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Different patterns of myocardial iron distribution by whole-heart T2* magnetic resonance as risk markers for heart complications in thalassemia major

Antonella Meloni [a,1], Gennaro Restaino [b,1], Zelia Borsellino [c,1], Vincenzo Caruso [d,1], Anna Spasiano [e,1], Angelo Zuccarelli [f,1], Gianluca Valeri [g,1], Patrizia Toia [h,1], Cristina Salvatori [a,1], Vincenzo Positano [a,1], Massimo Midiri [h,1], Alessia Pepe [a,*]

[a] CMR Unit, Fondazione G. Monasterio CNR-Regione Toscana, Pisa, Italy
[b] Radiology Department, "John Paul II" Catholic University, Campobasso, Italy
[c] Ematologia-Emoglobinopatie, Civico Hospital-ARNAS, Palermo, Italy
[d] Centro Microcitemia, "Garibaldi" Hospital, Catania, Italy
[e] Centro per la Cura delle Microcitemie, Cardarelli Hospital, Napoli, Italy
[f] Centro trasfusionale, Osp. Giovanni Paolo II, Olbia, Italy
[g] Radiology Department, University of Ancona, Ancona, Italy
[h] Istituto di Radiologia, Policlinico "Paolo Giaccone", Palermo, Italy

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ABSTRACT

Background: The multislice multiecho T2* cardiovascular magnetic resonance (CMR) technique allows to detect different patterns of myocardial iron overload (MIO). The aim of this cross-sectional study was to verify the association between cardiac complications (heart failure and arrhythmias), biventricular dysfunction and myocardial fibrosis with different patterns of MIO in thalassemia major (TM) patients.
Methods: We considered 812 TM patients enrolled in the Myocardial Iron Overload in Thalassemia (MIOT) Network. The T2* value in all the 16 cardiac segments was evaluated.
Results: We identified 4 groups of patients: 138 with homogeneous MIO (all segments with T2* < 20 ms), 97 with heterogeneous MIO (some segments with T2* < 20 ms, others with T2* ≥ 20 ms) and significant global heart iron (global heart T2* < 20 ms), 238 with heterogeneous MIO and no significant global heart iron, and 339 with no MIO (all segments with T2* ≥ 20 ms).
Compared to patients with no MIO, patients with homogeneous MIO were more likely to have cardiac complications (odds ratio—OR = 2.67), heart failure (OR = 2.54), LV dysfunction (OR = 5.59), and RV dysfunction (OR = 2.26); patients with heterogeneous MIO and significant global heart iron were more likely to have heart failure (OR = 2.38) and LV dysfunction (OR = 2.39).
Conclusions: Cardiac complications, heart failure and dysfunction were correlated with MIO distribution with an increasing risk from the TM patients with no MIO to those with homogeneous MIO. Using a segmental approach, early iron deposit or homogeneous MIO patterns can be characterized to better tailor chelation therapy.

1. Introduction

Beta-thalassemia major (TM) is a genetic disorder characterized by a life-threatening anemia that requires regular blood transfusions [1]. These extensive, lifelong blood transfusions lead to iron overload. Uncontrolled iron overload is toxic and can result in severe organ dysfunction and damage [2]. The heart is a target lethal organ [3] and cardiac complications continue to dominate the leading causes of death in TM [4].

In transfused but unchelated patients, the typical age at death was 10 years. With the introduction of deferoxamine treatment in the late 1970s, by the years 2000 68% of the Italian white patients were still alive at the age of 35 years and the survival was strongly dependent on birth cohort [3].

Although the mean age remains low, nowadays thanks to the introduction of new oral chelators and especially the spreading out of the cardiovascular magnetic resonance (CMR) T2*, the prognosis of TM patients is opening [5].

Iron-induced heart damage is both treatable and potentially reversible if intensive iron chelation treatment is started in time [6] and

* Corresponding author at: CMR Unit, Fondazione G. Monasterio CNR-Regione Toscana, Via Moruzzi, 1-56124 Pisa, Italy. Tel.: +39 503153525; fax: +39 503153535.
E-mail address: alessia.pepe@ftgm.it (A. Pepe).
[1] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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the T2* CMR offers a valuable and reliable means to design tailor-made chelation therapies customized for each patient and to evaluate of their efficacy.

The image acquisition is usually limited to a single slice and the T2* value, inversely proportional to iron concentration, is measured in one region of interest (ROI) drawn in the mid-ventricular septum [7]. Mid-ventricular septal iron concentration was shown to be highly representative of mean global myocardial iron by a histological validation of the T2* CMR technique [8]. In that study, iron distribution throughout the hearts showed no systematic segmental variation. However, 11/12 hearts showed heavy iron burden (global heart T2* < 12 ms) and one heart showed no iron in any segment. Thus, the study did not take into account hearts with intermediate iron overload, where a heterogeneous distribution of the T2* values was proven to be present [9].

The multi-slice approach was developed for a segmental assessment of the T2* distribution in the whole heart [10] and allows detection of heterogeneous iron distribution [9,11]. Moreover, in a preliminary study the different patterns of myocardial iron overload (MIO) were correlated to liver iron concentrations and serum ferritin levels [10], proven indicators of poor prognosis in iron-loaded patients.

The aim of this cross-sectional study was to verify whether different patterns of MIO could be related to a different risk of cardiac complications (heart failure and arrhythmias), biventricular dysfunction and myocardial fibrosis in a large cohort of TM patients.

2. Materials and methods

2.1. Study population

We considered data on 812 TM patients (391 M, 30.4 ± 8.6 years), consecutively included in the Myocardial Iron Overload in Thalassemia (MIOT) database [12] where clinical and instrumental data are recorded from birth to the date of the first magnetic resonance imaging (MRI) (September 2006–June 2010).

All patients had been regularly transfused since early childhood and only the 0.9% of them was not chelated. MRI scanning was performed in the week immediately prior to scheduled blood transfusion.

The only cardiac complications active at the time of the CMR were heart failure and arrhythmias.

All patients gave written informed consent. The study complied with the Declaration of Helsinki and was approved by the institutional ethics committee.

2.2. Images acquisition and analysis

MRI was performed on a 1.5 T scanner (GE Excite HD) using an eight-element cardiac phased-array receiver surface coil and ECG-gating.

For iron overload assessment, a validated T2* gradient-echo multiecho sequence was used. The intersite, interstudy, intraobserver, and interobserver variability of the proposed methodology had been previously assessed [13,14]. For the measurement of MIO, a multislice approach was adopted [10]. Three parallel short-axis views (basal, medium and apical) of the left ventricle (LV) were acquired at 10 echo times (TEs 2.0–21.8 ms, echo spacing 2.20 ms) in a single end-expiratory breath-hold. Acquisition sequence details are provided in [11]. A medium-hepatic slice was obtained at 10 TEs (TEs 2.0–20.9 ms, echo spacing 2.1 ms) in a single end-expiratory breath-hold [15]. Image analysis was performed using a custom-written, previously validated software (HIPPO MIOT®) [16]. The software provided the T2* value on each of the 16 segments into which the LV can be divided, according to the standardized AHA/ACC model [17] (Fig. 1). Moreover, the global T2* value averaged over all segmental values and the T2* value in the mid-ventricular septum were automatically provided. Susceptibility artifacts were corrected using an appropriate correction map [16]. Liver T2* value was calculated in a region of standard dimension, chosen in a homogeneous area of parenchyma [15]. As recommended [18], liver T2* was converted into liver iron concentration (LIC) by using Wood's calibration curve [19].

For the evaluation of cardiac function, steady-state free procession cines were acquired during 8-second breath holds in the vertical and horizontal long axis planes, with subsequent contiguous 8-mm short axis slices from the atrio-ventricular groove to the apex. Thirty cardiac phases were acquired per heart beat and images were analyzed using MASS® software (Medis, Leiden, The Netherlands) [20].

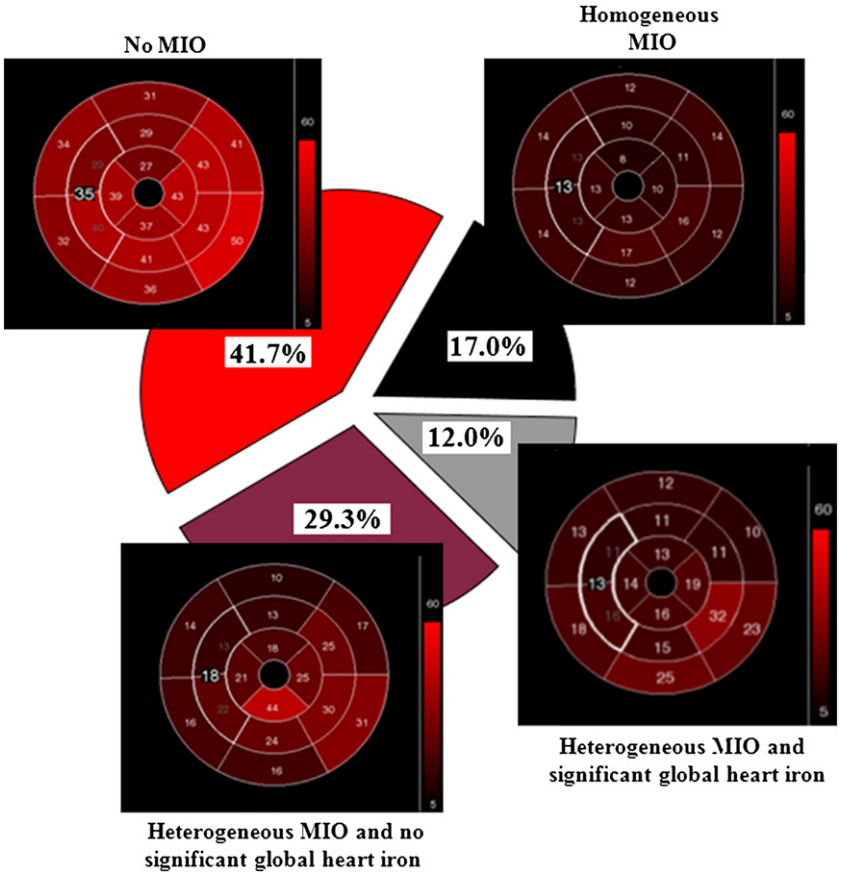

Fig. 1. Representative bull's-eye maps identifying the 4 patterns of MIO. The pie chart specifies the percentage of patients for each pattern.