Heart failure in haemoglobinopathies: pathophysiology, clinical phenotypes, and management

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Hereditary haemoglobinopathies, mainly beta-thalassaemia and sickle cell disease, constitute the most common monogenic disorders in humans, and although once geographically confined, they are currently globally distributed. They are demanding clinical entities that require multidisciplinary medical management. Despite their genotypic and phenotypic heterogeneity, the haemoglobinopathies share several similarities in pathophysiology, clinical manifestations, therapeutic requirements, and complications, among which heart failure (HF) represents a leading cause of mortality and morbidity. However, haemoglobinopathies have generally been addressed in a rather fragmentary manner. A unifying approach focusing on the underlying similarities of HF attributes in the two main entities might contribute to their better understanding, characterization, and management. In the present review, we attempt such an approach to the pathophysiology, clinical phenotypes, and management of HF in haemoglobinopathies.

Keywords
- Thalassaemia
- Sickle cell disease
- Heart failure
- Cardiomyopathy
- Pulmonary hypertension
- Iron overload

Introduction

Hereditary haemoglobin disorders, also termed haemoglobinopathies, include mainly beta (β)-thalassaemia (BThal) and sickle cell disease (SCD), and represent the most common monogenic disorders in humans. These entities were once confined to specific geographical regions, including the Mediterranean basin, the Middle East, North India, South-east Asia, and the Indochina Peninsula in the case of BThal and the sub-Saharan Africa in the case of SCD. However, the widespread immigration of the affected populations rendered these conditions globally distributed.¹,²

Heart disease represents a leading cause of mortality in BThal patients,²—⁵ as well as a significant cause of morbidity and a main determinant of prognosis in SCD.⁶,⁷ At the same time, the haemoglobinopathies are clinically demanding conditions with multisystem complications and need for life-long therapy and follow-up, ideally in dedicated centres. Moreover, by virtue of modern therapy, the survival of patients currently tends to reach that of the normal population, and thus both the clinical spectrum of these entities and the need for long-term management are increasing.⁵,⁸ Despite the associated medical and socio-economic burden and the resulting clinical challenges, cardiovascular involvement in haemoglobinopathies had generally been overlooked. As heart disease in haemoglobinopathies has been increasingly recognized over the past years,¹,²,⁷,⁹ it is becoming clear that, despite the diversities, the two main determinants of the cardiovascular phenotype in these patients, namely the molecular defect and its consequences on one hand and the disease-specific therapeutic requirements on the other, are largely common. Thus, a unifying approach focusing on the underlying similarities of heart failure (HF) attributes in the two main entities might contribute to their better understanding, characterization, and management. In the present review, we attempt such an approach to the pathophysiology, clinical phenotypes, and management of HF in haemoglobinopathies.

Pathophysiology

The basic molecular defect in both BThal and SCD is related to the β-globin chain of haemoglobin A. In BThal, the defect is quantitative, characterized by a reduction or total depletion...
of β chain synthesis, and the severity of β chain deficiency determines the clinical phenotype, which extends from the severe and transfusion-dependent thalassaemia major (TM) to the milder and often transfusion-independent thalassaemia intermedia (TI). In SCD, in contrast, the defect is qualitative, as a substitution at the sixth amino acid residue in the β chain results in synthesis of an abnormal haemoglobin, termed haemoglobin S, instead of the normal haemoglobin A. Both in BThal and in SCD, the molecular defects lead to the development of chronic haemolysis resulting in anaemia and eventually cardiovascular dysfunction, including LV dysfunction, pulmonary hypertension (PH), and right ventricular (RV) dysfunction (Figures 1 and 2).

**Chronic haemolysis**

This is the end result of the molecular defects in both disease entities. Chronic haemolysis causes anaemia, which, when significant and untreated, is associated with a high cardiac output state. On the other hand, anaemia correction with repetitive blood transfusions, unless properly coupled with iron chelation, leads to myocardial iron deposition and thus iron overload cardiomyopathy. Chronic haemolysis is furthermore related to a complex vasculopathy, as described in detail later.

**Left ventricular dysfunction**

The main pathogenetic mechanisms resulting in LV dysfunction include high output state, iron overload, vascular disease, myocardial ischaemia, myocarditis, and valvular disease.

**High output state**

This results from a combination of factors including (i) chronic anaemia and the resulting compensatory bone marrow expansion; (ii) the increased percentage of haemoglobin F, which has a high oxygen affinity and thus a reduced tissue oxygen delivery; (iii) the frequently co-existent liver disease, caused by blood-borne viral infections, iron overload, and extramedullary haematopoiesis; and (iv) potentially a particular elastic tissue disorder, discussed in detail below, which may render the vessels more susceptible to dilatation by volume overload. The high output state leads to LV dilatation and eccentric hypertrophy, and may ultimately result in high output HF. Anaemia and its compensatory reactions are effectively attenuated by regular blood transfusions, and therefore a high output state is a crucial mechanism in patients who are not regularly or properly transfused, namely many of those with TI and SCD as well as poorly treated TM patients.

**Iron overload**

Iron overload results primarily from repetitive blood transfusions and secondarily from ineffective erythropoiesis, increased peripheral haemolysis, and increased intestinal iron absorption. In the presence of iron overload, the excess iron, after the saturation of the reticulocyte system, deposits in hepatocytes and then in cardiomyocytes through L-type calcium channels. The accumulated iron overcomes the cellular antioxidative mechanisms and causes peroxidative injury to cellular structures. As a result, iron overload has been associated with the development of LV cardiomyopathy, which is characterized by early LV...
diastolic dysfunction with restrictive filling that usually progresses to LV dilatation with systolic dysfunction, although this may not be the case in all patients. Studies with cardiovascular magnetic resonance (CMR) imaging have shown a strong and graded relationship between myocardial iron load, as evaluated by the T2 relaxation time, and LVEF in the presence of myocardial iron overload, defined as a T2 < 20 ms. As iron overload results mainly from multiple transfusions, it has a far more important impact in transfusion-dependent patients, namely those with TM or other patients who are selectively treated with regular blood transfusions. Transfusion therapy is currently coupled with iron chelation therapy that prevents and/or attenuates the deleterious effects of iron overload. Thus, besides repetitive transfusions, the lack of a proper iron chelation regimen is also required for the development of iron-induced cardiac damage. Iron overload confers some additional consequences that may indirectly contribute to heart disease. Thus, besides cardiomyopathy, excess iron also causes hepatic dysfunction and endocrine disorders, such as hypothyroidism, hypoparathyroidism, and diabetes mellitus, that may further affect cardiac function. In this context, the role of non-cardiovascular co-morbidities in the pathogenesis, progression, and outcome of HF has been stressed lately. In addition, the immune system may also be impaired in the presence of iron overload, hence leading to increased susceptibility to infections and high occurrence of peri-myocarditis.

**Vascular disease**

A complex macro- and microvasculopathy has lately emerged as a third component in the pathogenesis of LV dysfunction in haemoglobinopathies, in addition to a high output state and iron overload. Endothelial dysfunction and increased arterial stiffness have been described in both BThal and SCD. One implicated mechanism is the haemolysis-induced nitric oxide (NO) deficiency, a well-described phenomenon in chronic haemolytic anaemias. However, a critical evaluation of the available evidence indicates that haemolysis-induced NO deficiency is only one of the pathogenetic factors involved. Additional mechanisms include a hypercoagulable state associated with the pre-coagulant surface of defective erythrocytes and the sickling process in patients with SCD, which results in repetitive episodes of microvascular occlusion and reperfusion in the post-capillary venules. Moreover, an acquired elastic tissue defect that resembles hereditary pseudoxanthoma elasticum has been described, with an impressively high frequency in patients with haemoglobinopathies. The defect has also been related to haemolysis and leads mainly to skin, ocular, and vascular manifestations, the latter including arterial calcifications and increased susceptibility to rupture. The detrimental effects of endothelial dysfunction on the cardiovascular system are well described. Increased arterial stiffness, on the other hand, uncouples LV systolic and diastolic function from arterial function, and thus increases the pressure that is presenting to the left ventricle during systole and affects the perfusion of coronary vessels during diastole.

**Myocardial ischaemia**

Myocardial ischaemia is a particular mechanism of LV dysfunction in patients with SCD. Ischaemia is not associated with the presence of typical CAD, as significant coronary artery lesions are not generally seen in those patients. It seems to result mainly from small-vessel disease, in which the sickling process plays the key role. This process may be triggered by an inflammatory response during exercise, and it may further be aggravated by the aforementioned vascular disorders seen in haemoglobinopathies and the increased oxygen demand in the presence of a high output state.

Myocardial fibrosis, mainly in the form of small patchy scars, has been detected in TM patients by late gadolinium enhancement
In brief, several mechanisms related to the disease Lung disease, in LV diastolic abnormalities ≥ The frequency, extent, aetiology, and patho-genetic importance of the finding, which were later questioned by another study, are yet to be determined.

**Myocarditis**
Myocarditis has been identified as a cause of HF in patients with BThal, as described later in detail.

**Valvular disease**
Valvular disorders, potentially associated with the aforementioned high output state and elastic tissue defects, have been described with increased prevalence in patients with haemoglobinopathies, and may also contribute to the pathophysiology of LV dysfunction by causing either pressure or volume overload. Each of the above mechanisms affects one or more of the three main determinants of LV function, namely preload, afterload, and myocardial contractility, and their dynamic combination in each particular patient determines the final phenotype. In addition, it has been shown that the clinical expression of LV dysfunction may be influenced by the interference of other genetic and immuno-inflammatory factors, such as the human leucocyte antigen (HLA) genotype, the occurrence of myocarditis, or the intrinsic antioxidant properties determined by the apolipoprotein E allele.

**Pulmonary hypertension**
The complex and multifactorial pathophysiology of PH in the haemoglobinopathies has recently been described in detail elsewhere. In brief, several mechanisms related to the disease itself, including chronic haemolysis, anaemia, NO deficiency, elastic tissue defects, macro- and microvascular disorders, and hypercoagulability, in association with potentially co-existent LV dysfunction and lung disorders lead to high cardiac output and increased pulmonary vascular resistance, the product of which determines the pulmonary artery pressure. Lung disease, in particular, may result from repetitive respiratory tract infections, vascular disorders with in situ thrombosis, elastic tissue defects, iron overload and, in the case of SCD, the sickling process with the resulting ischaemia/reperfusion injury on the one hand and acute chest syndrome on the other.

**Right ventricular dysfunction**
Systolic and diastolic LV dysfunction and PH are significant secondary causes of RV dysfunction. Furthermore, all the aforementioned mechanisms involved in the pathogenesis of LV dysfunction may also affect primarily RV function, and reports have stressed the presence of primary or iron-induced RV dysfunction in TM patients.

**Common pathogenetic pathways in β-thalassaemia and sickle cell disease**
Cardiovascular disease in BThal and SCD shares common basic pathogenetic pathways derived by the similarities in the molecular basis and the applied therapy. The relative impact and contribution of each one of those mechanisms determines the final phenotype. In the most prevalent and severe form of BThal, TM, regular blood transfusions, which are necessary for survival, counteract the consequences of haemolysis, but the resulting iron overload leads to LV dysfunction if not properly treated with chelating agents. In the less severe form of BThal, TI, patients generally survive without transfusions and therefore their anaemia remains untreated and leads ultimately to high cardiac output, vascular disorders, and PH. On the other hand, SCD patients, with the additional microvascular obstruction caused by haemoglobin S, suffer from a combination of chronic anaemia and vascular disorders with a lesser contribution of iron overload.

**Clinical phenotypes**

**Left ventricular cardiomyopathy**
The two main forms are iron overload cardiomyopathy and high output cardiomyopathy.

**Iron overload cardiomyopathy**
In regularly transfused TM patients with iron overload, LV dysfunction is the main cardiac manifestation. LV diastolic abnormalities are seen with an increasing frequency, even in the early stages and in young individuals. In the advanced stages, two distinct phenotypes are distinguished, the most frequent dilated cardiomyopathy phenotype, characterized by LV dilatation and reduced contractility, and the less frequent restrictive cardiomyopathy phenotype with LV restrictive filling, preserved systolic function, and subsequent PH and RV dysfunction. The physical history of LV dysfunction is largely attenuated by proper iron chelation therapy that prevents LV functional impairment and may also reverse LV systolic dysfunction and HF.

In the presence of cardiac siderosis (T2* < 20 ms), T2* relaxation time is inversely correlated with LVEF. Patients with severe cardiac iron burden (T2* < 10 ms) in particular are at increased risk for development of HF; the annual relative risk for HF in those patients was 160 in a prospective study on 652 TM patients. In contrast, in regularly transfused and properly chelated TM patients without myocardial iron load (T2* ≥ 20 ms), LVEF is generally preserved and it has been proposed that a higher threshold for LVEF such as 60% should be used in those patients, as LV contractility is generally increased due to volume overload resulting from the residual anaemia. However, reduced LVEF is still encountered in properly treated TM populations as well as in patients without cardiac siderosis (T2* ≥ 20 ms). Potential explanations for such findings are the presence of residual myocardial injury from previous severe iron overload that was effectively treated with intensive iron chelation, the interference of immune genetic factors known to affect the susceptibility to iron toxicity (such as the HLA phenotype or the apolipoprotein E allele), the indirect iron toxicity described above, and the fact that T2* reflects mainly the haemosiderin-bound iron and not the most toxic free (labile) iron.
High output cardiomyopathy
In non-transfusion-dependent TI and SCD patients, LV involvement is mainly characterized by dilatation and eccentric hypertrophy, normal or mostly increased contractility, and diastolic filling compatible with volume overload.\textsuperscript{17,18,20,21,50} The same abnormalities may also be seen in poorly transfused TM patients. The severity of the high output state depends on the severity of chronic anaemia. Actually, before the introduction of regular transfusions in the 1970s, TM patients, who suffer from the most severe anaemia compared with the other haemoglobinopathies, died mostly during the second decade of life due to high output HF, and Engle reported a 37% survival at age 16 in 1964.\textsuperscript{51}

Although LVEF is generally preserved in TI patients,\textsuperscript{17,18} it may be affected in a minority of SCD patients. Thus, 16% of patients in a large cohort of 3800 patients with homozygous sickle cell anaemia (SCA) had a reduced LV shortening fraction.\textsuperscript{52} Reduced LVEF was furthermore encountered in 3% of 115 patients with SCD.\textsuperscript{21} Myocardial ischaemia, an additional parameter in SCD, may be related to those findings.

Pulmonary hypertension
Pulmonary hypertension is the main cause of HF in non-regularly transfused TI patients, with a prevalence of nearly 60% in a cohort of 110 patients with a wide age range; PH was associated with HF in 5% of cases due to peripheral congestion resulting from RV failure, while LV contractility was preserved in all patients.\textsuperscript{17}

In SCD, PH occurs in approximately one-third of patients with homozygous SCA and has been related to adverse prognosis. It was encountered in 32% and 40% of patients in two cohorts of 195 and 235 patients, respectively, and in both studies PH was a crucial determinant of patients’ survival.\textsuperscript{6,52} In addition, exercise echocardiography revealed an abnormal response of LV diastolic function followed by an increase in pulmonary artery pressure on exertion in SCA patients with normal resting pulmonary artery pressure.\textsuperscript{53} In the other form of SCD, sickle thalassaemia (SThal), a double heterozygous state for SCD and BThal, PH is generally less prevalent and severe, affecting approximately a quarter of patients, and does not usually lead to congestive HF, but it is still associated with worse prognosis.\textsuperscript{20,21,54} In a cohort of 115 SThal patients, although PH was found in 27% of cases, severe PH was present in <3%.\textsuperscript{21} It should be stressed that the prevalence of PH reported by the different studies is dependent upon the method (echo or catheterization) and the cut-off value used for the diagnosis of PH.\textsuperscript{1}

Right ventricular dysfunction
Right ventricular dysfunction and failure is a heterogeneous and poorly understood condition that has generally been overlooked.\textsuperscript{55} RV dilatation is a common finding accompanying LV dilatation in the context of volume overload, particularly in cohorts of non-transfused TI and SCD patients or poorly treated TM patients.\textsuperscript{17,18,20,21,52} On the other hand, two studies from the same centre have stressed the presence of a particular form of RV cardiomyopathy in regularly transfused TM patients, not associated with LV dysfunction or PH, with systolic and/or diastolic abnormalities and a haemodynamic pattern similar to that observed in patients with RV infarction.\textsuperscript{41,42} Recently, it was shown that there was a close correlation between myocardial iron, as assessed by T2*, and RVEF, quite similar to that observed between T2* and LVEF.\textsuperscript{43}

Pericarditis and myocarditis
Acute pericarditis was quite frequent in poorly treated TM patients. Before the era of regular therapy in the mid 1960s, acute pericarditis occurred in at least half of patients during the first two decades of life; Engle reported a history of acute pericarditis in 19 of 41 patients at ages ranging between 6 and 17 years.\textsuperscript{51} Nowadays, the effective management of anaemia and iron overload, two conditions that render patients more susceptible to infections, as well as the better quality and control of transfused blood have significantly limited the occurrence of pericarditis. A prevalence of 5% at a mean age of 16 years was reported in a cohort of 202 well-treated TM patients.\textsuperscript{37} A higher frequency of 8% was encountered in a group of 110 patients with TI not receiving transfusion therapy at a mean age of 26 years.\textsuperscript{17}

A clinical picture compatible with acute myocarditis was present in 4% of 1048 TM patients during a 10-year period between 1977 and 1986.\textsuperscript{39} The diagnosis was histopathologically confirmed by the Dallas criteria in at least half of those cases. Myocarditis led to LV dysfunction with development of acute and chronic HF in 23% and 28% of those patients, respectively, and was further associated with ventricular tachycardia in 9% of them. As in the case of pericarditis, the better management of anaemia and iron overload and the enhanced quality of the transfused blood have also resulted to the dramatic reduction of acute myocarditis in TM.

Angina
Following an initial observation of myocardial infarction in two SThal patients with patent coronary arteries,\textsuperscript{34} a subsequent study of radionuclide perfusion imaging in 30 SThal patients revealed stress-induced perfusion defects in 27% of them, reversible in all but one case; coronary angiograms did not reveal significant lesions in any of those patients.\textsuperscript{33} A case of unstable angina in a TI patient with severe calcified and yet patent coronary arteries has also been reported.\textsuperscript{57}

Besides myocardial ischaemia, acute chest pain in SCD patients may also result either from acute chest syndrome or from a thoracic painful crisis, and therefore the differential diagnosis among these three conditions is necessary in all SCD patients presenting with chest pain.\textsuperscript{7}

Arrhythmias
Rhythm disorders, including a wide spectrum of supraventricular and ventricular arrhythmias and conduction abnormalities, are usually seen in association with severe cardiac dysfunction.\textsuperscript{51,58} A high risk of arrhythmias, including AF, supraventricular tachycardia, ventricular tachycardia, and a case of ventricular fibrillation was
encountered in TM patients with myocardial iron overload in a prospective study on 652 TM patients. The risk of arrhythmias increased in parallel to the severity of cardiac siderosis, as the annual relative risk for arrhythmias was 4.6 in patients with T2* <20 ms and 8.8 in those with those with T2* <6 ms. Episodes of ventricular tachycardia have further been observed in association with acute myocarditis. Moreover, non-specific repolarization abnormalities have been reported sporadically in TM patients in association with intensive iron chelation therapy. Frequent supraventricular extrasystoles and episodes of AF have also been encountered in TI patients not receiving blood transfusions.

Valvular abnormalities

Valvular abnormalities and mainly calcification, mild to moderate mitral and tricuspid regurgitation, and mitral valve prolapse are not uncommon among patients with haemoglobinopathies, particularly not regularly treated TI and SCD cases. Some sporadic cases of calcific aortic stenosis have also been reported and underwent successful aortic valve replacement.

The main phenotypes of heart disease in haemoglobinopathies are summarized in Table 1.

<table>
<thead>
<tr>
<th>Cardiac phenotype</th>
<th>Haemoglobinopathy</th>
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<tbody>
<tr>
<td>Dilated cardiomyopathy: LV dilatation and reduced LVEF</td>
<td>TM</td>
</tr>
<tr>
<td>Restrictive cardiomyopathy: LV restrictive filling with preserved LVEF</td>
<td>TM</td>
</tr>
<tr>
<td>High output state: LV and RV dilatation, eccentric hypertrophy, and increased LVEF</td>
<td>TI, poorly treated TM, SCA, SThal</td>
</tr>
<tr>
<td>Isolated RV cardiomyopathy</td>
<td>TM</td>
</tr>
<tr>
<td>Pulmonary hypertension with preserved LVEF</td>
<td>TI, SCA, SThal</td>
</tr>
<tr>
<td>Acute myocarditis</td>
<td>TM</td>
</tr>
<tr>
<td>Acute pericarditis</td>
<td>Poorly treated TM, TI</td>
</tr>
<tr>
<td>Chronic constrictive pericarditis</td>
<td>Poorly treated TM, TI</td>
</tr>
<tr>
<td>Myocardial infarction or ischaemia without haemodynamically significant coronary artery lesions</td>
<td>SThal</td>
</tr>
<tr>
<td>Valvular disorders: calcification, mitral valve prolapse, mitral regurgitation, aortic stenosis</td>
<td>TI, poorly treated TM, SCA, SThal</td>
</tr>
</tbody>
</table>

RV, right ventricular; SCA, homozygous sickle cell anaemia; SThal, sickle thalassaemia; TI, thalassaemia intermedia; TM, thalassaemia major.

The introduction of CMR-derived T2* relaxation time for the assessment of iron overload a decade ago has revolutionized the management of haemoglobinopathy patients in terms of iron overload. The T2* technique allowed for the first time the non-invasive, reliable, and clinically robust quantification of myocardial and hepatic iron content and thus enabled the tailoring and monitoring of chelation therapy. Actually, it has been shown that the observed survival improvement in BThal patients in the UK over the last years, conferred by the reduction of iron overload, is partly attributable to the use of CMR imaging. The limited access to CMR examination is, however, an important issue in developing countries. Previous studies that compared echocardiography with CMR in TM patients showed a good overall correlation between echo-LVEF and CMR-LVEF and most, but not all, patients with impaired echo-LVEF also had cardiac siderosis according to CMR T2*. Additional echocardiographic markers were found to predict cardiac iron load with high specificity but low sensitivity. Myocardial deformation imaging by tissue Doppler and speckle tracking echocardiography was able to unmask subtle LV dysfunction in TM and SCA, and correlated with myocardial iron content as estimated by CMR T2* imaging. Furthermore, dobutamine stress echocardiography was able to predict functional class worsening and resting LV systolic dysfunction within 2 years in a small group of TM patients, but was not predictive of 1-year mortality in another small study in TM patients.

Other cardiovascular modalities including ambulatory ECG, stress testing, and cardiac catheterization may be used in the presence of the corresponding indications. As concerns biomarkers, there is conflicting evidence on the value of natriuretic peptides in predicting diastolic dysfunction, as estimated by Doppler echocardiography, or myocardial iron overload as estimated by CMR T2* in patients with BThal. In patients with SCD, elevated NT-proBNP values above 160 ng/L have been associated with the presence of echocardiographic findings indicative of increased pulmonary artery pressure in patients with SCA and SThal, and represented an independent predictor of mortality in these patients. It seems that natriuretic peptides may be used in combination with clinical evaluation, echocardiography, and CMR.

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Heart failure in haemoglobinopathies

**Basic workup**
Clinical examination, electrocardiogram, chest radiogram, echocardiography, biomarkers

**Repeat:**
- annually, if normal
- every 6-12 months in iron overload (T2*<20 ms)
- every ≤6 months in heart disease
- on development or change of symptoms

**Patients on regular transfusions**
Basic workup *plus*
T2* magnetic resonance imaging

**Repeat:**
- every ≥2 years, if normal
- every ≤12 months in iron overload (T2*<20 ms) or heart disease
- on development of symptoms or diagnosis of heart disease

**Figure 3** Basic algorithm for the cardiac evaluation of patients with haemoglobinopathies.

Management

Besides the molecular defect, the applied therapy is the other significant determinant of the cardiovascular phenotype, affecting not only the severity or the prognosis of the disorders but also their form and type. Disease-specific measures include blood transfusions, regular or upon demand, exchange transfusions, iron chelation regimens, and hydroxyurea.

**Disease-specific therapy**

In TM, modern therapy, consisting of regular blood transfusions to maintain a pre-transfusion haemoglobin level of ≥10 g/dL combined with proper iron chelation regimens guided by CMR, has dramatically improved the prognosis and survival of patients, preventing the development of LV dysfunction and HF. Thus, in contrast to the early survival rates of 37% in the second decade of life reported in the mid 1960s or of 25% in the third decade in the early 1980s, prognosis rose to 83% survival beyond age 40 in the mid 2000s and to 89% at age 40–49 in the late 2000s. This dramatic survival improvement was mainly accomplished by the reduction of cardiac mortality. Besides the desirable prevention of iron overload cardiomyopathy, its effective management and even reversal is also possible by virtue of the currently available iron chelators. In particular, regimens combining two different chelators (deferoxamine and deferiprone) have proved quite effective in improving LV systolic function in TM patients with severe myocardial siderosis. A detailed discussion on the prevention and management of myocardial iron overload can be found elsewhere. The understanding of the role of L-type calcium channels in the development of myocardial iron overload has led to clinical trials investigating the effectiveness of calcium channel blockers as an adjunct to iron chelators. In a small trial in 15 TM patients, amlodipine enhanced the effectiveness of standard chelation regimens, while two ongoing phase II or III trials, the Amlodipine in the Prevention and Treatment of Iron Overload in Patients With Thalassemia Major (AmloThal, NCT01395199) and the Amlodipine for Myocardial Iron in Thalassemia (AMIT, NCT02065492), are expected to provide more solid evidence.

The rest of haemoglobinopathy patients with either TI or SCD are mostly not transfusion dependent and therefore remain traditionally without regular transfusion–chelation therapy. According to current practice, the latter is usually started upon the occurrence of disease complications including cardiac disorders. Phlebotomy and hydroxyurea are also used in selected cases. The early application of transfusion–chelation therapy in order to prevent and not to treat the complication resulting from chronic anaemia in those patients has been stressed by some investigators. Actually, in TI patients, in whom PH is the main cardiac abnormality, it has been shown that the early application of regular transfusion–chelation therapy and the use of hydroxyurea have significantly reduced the occurrence of PH.
A basic therapeutic algorithm for patients on regular transfusion therapy is outlined in Figure 4.

**Heart failure therapy**

In addition to disease-specific modalities, HF therapy with neuro-hormonal inhibitors and other medications should also be applied according to the established indications and guidelines. In a cohort of 52 TM patients with HF, the combination of regular transfusion–chelation regimens with proper HF medication resulted in a 5-year survival rate similar to that of the regular HF population. Cardiac transplantation may be a further option for advanced iron overload cardiomyopathy, either alone or in combination with hepatic transplantation, in cases with co-existent end-stage liver disease.

**Pulmonary arterial hypertension therapy**

Regarding pulmonary arterial hypertension-specific therapies, there are few reports with small numbers of patients on phosphodiesterase inhibitors such as sildenafil and endothelin antagonists such as bosentan showing some beneficial effects. However, two attempts at large-scale testing of those agents in SCD were not successful, and the corresponding trials were discontinued due to adverse events or poor recruitment, respectively.

**Conclusions and open issues**

Heart disease, and HF in particular, represents a primary cause of morbidity and mortality in patients with haemoglobinopathies. A universal prevalence or other epidemiological measures on HF or other cardiovascular complications cannot currently be reported in those patients, as published data concern different subpopulations of haemoglobinopathies, distinct aspects of cardiac involvement, and diverse regional groups. A unified consideration of cardiovascular disease in haemoglobinopathies may be the first step to overcome the hitherto fragmented approach. In addition, large-scale comprehensive and representative registries may generate updated evidence and frame the current status and unmet needs regarding cardiovascular involvement in these patients.

Nowadays, HF in inherited haemoglobinopathies is characterized by a striking paradox. Among patients with the different haemoglobin defects, those who currently have the best cardiovascular status and the highest quality of life are those with the most severe defect, the typical transfusion-dependent TM, provided that they are regularly treated in specialized centres and have access to all recommended diagnostic and therapeutic modalities. This observation determines the two main issues that need to be addressed in the near future. The first is the access to regular transfusion–chelation therapy, CMR, and regular follow-up for all TM patients in several developing countries, particularly in North Africa and Asia, in which a high prevalence of the disease is present. The second is the establishment of criteria for the early onset of disease-specific therapy in TI and SCD patients in order to avoid cardiovascular and other complications. These two open issues, a socio-economic and a scientific one, respectively, constitute today’s main challenges in the field of haemoglobinopathies.

**Conflict of interest:** none declared.
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References


