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Relationship between myocardial T2* values and cardiac volumetric and functional parameters in β-thalassemia patients evaluated by cardiac magnetic resonance in association with serum ferritin levels

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ABSTRACT

Purpose: Myocardial T2* cardiovascular magnetic resonance provides a rapid and reproducible assessment of cardiac iron load in thalassemia patients. Although cardiac involvement is mainly characterized by left ventricular dysfunction caused by iron overload, little is known about right ventricular function. The aim of this study was to assess the relationship between T2* value in myocardium and left–right ventricular volumetric and functional parameters and to evaluate the existing associations between left–right ventricles volumetric and functional parameter, myocardial T2* values and blood ferritin levels.
Materials and methods: A retrospective analysis of 208 patients with β-thalassemia major and thalassemia intermedia was performed (109 males and 99 females; mean age 37.7 ± 13 years; 143 thalassemia major, 65 thalassemia intermedia). Myocardial iron load was assessed by T2* measurements, and volumetric functions were analyzed using the steady state free precession sequence.
Results: A significant correlation was observed between EFLV and T2* ($p = 0.0001$), EFRV and T2* ($p = 0.0279$). An inverse correlation was present between DVLV and T2* ($p = 0.0468$), SVLV and T2* ($p = 0.0003$), SVRV and T2* ($p = 0.0001$). There was no significant correlation between cardiac T2* and LV–RV mass indices. A significant correlation was observed between T2* and serum ferritin levels ($p < 0.001$) and between EFLV and serum ferritin ($p < 0.05$).
Conclusion: Myocardial iron load assessed by T2* cardiac magnetic resonance is associated with deterioration in left–right ventricular function; this is more evident when T2* values fall below 14 ms. CMR appears to be a promising approach for cardiac risk evaluation in TM patients.

1. Introduction

β-Thalassemia is an inherited single gene disorder caused by impaired synthesis of the β globin chain of hemoglobin leading to various degrees of defective b- chain production, an imbalance in α/β globin chain synthesis, ineffective erythropoiesis and anemia. Extremely different phenotypes exist within the β-thalassaemia syndromes: at one end of the spectrum, there is β-thalassaemia minor, a clinically silent, mildly hypochromic and microcytic anemia. At the other end, there is β-thalassaemia major (TM) characterized by a severe anemia requiring lifelong transfusions to prolong survival and allow normal development. This leads to iron overload and toxicity, resulting in severe endocrine, liver and cardiac dysfunctions. The term β-thalassaemia intermedia (TI) was used to describe patients who had clinical manifestations that are too severe to be defined minor yet too mild to be defined major, although a substantial overlap between the three conditions can be often observed [1–4].

Despite recent improvements in patient care, iron overload cardiomyopathy is still a leading cause of death in TM and TI patients [5]. Thus, early detection of myocardial iron overload is primary. Over the past decade, magnetic resonance (MR) imaging derived relaxation time parameter T2* has emerged as an important tool to noninvasively quantify cardiac iron load. T2* varies inversely with iron concentration because iron interferes with local magnetic field homogeneity and accelerates transverse signal decay [6]. Recently, T2* cardiovascular MR imaging with a single slice

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approach has been validated as a quantitative method for evaluating myocardial iron overload [7]. The aim of this study was to assess the relationship between T2* value in myocardium and left–right ventricular volumetric and functional parameters and to evaluate the existing associations between left–right ventricles volumetric and functional parameter, myocardial T2* values and blood ferritin levels.

2. Materials and methods

A total of 208 Patients (109 males and 99 females; mean age 37.7 ± 13 years; body surface area (kg/m^2) 1.6 ± 0.2; 143 TM, 65 TI) underwent cardiac magnetic resonance (CMR) examinations. All patients were under chelation therapy with a desferrioxamine infusion, an oral chelator (deferiprone or deferasirox) or combination therapy desferrioxamine and deferiprone. No Patients presented clinical signs of cardiac failure or pulmonary hypertension. The study was approved by the local ethics committee and the patients gave their informed consent. All MR examinations were performed using a 1.5 T scanner (Avanto, Siemens, Erlangen, Germany). To assess heart T2*, a short axis mid-ventricular cardiac gated gradient multiecho dark blood single breath-hold sequence was acquired at eight echo-times (TE = 1.56–17.17 ms) and a slice thickness of 10 mm. A delay time of 0 ms after the R-wave trigger was chosen to obtain high quality image minimizing blood flow and myocardial wall motion artifacts. For analysis a homogeneous full-thickness region of interest (ROI) was chosen in the interventricular septum that surrounded both epicardial and endocardial borders. The signal intensity of this region was assessed for each image and plotted against the TE to form an exponential decay curve using dedicated software (CMRtools; Cardiovascular Imaging Solutions, London, UK). To obtain T2*, an exponential trend-line was fitted with an equation in the form $y = Ke^{-TE/T2^*}$, where K is a constant and y is the image signal intensity (Fig. 1). The lower limit of normality for T2* in the assessment of myocardial iron load has been considered 20 ms [6]. Patients with T2* > 20 ms were considered to be free of cardiac iron overload, while Patients with T2* < 20 ms were considered to have cardiac overload. To assess left and right ventricles volumes and functions, breath-hold short-axis slices from the base to apex were acquired with a 10 mm slice thickness and no gap, using steady state free precession sequence (SSFP). Semi-automated software (CMRtools; Cardiovascular Imaging Solutions, London, UK) was used to assess the left ventricle end-diastolic volumes (LVDV) and left ventricle end-systolic volumes (LVSV), right ventricle end-diastolic volumes (RVDV) and right ventricle end-systolic volumes (RVSV), ejection fractions (EF) and mass of both ventricles. The endocardial and epicardial borders were outlined during the cardiac cycle in the short axis slices; then the mitral and aortic valve planes were tracked. Papillary muscles were subtracted by the program. Since the body habitus may be below average in TM patients, all parameters were indexed to the body surface area, calculated using the Mosteller formula (m^2 = [(height (cm) × weight (kg)/3600)]$^{1/2}$) from the patients' height and weight at the time of the MR examination [8].

2.1. Statistical analysis

The correlation between T2* and each parameter measured (i.e., DMLVindex, DMRVindex, DVLVindex, DVRVindex, EFLV, EFRV, SVLVindex, SVRVindex, Stroke Volume LVindex and Stroke Volume RVindex) was examined by simple regression analysis using Pearson's correlation coefficient (r); the significance of the simple regressions (ρ) was also calculated. A further analysis was carried out to assess the influence of T2* on the values of four parameters, those with the highest R-values (i.e., EFLV, EFRV, SVLVindex, SVRVindex). The sample of 208 patients was split into two groups: (1) the former includes patients with severe iron accumulation (T2* ≤ 10 ms) and moderate iron accumulation (10 ms < T2* ≤ 14 ms); (2) the second one includes patients with mild iron accumulation (14 ms < T2* ≤ 20 ms) and without iron accumulation (T2* > 20 ms). Differences in the above mentioned four parameters between the two groups were tested using Student's t-test. All the statistics were developed in the MATLAB® (MathWorks, Inc.) environment.

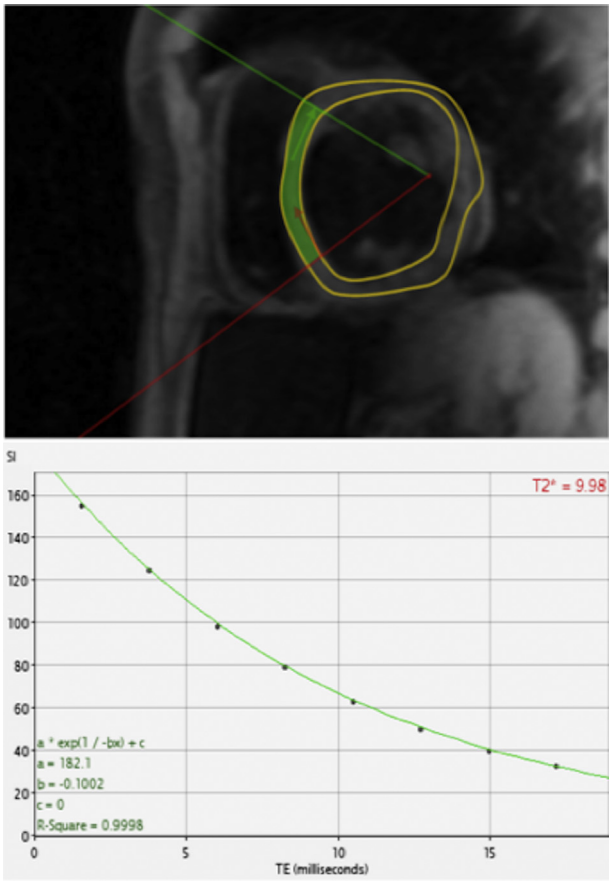

Fig. 1. Patient with severe myocardial siderosis. (a) A full-thickness region of interest was drawn in the interventricular septum. (b) The signal intensity of this region for each echo time was measured and plotted as exponential signal decay curve.

3. Results

The mean serum ferritin level was 1033.8 ng/ml and the mean cardiac T2* was 29.4 ms, in this cohort of Patients: a moderate–severe myocardial iron overload (T2* < 14 ms) was observed in 23 Patients (11%). The mean EFLV, EFRV, DVLVindex, SVLVindex, DVRVindex, SVRVindex, Stroke Volume LVindex, Stroke Volume RVindex, LV mass index and RV mass index derived from MRI were respectively 68 ± 7.5%, 61 ± 11.2%, 77.7 ± 21.3 ml/m^2, 26 ± 11.8 ml/m^2, 75 ± 20.1 ml/m^2, 30.2 ± 14 ml/m^2, 51 ± 12 ml/m^2, 45.2 ± 11.2 ml/m^2, 135.9 ± 45.1 g/m^2 and 32.7 ± 22.4 g/m^2. A significant correlation was observed between EFLV and T2* (R^2 = 0.0737; p = 0.0001) (Fig. 2), between EFRV and T2* (R^2 = 0.0233; p = 0.0279) (Fig. 3). An inverse and significant correlation was present between DVLV and T2* (R^2 = 0.019; p = 0.0468), SVLV and T2* (R^2 = 0.0610; p = 0.0003), SVRV and T2* (R^2 = 0.0393; p = 0.0001) (Figs. 4–6). There was no significant correlation between cardiac T2* and LV–RV mass index (R^2 = 0.0028; p = 0.4444; $R^2 < 10^{-5}$; p = 0.9647). A statistically significant correlation was observed only between T2* and ferritin (R^2 = 0.2059, p < 0.001) and between EFLV and