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Early detection of myocardial dysfunction in poorly treated pediatric thalassemia children and adolescents: Two Saudi centers experience

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HIGHLIGHTS

- Cardiac complications are among the most serious complications in Beta Thalassemia Major Patients.
- Tissue Doppler imaging can detect cardiac dysfunction in pediatric thalassemics before development of overt heart disease.
- Patients with normal global functions, by conventional echo, have abnormal ventricular functions detected by TDI.
- TDI is superior to Echo-Doppler in detection of early myocardial damage in asymptomatic thalassaemic patients.

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ABSTRACT

Background & Objective: Cardiac complications are among the most serious complications in Beta Thalassemia Major Patients. Our aim was to evaluate the value of tissue Doppler imaging (TDI) for early detection of myocardial dysfunction in pediatric and adolescent patients with B-TM before development of overt heart failure or cardiomyopathy.

Patients and methods: 100 thalassemic patients below 18 years old and 100 healthy, age & sex matched controls were enrolled in our case-control study. Cases were selected from those attending outpatient clinics and inpatient wards, King Abdulaziz University hospital and Alhada Armed Forces Hospital, Saudi Arabia, between January 2014 and January 2015. They were subjected to echo-Doppler examination for both septal and lateral walls of the basal mitral and tricuspid annuli assessing the systolic myocardial velocity (S wave), early diastolic myocardial velocity (Ea wave) and late diastolic myocardial velocity (Aa wave).

Results: Patients with thalassemia have RV and LV dysfunction on the basis of abnormal TDI derived myocardial velocities. There was a statistically significant differences between patients and controls regarding (Aa) and (S) of the septal wall of the basal mitral annulus and (Ea) of the lateral wall of the mitral annulus. Also patients with thalassemia have significantly higher (S) of the basal tricuspid annulus. These abnormalities were not detected by conventional echo-Doppler.

Conclusion: Clinically asymptomatic thalassemic children and adolescents who had normal global functions by conventional echo-Doppler were found to have abnormal left ventricular and right ventricular dysfunctions detected by TDI. TDI is superior to Echo-Doppler in detection of early myocardial damage in asymptomatic thalassaemic patients.

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1. Introduction

Beta thalassemia major is the most common chronic hemolytic anemia among children and adolescents across the world [1]. Beta-thalassemia is prevalent in Mediterranean countries, the Middle East, including Saudi Arabia, Central Asia, India, Southern China, and the Far East as well as countries along the north coast of Africa and in South America. The highest carrier frequency is reported in Cyprus (14%), Sardinia (10.3%), and Southeast Asia [2–3]. The high prevalence in the Middle East can be attributed the high prevalence (25–60%) of consanguineous marriages [4].

About 1.5% of the global population are carriers of beta thalassemia, with about 60,000 symptomatic individuals born annually. The total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the world [5]. According to Thalassemia International Federation, only about 200,000 patients with thalassemia major are alive and registered as receiving regular treatment around the world [6].

Regular blood transfusion programs and chelation treatment have considerably improved the survival of patients with thalassemia. However, a consequence of chronic transfusion therapy is secondary iron overload, which adversely affect function of the heart, liver and other organs, causing severe morbidity and shorten the life expectancy [1].

Despite improved survival after the use of iron chelators, the cardiac complications are still the primary leading cause of death for young adults with β-thalassemia major [7]. Cardiac dysfunctions in β-thalassemia major have traditionally been attributed to iron-overload [8] related to repeated transfusions and increased intestinal absorption rate combined with a sustained state of increased cardiac output [9].

Cardiac complications, include pericarditis, myocarditis, HF, and arrhythmias [10,11]. However, with proper chelation treatment, pericarditis and myocarditis are now rare [12]. The most common clinical features are dilated cardiomyopathy (with restrictive features) and arrhythmia, primarily atrial fibrillation (AF). In severe cases, ventricular arrhythmias become more common, and ectopic atrial tachycardia, flutter, and chaotic atrial rhythms may also occur [13].

The age of cardiac death depends primarily on the access to transfusions and chelation. In transfused, but unchelated patients, the typical age at death was 10 years, primarily of cardiac causes [14].

One unit of transfused red blood cells contains approximately 250 mg of iron [15], while the body cannot excrete more than 1 mg of iron per day. A patient who receives 25 units per year, accumulates 5 g of iron per year in the absence of chelation [16].

Although iron chelation therapy can prevent and delay myocardial dysfunction due to the progressive increase of heart iron burden, once dysfunction has become clinically evident it is difficult to reverse [17,18].

Long term control of serum ferritin has been related to protection from cardiac involvement and with improved survival if levels are less than 2500 μg/L [19] with even better outcomes at levels <1000 μg/L [20]. However, serum ferritin is a poor marker of iron balance because ferritin levels change with inflammation/infection, or ascorbate deficiency, and depends on the intensity of blood transfusion, making its reliability uncertain [20].

Detection of early cardiac abnormality is difficult [18,21]. Symptoms and echocardiographic abnormalities arise late in the course of the disease. Usually, patients have normal exercise capacity, with systolic dysfunction occurring in the final stage of disease [21]. Abnormality of longitudinal fiber motion is a sensitive marker of early myocardial dysfunction. Hence, tissue Doppler imaging can be beneficial in the quantitative assessment of regional myocardial function [22,23].

Magnetic resonance imaging (MRI) with the T2* technique is the best method for the detection of tissue iron deposition worldwide. It is noninvasive, and suitable for moving organs like heart [18,24,25]. In children with hemoglobinopathy who received transfusion and chelation, the cardiac T2* was <20 ms only after 10 years of age [26,27]. However, younger onset of cardiac iron, as young as 7 years, has been occasionally reported in TM, especially when poorly chelated [28].

The aim of this study was to investigate the value of using Tissue Doppler Imaging in the detection of non-overt cardiac dysfunction in pediatric and adolescent patients with beta thalassemia major.

2. Patients and methods

We carried a multicenter case-control study on pediatric and adolescent patients of β-TM. Patients were selected from those attending outpatient clinics and inpatient wards, King Abdulaziz University Hospital and Alhada Armed Forces Hospital, Saudi Arabia, between January 2014 and January 2015. It included 100 patients with β-TM aged below 18 years old. Patients were prescribed oral iron chelator; Deferasirox in dose of 20–40 mg/kg. Patients were considered as poorly treated if they were not compliant to their oral iron chelator. We excluded cases with congenital or rheumatic heart disease to exclude structural cardiac disease, including regurgitant valvular lesions, as detected by echocardiography, which may cause ventricular dilatation. We also excluded cases with history of smoking, hypertension, present or past history of overt heart failure. In addition, we excluded other causes of heart failure, other than iron overload, including biochemical causes such as hypercalcemia and thyrotoxicosis. The control group had one hundred age and sex matched apparently healthy individuals with normal cardiovascular status. The study was approved by the research and ethical committees of the contributing hospitals. Written informed consents were obtained from participants or their parents.

All cases and controls were subjected to full history taking (for symptoms of heart failure, co-morbid diseases, drug history and history of transfusions), thorough clinical examination (for signs of heart failure such as gallop rhythm, raised jugular venous pressure and delayed capillary refill), laboratory investigations (CBC and serum ferritin) and imaging using Echo-Doppler and TDI. All echocardiography examinations were done to the patients after receiving blood transfusion as anemia can affect the echocardiographic findings (e.g. marked anemia can cause high cardiac output heart failure).

2.1. Echo-Doppler examination included

(A) M-Mode and two dimensional echo to measure left ventricular end systolic diameter (LVESD), left ventricular end diastolic diameter LVEDD, left ventricular mass (LVM), ejection fraction (EF%), fractional shortening (FS%), and tricuspid annular plane systolic excursion (TAPSE).
(B) Conventional Doppler.
(C) Tissue Doppler imaging.

2.2. Echo-Doppler technique

By using ATL 5000 echocardiography machine, tissue Doppler imaging data were acquired transthoracically using a 2.5 or 3.5 MHZ transducer. The mitral inflow velocity pattern was recorded in the apical 4-chamber view with the pulsed wave Doppler sample volume positioned at the tip of mitral leaflets during