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The role of cardiac magnetic resonance in the assessment of Thalassaemia Intermedia patients.

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Content

Abbreviations

CHF: Cardiac heart failure

CMR: Cardiac Magnetic Resonance

CO: Cardiac output

CMR-PC: Cardiac magnetic resonance with phase contrast

CT: Computed tomography

ESC: European Society of Cardiology

Hb: Haemoglobin

HCOS: High cardiac output state

LGE: Late gadolinium enhancement

LV: Left ventricular/ventricle

LIC: Liver iron concentration

mPAP: Mean pulmonary arterial pressure

MRI: Magnetic resonance

MIO: Myocardial Iron Overload

NO: Nitric Oxide

NTBI: Non-transferrin-bound iron

NTDT: Non-transfusion-dependent Thalassaemia

PC: Phase contrast

PCWP: Pulmonary capillary wedge pressure

PHT: Pulmonary Hypertension

PVR: Pulmonary vascular resistance

TD: Transfusion-dependent

TI: Thalassaemia Intermedia

TM: Thalassaemia Major

VHD: Valvular Heart Disease

RBC: Red blood cell

RT-TI: Regularly transfused Thalassaemia Intermedia

RCHF: Right Cardiac Heart Failure

RHC: Right heart catheterization

RV: Right ventricle

SCMR: Society for Cardiovascular Magnetic Resonance

SV: Stroke volume

Abstract

Beta-Thalassaemia is a hereditary haemoglobin disease caused by synthesis reduction of beta-globin chains that leads to three distinct phenotypes of the disease (1). Thalassaemia minor (carrier state) is the less severe form, characterized by a mostly asymptomatic hypochromic microcytic anaemia (2). The two other phenotypes correspond to haemolytic anaemia and include Thalassaemia Major (TM) and Thalassaemia Intermedia (TI), that are distinguished by severity and transfusion dependency (21). TM is transfusion dependent since birth, while TI only requires transfusion at more advanced ages and during haemolytic crisis with known triggers (13,21). This is why TI belongs to the non-transfusion dependent thalassaemia (NTDT) group (6).

Several complications can be found in TI patients, mainly related to ineffective erythropoiesis that leads to a state of primary iron overload in the absence of transfusion therapy (8). Cardiac complications are the main cause of mortality in patients with both TI and TM (12). In TI cardiac involvement is related to the long-term exposure to chronic anaemia and tissue hypoxia determining a high cardiac output state (HCOS) cardiomyopathy (12).

Cardiac magnetic resonance (CMR) is considered the non-invasive gold standard method to evaluate cardiac function (15). Several techniques such as CMR with phase contrast (CMR-PC), fluoroscopy, late gadolinium enhancement (LGE), and T2* relaxation times can be used for the evaluation and monitorization of several cardiac complications founded in TI, such as the high cardiac output state (HCOS), Pulmonary Hypertension (PHT), Right Cardiac Heart Failure (RCHF), Iron Overload Cardiomyopathy and Valvular Heart Disease (VHD).

The role of CMR is well established in the early diagnosis and follow-up of cardiac dysfunction of TM, but is not clearly defined in TI, once it presents with a wide spectrum of cardiac manifestations. The goal of this review article is to better understand the different cardiac complications we can find in TI patients and how CMR can be helpful to clinicians in their approach. We also want to clarify how iron deposition can occur in TI patients, the importance of iron cardiomyopathy and how CMR T2* can play a role in its evaluation.

The articles gathered for this review, were searched between January 2021 and January 2023 in *PubMed's* database. We selected review, meta-analysis and investigation articles with relevance to the subject written in English with free access and published between 2001 and 2022. Additionally, we gathered articles suggested by the database search engine and from bibliographic references that were also relevant.

Key words: *Thalassaemia Intermedia, Cardiac Magnetic Resonance, Iron Overload, High Cardiac Output, Pulmonary Hypertension, Right Heart Cardiac Failure, Valvular Heart Disease.*

Introduction

Beta Thalassaemia is an inherited haemoglobin (Hb) disorder caused by a quantitative defect in beta-globin chains, leading to alpha/beta chains imbalance, ineffective erythropoiesis, chronic haemolytic anaemia and, in the most severe cases, transfusion dependency (1,2). Historically, β-Thalassaemia is highly prevalent in the Mediterranean, Middle East and Southeast Asia, and migration patterns have increased the prevalence of this haemoglobinopathy in North America and Northern European countries, increasing its burden on healthcare systems (3). Even in Portugal we have been observing an increasing prevalence of haemoglobinopathies carriers due to migration of populations (*personal data*).

Beta-Thalassaemia encompasses a heterogeneous spectrum of phenotypic manifestations, dividing patients into three phenotypic subgroups. Thalassaemia Minor is the less severe form of disease and corresponds to carrier patients who have mild microcytic hypochromic anaemia with no obvious clinical manifestations (2). The most severe phenotype is Thalassaemia Major (TM), that consists in patients that have severe haemolytic anaemia and need to be regularly transfused since shortly after birth (2). In between these two phenotypic ends we can find Thalassaemia Intermedia (TI) patients, who have a moderate to severe haemolytic anaemia (Hb 7 to 10 g/dL) and require occasional transfusions in specific circumstances such as pregnancy, surgery, or acute infection (4).

More recently, patients with haemolytic anaemia started being divided accordingly to their transfusion requirements, and the terms transfusion-dependent (TD) and non-transfusion-dependent thalassaemia (NTDT) became more widely used (5). TI belongs to the group of NTDT (6). However, patients with NTDT can be transformed in TD later in life due to chronic complications. Therefore, beta-thalassaemia should always be considered a continuous spectrum of patients able to move from one phenotype to another as with management or natural progression of disease (7,8).

The best initial diagnostic approach in TI is to combine analysis of red blood cells (RBC), including a peripheral blood smear, together with measurement of the different haemoglobins by electrophoresis or high-performance liquid chromatography (9). RBC indexes show microcytic anaemia, and the peripheral red blood smear (fig. 1) demonstrates morphologic changes in the erythrocytes, such as microcytosis, hypochromia, anisocytosis, poikilocytosis, target cells and, eventually, nucleated RBCs (10). Electrophoresis shows a decrease in HbA relative quantity, HbA2 > 3.5 % and HbF> 5% and diagnosis is confirmed by Beta globin genotyping (11).

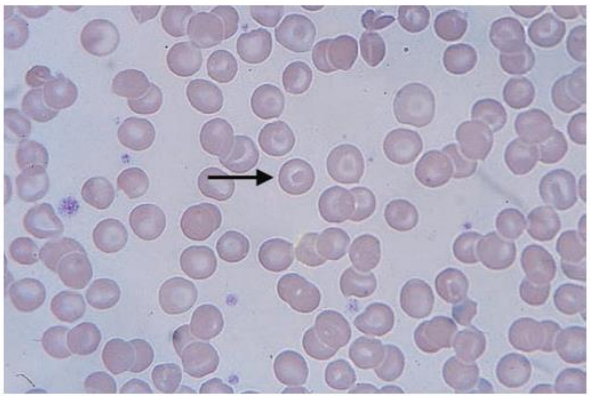

***Figure 1**- Peripheral smear in a case of thalassaemia (target cell is indicated by an arrow);*

Image obtained from: Banerjee T, Aniyery RB. Thalassemia and its Management during Pregnancy.

TI is associated with great morbidity and without an appropriate intervention several complications (fig. 2) develop with age, with a notable incidence beyond the age of 35 years (8). The ineffective erythropoiesis seen in NTDT leads to a state of primary iron overload in the absence of transfusion therapy, which is associated with hepatic fibrosis, thrombosis, pulmonary hypertension (PHT), endocrinopathies, cerebrovascular disease, leg ulcers, osteoporosis, and progressive bone marrow expansion and bone changes (8).

Cardiac complications are the main cause of mortality in patients with both TI and TM (12). The prominent finding in TM is a left ventricular dysfunction due to the toxic iron accumulation in the heart caused by transfusion therapy (1). Cardiac magnetic resonance (CMR) with T2* time acquisition can be used to measure iron concentration in the heart before the detection of clinical signs and symptoms of iron overload cardiomyopathy (13,14). However, in NTDT cardiac iron overload is not typically seen and cardiac involvement is mainly related to the long-term exposure to chronic anaemia and tissue hypoxia determining a high cardiac output state (HCOS) cardiomyopathy (12). It is also possible to find other cardiovascular abnormalities in NTDT patients, such as PHT, arrhythmias, valvular heart disease (VHD), cardiomegaly and pericardial disorders (1).

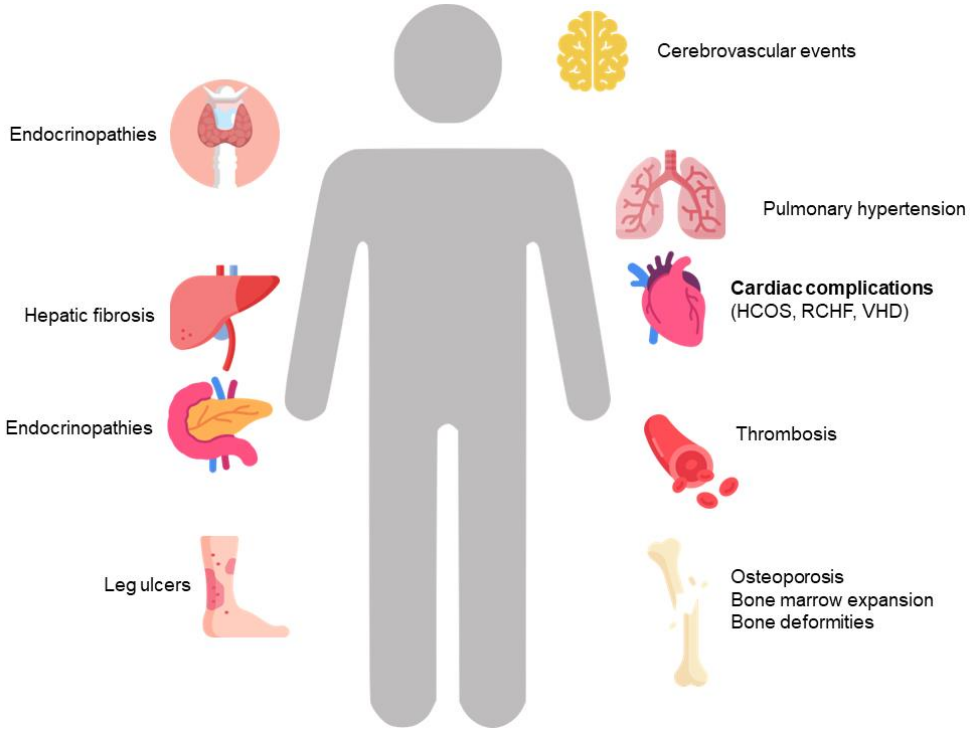

***Figure 2**- Complications in TI patients.*

HCOS: High cardiac output state, RCHF: Right cardiac heart failure, VHD: Valvular heart disease

Nowadays, CMR is considered the non-invasive gold standard method to evaluate cardiac function (15). CMR using phase contrast (CMR-PC) can provide both non-invasive assessment of heart function and right ventricular morphologic changes, being a great asset for patients who need regular assessment of cardiac output (CO), for example in the monitorization of patients with PHT (16). It can also be used to guide catheter navigation in right heart catheterization (RHC) using fluoroscopy for direct invasive measurements of CO, pulmonary vascular resistance (PVR), mean

pulmonary arterial pressure (mPAP), and pulmonary capillary wedge pressure (PCWP), which are important for diagnosis, risk stratification and follow-up in PHT patients (17, 18). CMR seems to also play an important role in RV assessment because it is harder to characterize its function by 2-dimensional echocardiography (19).

The great ambiguity of CMR techniques and it's high spatial and temporal resolution make it useful in almost every cardiac complication observed in TI patients, even though it has some limitations that might compromise its use. The role of CMR T2* in the evaluation of cardiac iron deposition in TM patients is well established, but in TI, the iron overload in the heart is difficult to predict and the role of CMR T2* is not well established. In this review article we combine the evidence that exists about cardiac complications in TI and how CMR can be helpful to clinicians in their approach. We also want to clarify how iron deposition can occur in TI patients, the importance of iron cardiomyopathy and how CMR T2* can play a role in its evaluation.

Methods

The articles gathered for this review, were searched between January 2021 and January 2023 in *PubMed's* database. Key words mainly utilised were Thalassaemia Intermedia, Cardiac Magnetic Resonance, Iron Overload, High Cardiac Output, Pulmonary Hypertension, Right Heart Cardiac Failure and Valvular Heart Disease. We selected review, meta-analysis and investigation articles with relevance to the subject written in English with free access and published between 2001 and 2022. Additionally, we gathered articles suggested by the database search engine and from bibliographic references that were also relevant. The flow chart bellow (fig.3) summarizes the selection of articles conducted by our study group.

The discussion was structured to approach each cardiac complication encountered in TI patients individually. Each subchapter corresponds to a different cardiac complication and the role of CMR in their diagnosis, prognosis, and follow-up. We have also highlighted the basic approach to these complications and their physiopathology.

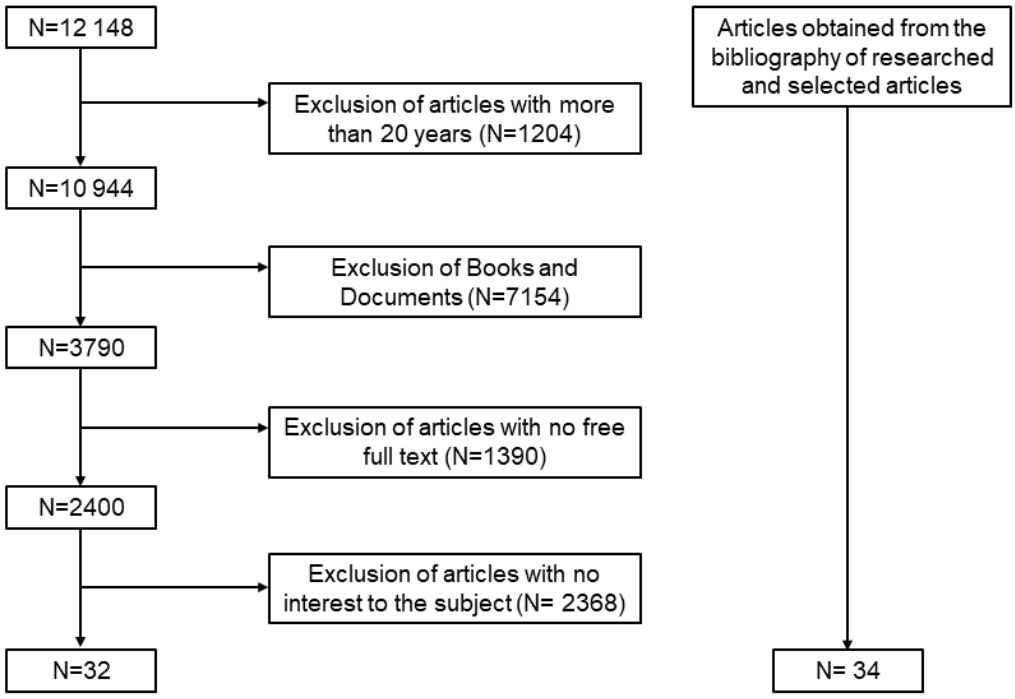

Figure 3 *– Flow chart summarizing the methods for article selection in this study. N: number of articles.*

Results/Discussion

TI belongs to NTDT and usually has a later clinical onset with blood transfusions not being needed in the first years of life, in disagreement with TM where transfusions are required almost since birth (12). If NTDT patients remain untreated, complications from the chronic haemolytic anaemia and tissue hypoxia, such as increased erythropoiesis with bone marrow expansion and increased intestinal iron absorption can occur (1). In TM these complications are partially avoided by the transfusion-chelation therapy (12).

In TI patients, clinical practice recommends transfusion therapy in children with growth and development failure, and in adults to prevent or manage declines in the Hb levels and the complications that might appear, such as extramedullary erythropoiesis, PHT, thrombotic events, cardiomyopathy, and fatigue (6,20). In consequence of late onset and irregularity of transfusion therapy in TI patients, they are more prone to develop the complications related to the physiopathology and natural course of the disease, listed before.

Cardiac complications are one of the complications and the main cause of mortality in both TM and TI patients (12). While in TM, iron deposition in the heart is related to an iron overload cardiomyopathy with left ventricular dysfunction and heart failure, in TI patients heart disease occurs mainly due to chronic anaemia determining a high cardiac output state (1,21). In the last group, cardiomyopathy due to myocardial iron overload (MIO) seems to be infrequent and is related to iron absorption in bowel rather than to regular blood transfusions (21).

Several studies have shown that other cardiac complications can occur in TI, such as rhythm disorders, pericardial and valvular abnormalities, cardiomegaly, ventricular trabeculations, being the most prominent findings PHT and HCOS (1,4,20,21). On the development of this study, we realized that most of these complications are associated with each other, and that part of the physiopathology is shared between them (fig.4). In the further chapters of this discussion, we assess the different cardiac complications we encountered throughout the studies and analyse the role that CMR displays in each of them, for a better understanding of its role beyond the assessment of iron overload.

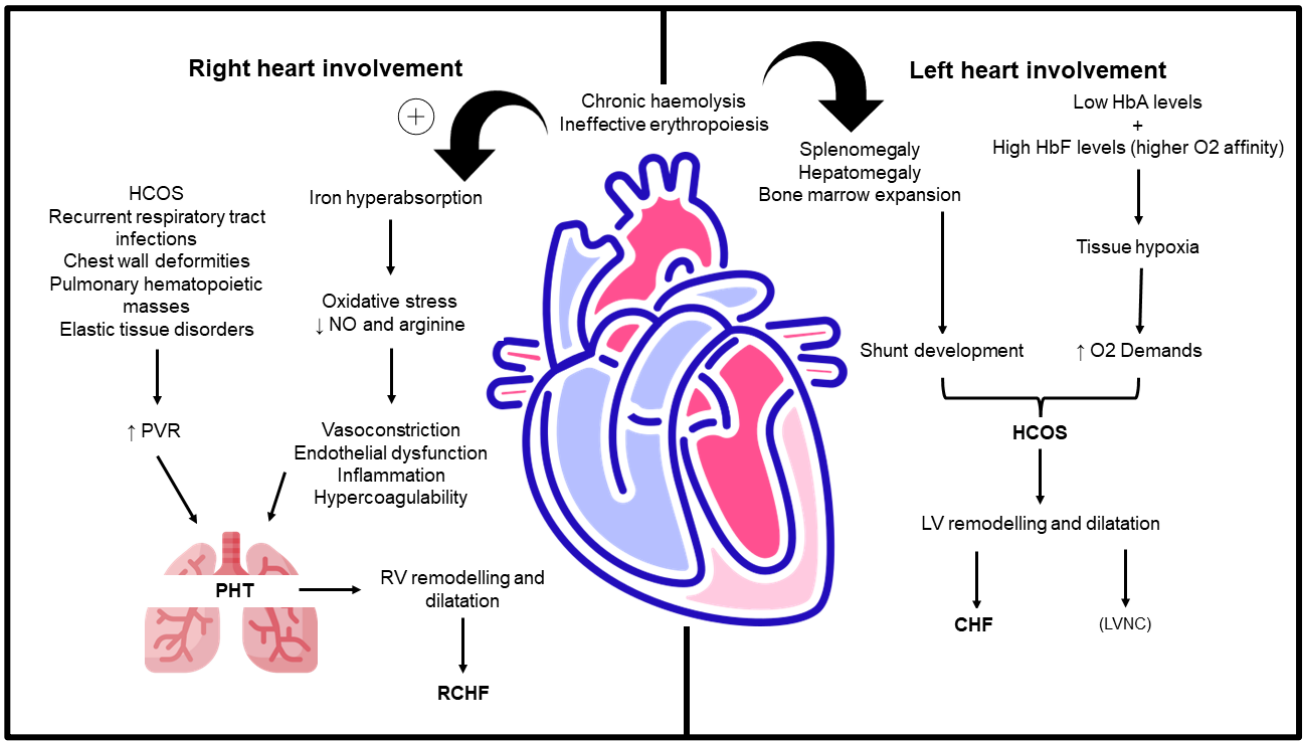

Figure 4 *– Flow chart summarizing the physiopathology of the main cardiac complications in TI patients. Hb: haemoglobin; HCOS: High Cardiac Output State; CHF: Cardiac Heart Failure; LVNC: Left ventricular non-compaction; NO: nitric oxide; PVR: pulmonary vascular resistance; PHT: Pulmonary Hypertension; RCHF: Right Cardiac Heart Failure*

High cardiac output state

In High Cardiac Output State (HCOS), cardiac function is normal, and the vascular resistance is low, either by vasodilatation or bypass between arterioles and capillary beds that activate neurohormones (22,23). Over time, chronic activation of the compensatory mechanisms to maintain a good perfusion of tissues, causes the heart to undergo hypertrophy with remodelling and dilation, leading to heart failure when the HCOS becomes insufficient to suppress the body needs (24).

In TI it is very common to find a HCOS. Echocardiographic measures showed a two-fold increase in cardiac output levels compared to normal subjects, and data using CMR also confirmed an HCOS in TI patients (1,25). Several factors contribute to its pathogenesis: the low levels of HbA and higher fetal Hb percentage which has a higher oxygen affinity, both synergistically contribute to tissue hypoxia that augments cardiac demands (12); Tissue hypoxia leads to bone marrow expansion and extramedullary haematopoiesis with splenomegaly and hepatomegaly, that contribute to the HCOS by causing vasodilatation and shunt development (12).

The most reliable method to measure cardiac output (CO) is by pulmonary artery catheterization with thermodilution and Fick method (16). However, it is an invasive method with several complications associated, and it is not very practical to measure oxygen consumption (16,26).

It is possible to calculate CO by assessing stroke volume and by CMR-PC (17, 27). Several studies have shown that CMR-PC correlates well with invasive measuring and has a high accuracy when compared to Fick's method [16, 28, 29]. It can provide both non-invasive assessment of the heart function and right ventricular morphologic changes, being a great asset for patients who need regular assessment of CO, for example in the monitorization of patients with PHT (16). Several factors can cause variations in measurements, like turbulent flow, accelerated jet flow, and convergent flow, seen in patients with moderate to severe valvular disease (16,26).

CMR can also be used to guide catheter navigation in RHC using fluoroscopy (also known as real-time CMR), avoiding ionizing radiation, and evaluating both anatomy and function with CMR and invasive haemodynamic measurements (17, 30). It has been shown that real-time CMR flow measurements are superior to Fick's method for calculation of CO and pulmonary vascular resistance (PVR), that are used for diagnosis, guide treatment and inform prognosis (31). We would like to highlight that both CMR and RHC can be performed during a single general anaesthesia (17). This is very useful in the Paediatric population, sparing the child the need for a second sedation.

Pulmonary hypertension

Pulmonary hypertension (PHT) is divided into 5 clinical subgroups. In TI, PHT is characterized by pre-capillary hypertension, and it is included in group 5 of PHT, associated with chronic haemolytic anaemia and unclear/multifactorial mechanisms (8). PHT represents a prominent finding in TI patients (12). In a cohort study with 110 TI patients, almost 60% had PHT with a mean age of 32.5 years (1). It is five times more frequent in TI than in TM, as revealed by RHC, and develops as patients grow older leading to right ventricular deterioration, being the main cause of cardiac heart failure (CHF) in this group of patients (1,32).

The physiopathology of PHT in NTDT is unclear, but several factors of the underlying disease have been indicated as potential contributors (1). In chronic haemolysis, iron overload plays a key role, causing strong oxidative stress, negative effects on nitric oxide and arginine availability, which promotes vasoconstriction, endothelial dysfunction, inflammation, and hypercoagulability (2,12). PVR is increased in these patients due to high CO, lung injury caused by recurrent respiratory tract infections, chest wall deformities, extramedullary pulmonary hematopoietic masses, and age-related diffuse elastic tissue disorders found in TI (1).

The hypercoagulability state seen in TI populations seems to also play a role in the pathogenesis of PHT. The incidence of clinical thrombosis is fourfold higher in NTDT compared to TDT, its mostly venous, and the incidence becomes even higher in patients older than 35 years old (8). The free α-globin that result from decrease β-chains synthesis, and the free iron, damage the red cell membrane. This leads to the exposure of negatively charged phospholipids that create a pro-coagulant surface, causing *in situ* thrombus formation within the pulmonary vascular bed (12). This combined with oxidative stress, endothelial dysfunction, expression of endothelial adhesion molecules, increased platelet aggregation and presence of platelet morphologic abnormalities, all lead to this hypercoagulability state (6).

Risk factors for PHT in NTDT patients include splenectomy, history of thrombosis, platelet counts ≥ 500 x 10^9/L, nucleated red blood cells ≥ 300 x 10^9/L and iron overload (8). The incidence of PHT and thromboembolic events in TI is higher if patients are splenectomised, probably due to the higher incidence of some factors that contribute to the hypercoagulability state encountered in patients that had splenectomy, such as procoagulant activity of microparticles, higher platelet and nucleated red blood cell counts, increased platelet activation, coagulation factors defects, depletion of antithrombotic factors, and endothelial inflammation, among others (2). Blood transfusions may control the hypercoagulability state and have been shown to significantly reduce PHT in patients with thalassaemia by improving ineffective erythropoiesis and decreasing the levels of pathological red blood cells with thrombogenic potential (2,8).

Routine testing in patients with clinical manifestations suggestive of PHT include electrocardiography, echocardiography, chest radiography and pulmonary function tests (33). Guidelines from the Thalassemia International Federation recommend TI patients to undergo annual

echocardiographic assessment of tricuspid-valve regurgitant jet velocity (34). As mentioned before, RHC is essential for diagnosis and classification. It allows direct measurement of mPAP, CO, pulmonary capillary wedge pressure (PCWP) and PVR, which are important for diagnosis, risk stratification and follow-up (18).

CMR plays a key role in the assessment of PHT, and it has many utilities. Real-time CMR uses fluoroscopy to guide RHC, allowing both high quality invasive hemodynamic evaluation and cardiac morphological and functional assessment, used as standard clinical procedure at National Institutes of Health in patients with PHT (17).

For some cardiovascular abnormalities, such as PHT, a very common cardiovascular disease seen in TI population, there is a need for frequent haemodynamic assessment, and using an invasive method like pulmonary artery catheterization becomes a problem (16). Several non-invasive methods have been developed in the last years, and CMR has been gaining importance. It provides information about heart function and right heart morphologic changes, without the need for invasive RHC or the need to assume oxygen consumption (Fick's method) (16).

PVR and its response to nitric oxide (NO) and oxygen is also essential to assess the need for vasodilator therapy in patients with PHT (31). Studies have shown that RHC with CMR flow fluoroscopy is more accurate than RHC with Fick's method to measure pulmonary blood flow, and that Fick's method is inferior to assess the physiological response to vasodilators (16, 17, 31).

Despite its accuracy in CO measurements, the role of non-invasive CMR-PC alone for estimation of mPAP, PCWP and PVR remains uncertain (18). This is why RHC is still the test of choice to confirm the diagnosis in an initial evaluation (8,16, 33). We also need to consider the logistical and financial limitations of regular CMR assessment of PHT patients, like costs, availability and expertise (18).

PHT is associated with great mortality and some parameters can be used for prognostic value, such as exercise capacity (33). Macdonald *et al* (2018), investigated the impact of pulmonary arterial hypertension on aortic flow using CMR-PC with exercise equipment that permitted exercise in a supine position. This study concluded that patients with PHT have reduced left ventricular stroke volume, reduced cardiac efficiency and rely on higher heart rates to increase CO when performing moderate exercise, compared to healthy individuals. However, this study only concerned patients with Pulmonary Arterial Hypertension, and no other class of PHT, like PHT in TI patients is covered, so further studies are needed to understand the role of CMR-PC in the evaluation of exercise capacity in this specific subgroup of patients.

Even though CMR displays all these advantages in the monitorization of PHT patients, Thalassemia International Federation guidelines do not even recommend CMR for the assessment of PHT in TI (35). We believe CMR should be considered as the test of choice for these patients follow-up as it is non-invasive and has high accuracy when compared to RHC. We also believe it would be beneficial to use CMR as a screening tool in TI patients with the risk factors mentioned

before, because it would allow for an early diagnosis, early therapy onset, and a delay of the progression of the disease. Further studies in TI patients are needed to validate these hypotheses.

Right heart involvement

PHT is the leading cause of heart failure in TI patients due to right heart insufficiency (12). In two major cardiological studies in TI patients, all of those with congestive heart failure had severe PHT and normal systolic left ventricular function (1,36).

In patients with PHT, there is a slow increase in right ventricular (RV) afterload, which causes wall stress and the development of compensatory mechanisms such as wall hypertrophy and increased contractility (19,33). The persistent high PVR leads to RV dilatation to maintain an efficient stroke volume (28). With time, RV systolic dysfunction develops, and CO decreases, leading to signs and symptoms of Right Cardiac Heart Failure (RCHF) (19).

According to the European Society of Cardiology (ECS) most recent guidelines, the diagnosis of RCHF is commonly performed by echocardiography (37). However, there is limitation to the quantification of RV function by 2-dimensional echocardiography (19). CMR 3-dimensional imaging is the gold standard for non-invasive quantitative evaluation of RV structure and function (38).

The role of CMR in the assessment of CHF is constantly evolving. It has great interest because it allows volumetric and function assessments, tissue characterization, stress testing, providing information of the whole heart, which is useful to confirm or uncover the underlying aetiology of CHF, to manage the disease and its evolution, and to help establish the prognosis (39). CMR-based detection of HF and its pathogenesis can also aid in early medical therapy initiation in symptomatic and asymptomatic patients at risk for CHF (39).

We strongly believe that CMR can be a great tool to evaluate right heart involvement in PHT due to its high-quality images that are not operator dependent and are free from ionizing radiation, making it the ideal modality for young patients who need regular follow-up, such as the ones with PHT in TI (40).

PHT develops with aging. In two of the biggest cardiological studies carried in TI patients, the mean ages of patients with PHT were 32.5 and 28.2 years, respectively, showing the early age onset of this cardiac complication in TI patients and underlying the need for early diagnosis and monitorization (1,36). We maintain our belief that CMR-PC could be used as an early diagnosis tool of PHT, to help prevent the beginning of symptoms and progression of disease to RCHF. Studies are needed to validate this hypothesis in TI patients, because we know that CMR-PC is inferior to RHC in the diagnosis of PHT and also to incorporate other risk factors for PHT that can change the onset age of disease.

Despite all its advantages, we cannot forget CMR has limitations, such as lack of availability, long acquisition time, the need for an experienced operator, parietal volume effects, cost, and contraindication in patients with metallic implants and other non-MR-compatible devices (39).

Left heart involvement

The left heart involvement in TI has some different pathological mechanisms than in TM. While in TM we have mainly an iron overload cardiomyopathy that eventually leads to left ventricular (LV) dysfunction and CHF, in TI there is manly an involvement of the right side of the heart mainly due to PHT, as described in previous chapters. However, the left ventricle is also affected in TI.

In TI, chronic haemolysis and iron overload are associated with endothelial dysfunction, elastic tissue injury and vasoconstriction (12). There is also a HCOS, so the LV has to maintain a HCOS through a dilated, yet rigid vascular bed, being in a constant state of volume and pressure overload, that can lead to ventricular impairment (12). RV dysfunction caused by PHT in TI patients, can also play a role in LV involvement in TI. Once RV becomes dilated in a presence of an intact pericardium, it eventually compresses the LV cavity (19). All these factors combined with aging, valvular disorders, coronary artery dysfunction and iron overload can cause increased susceptibility for heart decompensation and CHF (12).

CMR can be useful in LV assessment, but it plays a more central role in RV assessment (19). ECS 2021 guidelines for the assessment of CHF recommend CMR as a second-line imaging technique for the evaluation of myocardial structure and function in patients with poor echocardiogram acoustic windows (37). However, we concluded that LV and RV dysfunction can occur simultaneously in TI, and that RV dysfunction is more frequent. We believe that CMR is very useful in these patients, as it gives an evaluation of the whole heart and allows a simultaneous evaluation of both sides of the heart, saving time and healthcare resources application.

Another class I recommendation by ECS 2021 guidelines is the use of CMR for the characterization of myocardial tissue in Left Ventricle Non-Compaction (LVNC) (37). LVNC is characterized by the presence of prominent trabeculations with deep intertrabecular recesses and thin compact layer of the myocardium (41).

Prominent trabeculations have been reported by CMR studies as a possible morphological appearance of left ventricular myocardium of TM patients and regularly transfused TI patients (42-44). This finding rises the issue of a differential diagnosis between the LVNC cardiomyopathy and the negative remodelling that happens in TI patients due to the HCOS, PHT, and myocardial iron (21). CMR has become the method of choice for diagnosis of LVNC, due its ability to display anatomic and functional information (41). Macaione *et al* (2020), concluded that LV trabeculae were not infrequent in TI population and underlined the importance of applying the more restrictive planimetric Grothoff's criteria in patients positive for Piga's criterion, to distinguish LVNC from negative heart remodelling in TI.

Iron Overload cardiomyopathy

In TI patients, iron overload occurs primarily because of increased intestinal absorption caused by ineffective erythropoiesis and hepcidin dysregulation, but can also result from occasional blood transfusion therapy, which may be required to manage certain disease-related complications (8,45,46). Predicting intake in hyperabsorption disorders is more difficult than for transfusional hemosiderosis (47). NTDT have a slower progression of iron overload and generally develop complications later in life compared to those with TM who are chronically transfused (48,49).

In TI iron deposition typically spares reticuloendothelial organs, like the spleen and rarely leads to cardiac and endocrine involvement (2). In NTDT iron overload is cumulative as patients advance with age, leading to iron overload in clinically critical thresholds and associated morbidities like hepatic fibrosis, thrombosis, pulmonary hypertension, endocrinopathies, osteoporosis and cerebrovascular disease, with notable absence of cardiac iron (50,51). A careful and non-invasive monitoring of organ specific iron overload can be an important further step toward a better management of TI patients (4).

Several analytic indexes and imaging techniques can be used to monitor iron overload. The relationship between ferritin and liver iron burden is particularly weak in NTDT, and toxicity thresholds based upon ferritin can be dangerously misleading (52,53). Non-transferrin-bound iron (NTBI) appears once transferrin saturation exceeds 75-85%, and they are low molecular iron species that can enter parenchymal cells trough divalent metal channels and pinocytosis (47). The heart and endocrine glands are sensitive to chronic exposure to NBTI species, so transferrin saturations can code patient as either high or low risk for cardiac siderosis, based on the 75-85% saturation cut-off, especially in lower risk disease states, such as TI (47,54).

Liver iron can serve as a better indicator of whole-body iron, but it does not reflect heart iron (55). Magnetic resonance (MRI) using relaxation times (T2 and T2*) and relaxation rates (R2=1/T2 and R2*=1/T2*), can quantify iron overload, by measuring the effect of iron on water protons as they diffuse in the magnetically heterogeneous environment caused by iron deposition (53). Liver iron concentrations (LIC) exceeding 17 mg/g dry weight are associated with iron mediated hepatocellular damage and with increased risk of cardiac iron overload (51). However, low iron levels do not guarantee cardiac protection and control of total body iron by LIC is not sufficient for primary prevention of cardiac iron (56,57).

Cardiac T2* assessment with MRI can recognize pre-clinical iron accumulation. T2* values greater than 20 ms (milliseconds) are considered normal, below this value there is a significant prevalence of myocardial dysfunction, with an even higher prevalence for T2* values less than 10 ms (53). Several studies showed that cardiac iron deposition is rare in NTDT patients, and that there is no significant difference between the pre- and post- blood transfusions global heart T2* (5, 20, 57).

The pancreas and the heart both exclusively accumulate NTBI, which is more likely due to the same L-type calcium iron channels in the two organs (4,54). Pancreas is iron loaded with a clear heart, but the converse is never true (53). A study by Meloni *et al* (2021), showed that a normal global pancreas T2* value has a negative predictive value of 100% for cardiac iron, so in TI, pancreatic T2* measurements could serve as an early warning system for cardiac iron loading and should be routinely obtained. A pancreas R2* of 100 Hz (hertz) appears to represent a risk threshold (58).

The risk for extrahepatic iron loading varies considerably across different anaemia subtypes (57). Patients are divided in low, intermediate, and high risk for cardiac siderosis (47). Non-transfused iron overload syndromes, such as NTDT are at the lowest risk, rarely developing cardiac iron before the age of 30-40 years (51).

Despite the risk classification for cardiac siderosis, all patients should have an initial evaluation with assessment of LV function, and abdominal and cardiac MRI (53). Low risk patients, without significant pancreatic iron deposition (pancreas R2* < 100 Hz) can be sporadically monitored with abdominal MRI alone (every 5 years) (47). All patients with pancreas R2* greater than 100 Hz are considered 'standard' risk and have liver and cardiac iron assessments on a 12- to 24-month basis (59).

TI belongs to the NTDT group, and it should be monitored like a low risk hemoglobinopathy for cardiac siderosis until they develop pancreas R2* greater than 100 Hz, which places them at standard risk, as described before. However, TI can become TD later in life and the real question is if this change in the transfusion demands also changes the risk group for cardiac siderosis, and consequently, the way these patients should be monitored.

Another question that comes across is what time cut-off we can expect for significant cardiac iron deposition related to transfusion once it starts in TI patients. In intermediate risk patients, like in TM, cardiac iron occurs no less than seven to ten years after initiating transfusions when receiving appropriate transfusion and chelation therapy (60). We could adopt this time cut-off for TI patients in the TD category, but we also know that the physiopathology of iron overload in TI and TM is different, and that even in regularly transfused TI (RT-TI) patients, the deposition of cardiac iron is uncommon (5, 20, 57). Further studies are needed to understand if RT-TI patients become part of the intermediate risk group once they initiate regular transfusions, and if there is a time cut-off, we can apply to start monitoring them as intermediate risk patients.

Another important key modifier is the duration of exposure to circulating NTBI. Factors that increase NTBI exposure increase cardiac risk: increased transfusion, ineffective erythropoiesis and possibly splenectomy (47). A study by Meloni *et al* (2021), found higher pancreatic siderosis in splenectomised *versus* non-splenectomised RT-TI patients, confirming that splenectomy increases the risk of pancreatic siderosis. However, no data is available about the role of splenectomy in cardiac iron deposition, and further studies are needed to validate this hypothesis. Further studies

are also needed to comprehend if these factors that increase NTBI exposure can alter the time cut-off for cardiac siderosis in TI patients.

Other cardiac complications

In a study conducted by Aessopos *et al* (2001), investigators found a high frequency of endocardial degenerative lesions, such as thickening and calcification, which affect cardiac valves, mitral annulus and papillary muscles, causing moderate valvular regurgitation and occasionally mild to moderate aortic stenosis. Another case described fast evolution of aortic valve calcification with severe stenosis and need for valve replacement (61). This condition is often seen in older patients who are unable to be transfused (12).

The physiopathology of valve disease in TI patients seems to be related to the hyperkinetic state due to the HCOS typically seen in these patients and also to the elastic tissue abnormalities that resemble Pseudoxantoma Elasticum, conditioning a pseudoxantoma-like syndrome in TI patients which has endocardial, valvular and pericardial involvement (12).

Echocardiography is the key technique to diagnose VHD and assess its severity and prognosis, but other non-invasive methods such as CMR, can be useful in selected patients (62). The latest ECS guidelines for VHD (2021), recommend that in patients with inadequate echocardiographic quality or discrepant results, CMR should be used to assess the severity of valvular lesions (particularly regurgitant lesions), and to assess ventricular volumes, systolic function, abnormalities of the ascending aorta, and myocardial fibrosis (62). There are several advantages of using CMR for VHD assessment. It provides an unobstructed and complete view of the heart, does not require ionizing radiation, and contrast administration is not needed to quantify the severity of the disease (63).

Throughout this review we have realized that CMR is the gold standard non-invasive imaging tool to study the right side of the heart. This also applies for right-sided valves, especially the pulmonary valve, which is difficult to visualize on echocardiography (64) CMR is mainly considered the gold standard for evaluation of the pulmonary valve, right ventricular outflow tract and for the assessment of RV volumes and function (65).

Symptomatic arrythmias in thalassaemia patients pose a significant clinical risk and are mainly associated with significant iron overload but can also occur in patients with normal iron levels, this being attributed to fibrosis from past iron deposition (8). A longitudinal study by Ricchi *et al* (2020) in patients with TI who started transfusion therapy in adulthood, showed a significant increase in supraventricular arrythmias after the start of regular blood transfusions, supporting the link between this cardiac complication and iron overload (20). The emerging role of CMR measurements of cardiac fibrosis can be considered for the study of arrythmias in TI patients, using LGE and extracellular volume fraction (8,63).

We believe that other factors can also play a role in the pathogenesis of arrhythmias in TI patients. Myocardial fibrosis is a typical finding in VHD, and it is associated with ventricular

impairment and the development of arrhythmias (63). In a large observational study by Meloni *et al* (2021), both NTD and TD patients with TI that had a supraventricular arrythmia associated with other cardiac complication, had PHT as the second cardiac complication, raising the question if PHT can also play a part in arrhythmia development in these patients. Further studies are needed to understand the relationship between these cardiac complications in TI patients.

Other cardiac complications encountered in the study by Aessopos *et al* (2001), were pericardial disorders, including pericarditis and pericardial calcification (1). Echocardiography is the first line imaging technique in the suspicion of most pericardial disorders and is commonly used along with other complementary modalities like CT and CMR (66). CMR is a useful additional test specially when echocardiography is equivocal, localized disease is suspected, additional pathology is suspected, because it provides information on the extend of pericardial disease, abnormalities in surrounding structures and it provides a superior tissue characterization that includes estimative on the inflammation degree (67).

In TI patients with PHT and RV dysfunction, the presence of an intact pericardium causes the dilated RV to compress the LV, leading LV impairment (19). We believe that the presence of pericardial disorders such as pericarditis and constrictive chronic changes in the pericardium can alter the mechanic and haemodynamic interactions between the two sides of the heart. It would be useful to conduct studies to understand if these pericardial changes can have effects on prognosis and treatment choices in patients with RHCF, and how CMR can play a role.

Conclusion

Cardiac complications are a major cause of mortality and morbidity in TI. Nevertheless, we have concluded that cardiac complications are poorly studied in these patients. Even in the latest Thalassemia International Federation guidelines for NTDT patients, the only cardiac complication that has a guideline of its own is PHT. With the development of therapeutic options and the increasing lifespan of TI patients, there is also an increase in the comorbidities associated with the disease, including the cardiac complications. This is associated with a decrease in the quality of life of these patients. We believe that major cardiovascular studies with TI patients are needed to investigate the frequency, physiopathology and approach of the complications detailed along this study.

PHT in TI patients is associated with high morbidity and with RV dysfunction, ultimately leading to RCHF. These patients need frequent haemodynamic assessment, and using an invasive method like pulmonary artery catheterization is a problem (16). CMR-PC is a non-invasive method that does not require ionizing radiation, being very useful for the frequent assessments that these patients need. It can be used to accurately measure haemodynamic indexes, such as CO and PVR, that need to be assessed in PHT and in the HCOS seen in TI patients, and it is the gold standard to assess RV function and morphology. CMR can also be used with fluoroscopy to guide RHC (real-time CMR). This technique shows superior accuracy in quantification of CO and PVR, being the gold standard for the definitive diagnosis of PHT.

Even tough CMR can play a central role in the evaluation and monitorization of PHT in TI patients, Thalassemia International Federation guidelines for NTDT, do not even recommend CMR for the assessment of PHT in TI (35). We strongly believe that CMR could be used for the routine screening and follow-up of PHT patients, instead of echocardiography. Screening these patients with regular CMR studies, would allow for earlier diagnosis and help to institute early therapies, delaying the natural progression of PHT and diminishing its effects on patients' quality of life.

MIO cardiomyopathy seems to be infrequent in TI and is related to iron absorption in bowel rather than regular blood transfusions (21). Several studies showed that cardiac iron deposition is rare in NTDT patients, and that there is no significant difference between the pre- and post- blood transfusions global heart T2* (5, 20, 57). By belonging to the NTDT, TI should be managed as a low risk haemoglobinopathy for cardiac siderosis. However, iron absorption in TI is difficult to predict and patients can become TD later in life. Due to these factors, it is uncertain if the increase on transfusion demands can increase the risk for cardiac siderosis, demanding a more intensive monitorization. It is also uncertain if there is a time-cut off we can apply once transfusion is started, that is associated with a higher probability of significant cardiac iron accumulation. Further studies are needed to enlighten clinicians and improve the current guidelines.

Despite all its advantages, we cannot forget that CMR has limitations, such as lack of availability, long acquisition time, cost, and contraindication in patients with metallic implants and other non-MRI-compatible devices (39).

In conclusion, CMR can be useful in the assessment of every cardiac complication seen in TI. We believe that, if available, it should replace echocardiography as the first-line imaging technique for the annual follow-up of TI patients. It would allow for an early diagnosis, prognosis, and classification of PHT and a global evaluation of the hole heart morphology and function. It would also allow for an early detection of RV impairment due to PHT, evaluation of CO and LV impairment in HCOS, VHD, iron deposition and even evaluate myocardial fibrosis, a possible cause for arrythmias seen in this condition. Despite it being cost and time consuming, using CMR would be cost-effective in the long-term, because it would help prevent the comorbidities associated with the major cardiovascular complication in TI, and it would help diminish the burden of these diseases in the healthcare systems.

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