \)-thalassemia major have a higher-than-average possibility of developing malignancies.13 Chelation therapy should be intensified in patients undergoing chemotherapy with drugs known to exert an iron-mediated toxicity, such as anthracyclines,92 in order to minimize the risk of fulminant cardiomyopathy.12 Right ventricular involvement and the attending asynchrony of left ventricular contraction are frequent findings in end-stage, thalassemic heart failure. Resynchronization of contractility by means of atrial-synchronized biventricular pacing both improves contractility and alleviates symptoms in refractory systolic heart failure93 and should therefore be considered in selected thalassemic patients. Anticoagulation is indicated in patients with atrial fibrillation, in the occasional patient with ventricular thrombus, and in those with pulmonary hypertension (Figure 5). Due to coexisting hepatic disease, a lower-than-average anticoagulant dose is required. Restoration of sinus rhythm usually should be undertaken in appropriately prepared patients. Prophylactic antithrombotic treatment is additionally recommended in patients exposed to transient thromboembolic risk, including surgery and prolonged immobilization.52

Advanced or complete atrioventricular block will necessitate the implantation of a pacemaker device. Interestingly, malignant ventricular tachyarrhythmias occur rarely.10-12 This may be partly related to recovery of myocardial function in some patients or rapid decline of pump function in others.12 Implantation of a cardioverter-defibrillator is thereby rarely necessary. In exceptional cases, and when the fate of dysfunctional myocardium has not been clarified, automatic wearable defibrillators may be a therapeutic option. Finally, in carefully selected patients with end-stage disease, heart transplantation has been recommended.94 In fact, we are aware of one patient who is still alive 17 years after heart transplantation.

\section*{\( \beta \)-thalassemia intermedia}

\subsection*{Primary prevention—course of heart failure—therapeutic implications}

Both the natural history and the optimal management of the disease and its cardiac complications, as well as the etiology of death, remain poorly understood.1,95 In our experience, some patients who become transfusion dependent succumb to dilated cardiomyopathy with or without concomitant pulmonary hypertension and appear to have a worse outcome than those with isolated pulmonary hypertension. Clearly, future studies should clarify these issues and help establish stricter transfusion and chelation criteria.1 At present, initiation of treatment follows anemia severity, clinical information regarding iron loading as well as cardiac complications, including atrial fibrillation, pulmonary hypertension,5 or cardiomyopathy. Antithrombotic prophylaxis has been suggested for splenectomized patients at high transient thromboembolic risk (Figure 5).5,52 Anticoagulation should adhere to the same guidelines as in patients with the major phenotype, whereas oxygen administration as well as diuretic and digitalis treatment should be individualized. In documented pulmonary hypertension, a life-long therapy with vasodilators52 will be necessary.

\section*{\( \beta \)-thalassemia/hemoglobin E disease}

\subsection*{Primary prevention—course of heart failure—therapeutic implications}

Patients with the major phenotype are probably indistinguishable from other \( \beta \)-thalassemia major patients31 regarding iron loading and salutary effects of chelation treatment.

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure5}
\caption{Causes of heart failure in \( \beta \)-thalassemia intermedia and \( \beta \)-thalassemia major. Top: pulmonary arterial hypertension with severe right chamber dilatation in a patient with \( \beta \)-thalassemia intermedia. Pulmonary angiogram revealed chronic thromboembolic disease. Bottom: Severe biventricular dilated cardiomyopathy with large thrombus in the left ventricular apex (arrows) in a patient with \( \beta \)-thalassemia major and fatal outcome.}
\end{figure}
Patients with less severe disease may attain old age, but the main cause of mortality among older patients is cardiac. 29

Guidance of transfusion and chelation therapy has to follow the same principles applied for the general β-thalassemia patient. 95,96 It is recommended that chelation treatment be initiated at hepatic iron concentrations of higher than 4 mg iron/g liver, dry weight. 95 Unnecessary blood transfusions should be avoided, if possible. 1 Splenectomy of patients suffering from the intermedia phenotype who are free from cardiac disease should receive a life-long antiplatelet therapy, because they may exhibit a higher thromboembolic risk than other β-thalassemia intermedia patients. In addition, anticoagulation, vasodilators, and probably also initiation of blood transfusions will be required in patients with pulmonary hypertension. 97

Future perspective

Oral chelators such as deferiprone (“L1”) will improve adherence to chelation therapy and probably also prognosis in thalassemia. In nonrandomized trials, deferiprone alone or in combination with desferrioxamine seems to be at least as effective as desferrioxamine in reducing the incidence of cardiac disease and removing myocardial iron. 95,98,99

Hemoglobinopathies are desirable targets for genetic therapies. Successful allogeneic bone marrow transplantation reverses the β-thalassemia phenotype through stem cell replacement but is associated with toxicity and problems with donor availability. It is expected that both the discovery of the β-globin locus control region and progress in vector construction, as well as efficiency of gene transfer will result in the long-awaited eradication of β-thalassemia. 100

References


