REVIEW ARTICLE

Electrocardiographic Presentation, Cardiac Arrhythmias, and Their Management in β -Thalassemia Major Patients

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Beta-thalassemia major (β -TM) is a genetic hemoglobin disorder characterized by an absent synthesis of globin chains that are essential for hemoglobin formation, causing chronic hemolytic anemia. Clinical management of thalassemia major consists in regular long-life red blood cell transfusions and iron chelation therapy to remove iron introduced in excess with transfusions. Iron deposition in combination with inflammatory and immunogenic factors is involved in the pathophysiology of cardiac dysfunction in these patients. Heart failure and arrhythmias, caused by myocardial siderosis, are the most important life-limiting complications of iron overload in beta-thalassemia patients. Cardiac complications are responsible for 71% of global death in the beta-thalassemia major patients. The aim of this review was to describe the most frequent electrocardiographic abnormalities and arrhythmias observed in β -TM patients, analyzing their prognostic impact and current treatment strategies.

Ann Noninvasive Electrocardiol 2016;21(4):335–342

beta-thalassemia; electrocardiography; arrhythmias; heart; cardiac function; thalassemic cardiomyopathy; myocardial iron overload

INTRODUCTION

Beta-thalassemias are a group of inherited, autosomal recessive diseases characterized by reduced or absent synthesis of the beta globin chains of the hemoglobin tetramer, resulting in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals. Three main forms have been described: thalassemia major, thalassemia intermedia, and thalassemia minor. It is estimated that 1.5% of the world population, about 90 million people, are carriers of the β -thalassemia gene, the great majority in the developing world. The total annual incidence of symptomatic individuals is estimated at 1 in 100,000 people throughout the world and 1 in 10,000 people in the European Union. According to Thalassemia International Federation, only about 200,000 patients with thalassemia major are alive and registered as receiving regular treatment around the world.¹ The aim of our

review was to describe the most frequent electrocardiographic abnormalities and arrhythmias observed in beta-thalassemia major (β -TM) patients and to analyze their prognostic impact and the current treatment strategies.

CLINICAL FEATURES

Individuals with β -TM usually present within the first 2 years of life with severe anemia, requiring regular red blood cell (RBC) transfusions. Affected infants fail to thrive and become progressively pale. Feeding problems, diarrhea, irritability, recurrent bouts of fever, and progressive enlargement of the abdomen caused by spleen and liver enlargement may occur. If β -TM patients are untreated or poorly transfused, as it happens in some developing countries, the clinical picture of thalassemia major is characterized by growth retardation, pallor, jaundice, poor musculature, genu valgum, hepatosplenomegaly, leg

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DOI: 10.1111/anec.12389

ulcers, development of masses from extramedullary hematopoiesis, and skeletal changes resulting from expansion of the bone marrow.^{2,3} If a regular transfusion program that maintains a minimum Hb concentration of 9.5–10.5 g/L is initiated, then growth and development are normal until the age of 10–11 years. After the age of 10–11 years, affected individuals are at risk of developing severe cardiac, liver and endocrine glands complications related to posttransfusional iron overload, depending on their compliance with chelation therapy.³ Survival of individuals who have been regularly transfused and treated with appropriate chelation extends beyond age of 40 years.⁴

CARDIOVASCULAR INVOLVEMENT

Pathophysiology

The primary factor of cardiac damage is iron overload,^{5–7} which has both direct and indirect toxic effects. Iron overload results primarily from repetitive blood transfusions, as well as by hemolysis and increased intestinal absorption. In these patients, iron deposition in parenchymal tissues begins within 1 year of starting the regular transfusions. When the iron transfer capacities of transferrin are exceeded, as in the case of iron overload, a nontransferrin-bound form of iron appears, which is toxic and leads to tissue damage. The free iron can catalyze the formation of hydroxyl radical highly reactive, that attacks lipids, proteins and DNA, which ultimately lead to cell death and fibrosis.^{6–8} In addition, iron is toxic to the endocrine glands which support the heart and develop diabetes, impairing calcium metabolism, adrenal insufficiency, deficiencies of growth hormone and the sex steroids which further impair the heart function.^{9,10} The pathophysiology of heart disease and arrhythmias in β -thalassemia, however, is multifactorial, resulting

from iron cardiotoxicity, chronically elevated cardiac output secondary to anemia, coexisting metabolic and endocrine derangements as well as increased cardiac afterload because of accelerated vascular aging.^{11–15} Postulated mechanisms for the electrophysiological effects include inhibition of fast inward sodium currents, blockage of ryanodine calcium release channel, and oxidative stress-mediated changes in sarcoplasmic calcium release and reuptake.^{16–19}

Clinical Presentation and Evolution

Thalassemic cardiomyopathy and arrhythmias, caused by myocardial siderosis, are the most important life-limiting complications of iron overload in beta-thalassemia patients and are responsible for 71% of global deaths in these patients.²⁰ The β -TM cardiomyopathy, in terms of ventricular function, are usually present in two different phenotypes: (1) dilated cardiomyopathy phenotype, characterized by left ventricular dilatation and reduced contractility, leading to congestive heart failure; (2) a restrictive cardiomyopathy phenotype, characterized by restrictive left ventricular filling with subsequent pulmonary hypertension, right ventricular dilatation, and heart failure (HF). Clinically the β -TM cardiomyopathy is divided into three stages on the basis of symptoms and instrumental data (Table 1). In the early stage, patients are usually asymptomatic.²¹ Once myocardial dysfunction develops, symptoms are related to the degree of ventricular impairment. Arrhythmias are usual in the later stage. Unusual clinical presentations is syncope secondary to ventricular tachycardia or complete heart block.^{22,23}

The heart palpitations symptom is often not indicative of the actual cardiac involvement and the related clinical condition in β -TM population. The frequent occurrence of highly symptomatic but noncomplex arrhythmias (isolated

Table 1. Thalassemic Cardiomyopathy Stages

	Stage I	Stage II	Stage III
Symptoms	No symptoms	Decrease effort tolerance	Dyspnea and CHF
Echo	Possible diastolic dysfunction	LVEF > 60%, Mild PAH, Mild MR/TR	Dilated heart, low LVEF
MRI	Excess iron	Excess iron	Excess iron
Others	Stress Echo possible reduced LVEF		ECG: Arrhythmia

LVEF = left ventricular ejection fraction; CHF = congestive heart failure; PAH = pulmonary artery hypertension; MR/TR = mitral/tricuspid regurgitation.

supraventricular and ventricular ectopic beats) in the earlier disease stage causes immense anxiety for both patients and their physicians and it is a peculiar feature of beta-thalassemia major. The mismatch between symptoms and the severity of arrhythmias in β -TM patients may lead to a delayed diagnosis of potentially life-threatening arrhythmias and might explain the high incidence of sudden cardiac death reported in literature.

Electrocardiographic Presentation

Electrocardiographic abnormalities have been well documented in both the pre and postchelation era.^{24–29} New-onset electrocardiographic abnormalities are usually evident in β -TM with HF and may include electrocardiographic findings that suggest left-sided heart (Q1S3 pattern and extreme left-axis deviation) or right-sided heart involvement (S1Q3 pattern and right-axis deviation), new-onset T wave inversion beyond lead V₁, P wave prolongation or abnormalities, and a consistent decrease in QRS amplitude. In β -TM patients without HF, an abnormal electrocardiogram (ECG) was found in 46% (T wave abnormalities in 34% and right bundle-branch block in 12%).³⁰ Previously, the electrocardiographic changes could not be correlated with cardiac iron status for the lack of suitable diagnostic equipment. The diffusion of CMR T2* imaging, a reliable, sensitive, noninvasive imaging modality for assessing the iron overload, allowed us to monitor changes in myocardial iron during chelation therapy and to correlate the cardiac iron status to electrocardiographic findings. Detterich et al.³¹ showed that some electrocardiographic changes were more strongly associated with myocardial iron overload than others: bradycardia and repolarization abnormalities, including QT interval prolongation, leftward shift of the T wave axis, and generalized ST/T wave changes were most sensitive and specific for cardiac iron overload. In particular, combining a criteria of QT greater than 407 ms, or T wave axis less than 43 degrees, or abnormal reading (nonspecific ST/T wave changes, prolonged QTc, inferior lead T wave inversions, bradycardia) yielded a sensitivity of 89% and a specificity of 70% in identifying β -TM patients with cardiac iron overload. It is not known whether progressive alterations in electrocardiographic tracings occur before HF develops.

Iron Cardiac Toxicity and Cardiac Arrhythmias

Cardiac toxicity by iron is mainly attributed to iron overload gained by transfusions, and it occurs via the free radical-mediated pathway, interfering in the cardiomyocyte capacity to catalyze the formation of deleterious oxygen-free radicals. The highly toxic hydroxyl radicals are well known to damage the lipid-rich cell membrane (lipoperoxidation). Oxidative stress mediated iron toxicity also increases lysosomal fragility³² and decreases mitochondrial inner membrane respiratory enzyme activity, ATP,³³ protective antioxidant enzyme activity, myofibril elements, and number of mitochondria.³⁴ Iron overloaded cardiomyocytes have been shown to have a smaller overshoot potential and a shorter action potential duration than iron-free cardiomyocytes in the same heart.³⁵ An alteration in ion currents characterized by reduced Na⁺ currents may be an underlying mechanism.¹⁸ Reduced overshoot potential ensues as a result of decreased rapid phase 0 depolarization (fast sodium current). A reduction in the late fast sodium current during the plateau phase may result in the rapid shortening of the action potential duration because of the disturbance of a delicate balance of small currents. This electrophysiological heterogeneity, including the patchy nature of cardiac iron deposition, may provide the substrate for triggered activity and reentry and it may be involved in the genesis of arrhythmias in β -TM patients.^{36,37}

Cardiac Arrhythmias

Paroxysmal supraventricular tachyarrhythmias (atrial fibrillation, atrial flutter, intraatrial reentrant tachycardia) are the most common clinically relevant rhythm disturbances in β -TM patients.³⁸ Ectopic atrial tachycardia and chaotic atrial rhythm may also be seen, particularly in the presence of significant cardiac iron loading.^{39,40} Ventricular arrhythmias are more specific for iron cardiotoxicity. Frequent premature ventricular contractions, by themselves, are not specific for iron cardiomyopathy, but couplets, nonsustained ventricular tachycardia, or mixtures of frequent atrial and ventricular premature contractions should raise clinical suspicion.³⁸

Kirk et al.³² showed that cardiac T2* magnetic resonance (MR) identifies patients at high risk of

heart failure and arrhythmias from myocardial siderosis in thalassemia major, and is superior to serum ferritin and liver iron. Using cardiac T2* for the early identification and treatment of patients at high risk is a logical means toward reducing the high burden of cardiac mortality in myocardial siderosis. In their study, a cardiac T2* of <20 ms was present in 83% of patients who developed arrhythmias. The incidence of arrhythmias at 1 year in patients with the lowest cardiac T2* of <6 ms was 14%. The mean cardiac T2* in the arrhythmias patients was as follows: atrial fibrillation (AF) 13.6 ± 9.9 ms, supraventricular arrhythmias (SVT) 11.9 ± 7.1 ms, ventricular tachycardia (VT) 16.5 ± 9.3 ms, and ventricular fibrillation (VF) 9 ms. There was no significant difference between the cardiac T2* values for atrial and ventricular arrhythmias. In comparison with cardiac T2* >20 ms, there was a significantly increased risk of arrhythmia associated with cardiac T2* values <20 ms, with a relative risk of 4.6. This study showed a significant increase in risk of supraventricular and ventricular arrhythmias with increasing cardiac iron loading. Overall, the T2* threshold of 20 ms predicted arrhythmias with a sensitivity of 82.7% and specificity of 53.5%.

The precise incidence of arrhythmias in β -TM population is still challenged.^{32,41} The Myocardial Iron Overload in Thalassemia (MIOT) study, including 776 β -TM patients from 57 Italian thalassemia centers, showed a lower incidence of arrhythmias (3.2%) compared to other research cohorts of β -TM patients, such as the Kirk et al. cohort³² that showed an incidence of arrhythmias of about 14%. This difference could be attributed to the different population features. The MIOT study population presented a good compliance to chelation treatment and showed significantly lower body iron overload and myocardial iron overload than the study population reported by Anderson et al. All the patients had been chelated with deferoxamine for the majority of their lives, and some had later been switched to oral chelators alone or in combination, without significant difference in compliance between males and females.

Sudden Cardiac Death

β -TM patients are at increased risk for malignant arrhythmias and/or sudden cardiac death (SCD).

Historically, SCD accounts for $\approx 5\%$ of cardiac deaths and is associated with severe iron overload and increased QT dispersion, which suggests iron-mediated repolarization abnormalities and torsade de pointes as a causative mechanism.^{42,43} Noninvasive electrocardiographic markers are useful in clinical practice to predict malignant arrhythmias in some clinical conditions,^{44–49} including the β -thalassemia major.⁴³ Despite the majority of sudden cardiac death occurs in β -TM patients with end-stage thalassemic cardiomyopathy due to fatal cardiac tachyarrhythmias, our recent study⁴³ suggested a high incidence of sudden death among young men without clinical evidence of cardiac disease, with a 27% occurrence rate over a 26-year observation period. Those who experienced sudden death had ECGs that demonstrated a higher degree of QT and JT dispersion than the cohort who survived. In particular, a QT dispersion cutoff value >70 ms and JT dispersin cutoff >100 ms identify high-risk sudden death β -TM patients who need a careful cardiac monitoring. Other groups have not observed such a high incidence of sudden death^{50–52} although sporadic cases are not uncommon in β -TM.

Heart Block and Conduction Disturbances

Historically, before the availability of chelation therapy, complete heart block was relatively common in thalassemia patients, occurring in up to 40% of those aged over 15 years.⁵³ It is now rare in most communities, but may occasionally be encountered in the context of severe iron load.

Atrial Fibrillation

The risk of stroke/embolism is increased 5-fold in patients with AF compared to subjects in sinus rhythm. The cardio-embolic stroke has been reported in 0.25–0.46% of patients with β -TM in different endemic countries.⁵⁴ While patients with sickle – β thalassemia and thalassemia intermedia present asymptomatic ischemic lesions that spare the cortex,⁵⁵ patients with β -TM seem to suffer large hemispheric territorial infarcts in the presence of atrial fibrillation (AF) and cardiomyopathy.⁵⁶ The identification of β -TM patients with atrial fibrillation risk is of pivotal importance for the optimization of the medical

therapy to prevent thromboembolic stroke. Maximum P wave duration (P max) and P wave dispersion (PD) are two simple electrocardiographic markers considered to reflect the discontinuous and inhomogeneous propagation of sinus impulses and the prolongation of atrial conduction time.⁵⁷ PD was shown to be an independent risk factor for the development of atrial fibrillation.⁵⁸ It has been studied in some clinical conditions.^{59–61}

In our previous studies,^{62,63} we showed a significant increase in P wave dispersion, correlated with myocardial iron deposit, assessed by Cardiac Magnetic Resonance (CMR) T2 imaging, in β -TM patients with conserved systolic and diastolic cardiac function and we suggested the hypothesis that the abnormal P wave dispersion ≥ 35.5 ms and maximum P wave duration ≥ 111 ms may predict atrial fibrillation onset in beta thalassemia major patients, even when the cardiac function is conserved. For β -TM patients with atrial fibrillation onset high risk, we suggest a careful cardiac monitoring with serial ECG Holter monitoring or cardiac loop ECG recordings, to early detect atrial fibrillation onset and to evaluate the opportunity of prophylactic anticoagulation treatment.

Prognosis

The degree of myocardial iron-overload and any associated myocardial dysfunction influence the prognostic implications of a cardiac arrhythmia. Thus, in the case of a noniron overloaded patient, the development of an arrhythmia such as atrial fibrillation deserves simple investigation and possible pharmacological treatment including anticoagulation, but does not necessarily imply an adverse outcome. The same arrhythmia, in a heavily iron overloaded heart, particularly if cardiac dysfunction is present, may be the harbinger of severe decompensation and requires immediate response and probable hospitalization. Arrhythmias are life-threatening also in the presence of heart failure.⁶⁴ Therefore, the β -TM patients with palpitations management depends on the clinical situation taken as a whole, including iron loading status and cardiac function.

The survival of β -TM patients has significantly improved in recent decades, as a result of regular transfusions and chelation therapy. This favorable trend continues, thanks to the introduction of new oral iron chelators and imaging methods,

which allow better management of iron overload. However, the complications are still frequent and cardiac disease remains the leading cause of death in these patients.

It has been repeatedly reported that β -TM female patients have a better prognosis than males,^{11,65,66} as it happens in the general population. Marsella et al.⁴¹ compared the cardiac iron load as measured by T2* MR imaging in 776 transfusion-dependent beta thalassemia major patients and analyzed the survival and the occurrence of heart failure and cardiac arrhythmias in this population. The prevalence of cardiac disease (heart dysfunction and/or arrhythmias) was significantly higher in males than in females (28.4% vs 17% $P < 0.0001$). There was a significantly higher percentage of β -TM males with heart dysfunction than females (23% vs 16%, $P: 0.014$) the difference between sexes was statistically significant in the third decade of life. Global heart T2* values were significantly lower in both males and females with heart dysfunction than in those without dysfunction, but no difference was observed according to sex. This study showed that males and females with transfusion-dependent beta thalassemia major are at the same risk of accumulating iron in their hearts, but females tolerate iron toxicity better, possibly as an effect of reduced sensitivity to chronic oxidative stress.

MANAGEMENT OF ARRHYTHMIAS

Supraventricular Arrhythmias

The use of beta-blockers (BB), especially carvedilol and bisoprolol, is a standard part of the heart failure therapy and it is indicated in thalassemic cardiomyopathy when excessive sinus tachycardia is present to improve the long-term prognosis. Beta-blockers can be useful in controlling ectopic rhythms even when cardiac function is conserved. BB are generally well tolerated and the dosages should be low at first with careful slow upward titration over days and weeks. Sotalol may have advantages for the prophylactic treatment of atrial fibrillation/flutter. In a clinical context of supraventricular arrhythmias with hemodynamic instability, amiodarone is often successful in controlling atrial arrhythmias and can be a powerful temporizing measure during intensive iron chelation. Long-term therapy may be complicated by hypothyroidism because of

iron-mediated thyroid damage; however, amiodarone therapy can often be terminated successfully after 6–12 months.

For antiarrhythmic drugs intolerant β -TM patients and those whose AF is poorly controlled despite the use of such medication, ablation should be considered after they have undergone successful removal of cardiac iron (documented by CMR).

Calcium-antagonists and class I antiarrhythmic agents should be avoided, since they all have a tendency to produce negative inotropic effect. Their use has not been widespread, since arrhythmias tend to be associated with more severe levels of myocardial impairment. Without more formal study, the use of such drugs cannot yet be recommended for the treatment of patients with thalassemia. Digoxin might be used for ventricular rate control in late stage heart failure patients with atrial fibrillation. Cardioversion should be considered in patients who fail to respond to iron chelation therapy and pharmacological intervention. In the situation of acute heart failure, cardioversion from AF to normal rhythm should be considered early on, as re-establishing synchronized cardiac conduction improves cardiac failure. Beta-thalassemia patients with paroxysmal or persistent AF may respond to radiofrequency isolation of the pulmonary veins but, unlike the general population, the catheter based interventions should be avoided. In thalassemia, these procedures have a low success rate because of the absence of a true anatomic substrate of arrhythmias (there is no scar, but only a functional conduction impairment).

The cardioembolic stroke has been reported in 0.25–0.46% of patients with β -TM in different endemic countries.⁵⁴ No data are currently available regarding the prophylactic efficacy of antiplatelet or anticoagulant drugs for prevention of thromboembolism related to atrial fibrillation in β -TM population, and this now requires dedicated studies. However, considering the prothrombotic tendency, the anticoagulation therapy should be considered in all β -TM patients with isolated or recurrent AF episodes.

For acute AF complicated by hemodynamic compromise, for overt HF, or in the context of known severe myocardial iron overload (pragmatic definition of $T2^* < 10$ ms), the immediate approach should be the same as for ventricular arrhythmia. In both instances, there should be

attention given to anticoagulation. There is at least a theoretical potential for systemic embolization for these patients because of the combined features of the arrhythmia, possibly enlarged atrial size, and procoagulant features of the hematologic condition, exacerbated in many patients by asplenia.^{67–69}

Ventricular Arrhythmias

The management of ventricular arrhythmias in β -TM patients depends primarily on its hemodynamic stability. In a clinical context of arrhythmias with hemodynamic instability, once the diagnosis of ventricular arrhythmia has been made, treatment is urgent and consists of intense, uninterrupted chelation therapy (deferrioxamine by continuous intravenous infusion at doses of up to 75 mg/kg per day or more)^{70,71} and infusion of amiodarone by central vein.⁷² The supportive treatment should include normalization of electrolyte deficiencies, particularly potassium (target > 4.5 mmol/L), and the infusion of magnesium,⁷³ plus careful management of hyperglycemia, maintaining the blood glucose within appropriate ranges (4.0–6.0 mmol/L) by insulin infusions. In hemodynamically compromised patients, direct current defibrillation may be required. Treatment of potentially life-threatening ventricular arrhythmias in ambulatory β -TM patients with severe cardiac iron burdens is controversial, because the physiological substrate is potentially reversible, and early device therapy should be avoided. A defibrillation vest may represent a viable therapeutic bridge during intensive iron chelation therapy. If ICD device therapy is strictly necessary, we suggest to implant MRI conditional ICD and leads and to place the device on the right side, it may be advantageous in allowing better unrestricted imaging of the ventricular walls and septum, to allow for continued monitoring of myocardial iron content.

Heart Block and Conduction Disturbances

The heart block generally responds to adequate chelation therapy, but the speed of this response may be slow. However, in sporadic cases it should be required the use of pacemaker. It applies the same suggestions previously described for defibrillators.

CONCLUSION

Cardiac involvement represents an important complication of β -TM, resulting in increased mortality and morbidity rates. Cardiac arrhythmias are frequent in β -TM patients, particularly in the presence of significant cardiac iron loading, their management should be performed by cardiologists with knowledge of thalassemia and iron-related cardiotoxicity. The careful analysis of electrocardiogram may help to identify the high risk β -TM patients for atrial fibrillation onset or sudden cardiac death, even when the cardiac function is conserved. For these subgroups of patients, we suggest serial ECG Holter monitoring or cardiac loop ECG recordings to early detect atrial fibrillation or potential malignant arrhythmias and to evaluate the opportunity of prophylactic treatment.

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