Tesi

ROLE OF CARDIAC IMAGING IN EARLY DIAGNOSIS OF β-THALASSEMIA MAJOR’S IRON OVERLOAD CARDIOMYOPATHY

Settore scientifico disciplinare
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To my mother,

Model in life and determination to survive
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My PhD thesis is dedicated to my MOTHER and GRANDMOTHER.

My deepest love to my wife, DANA.

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Abstract

BACKGROUND:
Iron overload cardiomyopathy (IOC) results from the accumulation of iron in the myocardium, and it is the leading cause of death in patients receiving chronic blood transfusion therapy like patients with thalassemia major (TM). It has been documented that adequate medical therapy can reverse IOC when it is diagnosed before end-stage heart failure occurs, thus underscoring the importance of early detection of IOC, in which speckle tracking echocardiography (STE) can play an important role.

METHODS:
154 patients from a primary thalassemia unit were screened and after applying the exclusion criteria, 41 patients affected by TM, receiving long-term blood transfusions every 3 weeks and undergoing iron chelation therapy were prospectively enrolled. 41 healthy subjects, age and sex matched, were included as control group. Both TM patients and control group underwent STE and offline software analysis. T2* CMR exam in a single center was performed in the TM group to assess the myocardial iron overload.

RESULTS:
Although average values were within normal range, patients with TM had significantly higher LVEDD, LV mass, LVMi, LA volume, mitral and tricuspid A velocity, EDT, systolic pulmonary artery pressure (PAPs), septum Sm, and lower EF, LVEDV, LVESV, mitral and tricuspid E/A ratio and IVRT. The LV circumferential systolic strain was similar between groups, excepting the anterior and infero-septal walls (p=0.001 and 0.003 respectively), while longitudinal and radial systolic strain was different between controls and TM patients, being lower in the thalassemia group, almost for all segments of the left ventricle. Regarding strain rate (SR), when comparing the groups, the major difference was between radial SR at the level of the antero-septal, infero-lateral and antero-lateral walls (p=0.033, respectively 0.01 and 0.035). The cardiac T2* correlated only
with radial SR at the level of the infero-septal wall (p=0.009). The EF and FS measured with echo and CMR correlates well with T2* (p=0.001 and 0.002 for echo, respectively 0.026 and 0.007 for CMR). The longitudinal and circumferential global systolic strain was similar between control and thalassemic group (20.06 +/-1.53% vs. 20.8 +/-2.66%, p=0.09 and 19.9 +/-2.08% vs. 18.96 +/-2.72%, p=0.11) while radial global systolic strain was significantly lower in thalassemic patients (27.9 +/- 4.53% vs. 21.5 +/-7.9%, p<0.001).

CONCLUSIONS:
IOC is a potentially lethal, but treatable disease when diagnosed and treated early in its course. Iron studies, cardiac MRI with T2* measurement, echocardiographic assessment, and plasma BNP levels are all important diagnostic and prognostic tools to evaluate patients with iron-overload cardiomyopathy. Once heart failure develops, the prognosis is usually poor with precipitous deterioration and death, despite intensive chelation.

Conventional echo parameters do not provide enough informations for early ventricular dysfunction. 2D strain imaging is one of the latest techniques and may provide additional data for management of thalassemic patients suspected of iron cardiomyopathy.

The major advantage of 2D strain over conventional echo parameters is its superiority in detecting the subclinical cardiac involvement and the fact that is not affected by age and volume load and being not angle-dependent.

Keywords:
Iron - Overload, β-thalassemia major, Cardiomyopathy, Echocardiography, Heart disease
1. Introduction

Thalassemia is considered the most common genetic disorder worldwide\(^1\). This disorder is a congenital anemia that has in common deficient synthesis of one or more of the globin subunits of the normal human hemoglobins. The basic defect in β-thalassemia is a reduced or absent production of β-globin chains with relative excess of α-chains. The direct consequences are a net decrease in the hemoglobin production and an imbalance of globin chain synthesis which is the main determinant of clinical severity. The β-thalassemias include four clinical syndromes of increasing severity: two conditions are generally asymptomatic, the silent carrier state and β-thalassemia trait, and usually result from the inheritance of one mutant β-globin gene, and two require intensive medical management, thalassemia intermedia and thalassemia major (TM). The differentiation between thalassemia major and intermedia is essential for design of the appropriate treatment\(^2\). The clinical picture of β-thalassemia major includes features that are due to the disease itself, as well as others that represent the consequences of therapy and are, in a sense, iatrogenic. Patients receive periodic blood transfusions to keep hemoglobin levels compatible with life. Blood transfusions, together with increased intestinal iron absorption and chronic hemolysis, determine progressive iron overload in different tissues with secondary hemochromatosis. The accumulation of iron, if untreated, causes considerable morbidity and, ultimately, leads to death and so the importance to assess the iron stores\(^3-6\). The iron status of patients with transfusional iron overload can be measured by several methods: serum ferritin; transferrin saturation; labile plasma iron (LPI) and non-transferrin-bound iron (NTBI); liver iron concentration (LIC) by liver biopsy, hepatic magnetic resonance imaging (MRI), superconducting quantum interference device (SQUID) and heart iron concentration by cardiac MRI (CMR). Transferrin saturation correlates reasonably well with serum ferritin. After only a few years of transfusion, however, transferrin is usually completely saturated, even in well-chelated patients. Serum ferritin has, in general, been found to correlate well with iron stores. Several variables can interfere with the reliability of ferritin, such as chronic disease, malignancy, ascorbic acid deficiency and inflammatory disorders. Serial measurements of serum
ferritin remain a reliable parameter, as well as the easiest one, to evaluate iron overload and efficacy of chelation therapy. Assessment of LPI, an investigational technique which is redox-active, has the potential to provide a highly accurate assessment of iron burden, and several methods for measuring LPI have been developed. None of these methods provide an estimate of iron accumulation in the various organs, as its distribution is usually not homogeneous. At present, the most accurate way of estimating the iron burden is by direct measurement of iron concentration in the liver (LIC). The relationship between LIC and cardiac iron is complex. Some patients with increased LIC have normal cardiac iron levels, while others with cardiac iron overload may have a normal LIC. LIC is less important than cardiac iron in determining the immediate risk of heart failure. Needle biopsy is the invasive method, while noninvasive alternative methods include MRI and magnetic susceptometry. MRI, with the advantage of avoiding radiation exposure to the patient, has been used by several authors to demonstrate the presence of iron in the pituitary gland, the pancreas, the liver, and the heart. Both MRI and magnetic susceptometry are significantly affected by iron, and both show changes in iron overload. However, to date, only MRI can be applied to a moving organ such as the heart. CMR has also disadvantages, like being expensive, claustrophobic and local access remains an issue. Detection of iron deposition by MRI is based upon the ability of stored intracellular iron to enhance the magnetic susceptibility of the tissues and the principle of T2* relaxation measurements. The great advantage of the cardiac MRI T2* method or its inverse, R2*, is that it allows the indirect assessment of the degree of iron load in the heart. Of all quantitative MRI techniques used for assessment of cardiac iron overload in the last few years, R2* measurements appear to be the most appropriate. Cardiac complications such as heart failure and arrhythmias, caused by the so called “iron induced” cardiomyopathy, are considered to be the primary cause of death in patients with β-thalassemia major. Cardiac involvement in TM is generally characterized by iron-induced ventricular dysfunction, leading to heart failure. The degree of cardiac dysfunction is considered to depend on the quantity of iron deposited in individual myocardial fibers and the number of fibers affected. Myocardial iron deposition is not
homogeneous and does not occur until other organs such as spleen and liver become saturated. Iron cardiomyopathy is reversible, if intensive chelation starts in time, but diagnosis is often delayed by the unpredictability of cardiac iron deposition and the late development of symptoms and echocardiographic abnormalities. A direct measurement of myocardial iron would allow early diagnosis and treatment and help to reduce mortality\textsuperscript{9-11}. The recent studies are turning to depict the early stages of iron cardiomyopathy and thus the main idea of this research. The aim of this study was to clarify the role of cardiac imaging in the diagnosis of iron overload cardiomyopathy in patients with beta-thalassemia major and to set-up the usefulness of 2D strain echocardiography parameters in the early detection of regional myocardial disfunction of thalassemic patients.
2. Methods

Study population

The study was conducted in Taranto Hospital Department of Hematology – Microcythemia Center between April and July 2011. This prospective study included 41 patients affected by TM, receiving long-term blood transfusions every 3 weeks and undergoing iron chelation therapy and 41 healthy subjects, age and sex matched, included as control group. Demographic data, haematological and biochemistry parameters are listed in Table 1. The study was approved by local ethics committee and all the participants signed the informed consent. All the patients were in sinus rhythm at the time of the study. The exclusion criteria for both groups were: age > 10 years, thalassemia without transfusions, diabetes mellitus, hypertension, hypothyroidism, neoplasms, mild or severe valvulopathy, arrhythmias, prior cardiac surgery, implantable cardiac defibrillators or pacemakers, bad echo window and complete refuse of echo exam (patients who didn’t sign the informed consent). The blood pressure, weight, height, body surface area, NT-pro BNP and ferritin levels were measured in all patients. Thalassemic patients were on intense chelating therapy with deferipone (38%), deferoxamine (15%), deferasirox (36%) and combination deferoxamine + deferipone (11%). The patients enrolled in the study underwent conventional and advanced echocardiography and T2* CMR exam in a single center (Pisa) to assess the myocardial iron overload. A critical iron loading was defined as a T2* value less than the threshold of 20 ms (less than the lower limit value of the 95% confidence interval of the normal T2* value as described by Anderson et al.12), and values equal to or greater than this limit were considered to be uncritical. The enrolling flow chart of the study is shown in Figure 1.

Echocardiography parameters

Conventional and Tissue Doppler echocardiography

All patients and controls underwent echocardiographic examination according to the recommendations of the Joint American and European Society of Echocardiography using standard
parasternal and apical views through a commercially available ultrasound machine - Philips iE33 (Philips Healthcare, Bothell, WA, USA; Transducer: S5-1)) equipped with a harmonic 5-1 MHz variable-frequency phased-array transducer with PureWave Crystal Technology. Cardiac assessment was performed at 10 days after transfusion in order to obtain a stable haemodynamic steady-state and to minimize the influence of the anaemia to cardiac echo parameters. The patients rested for 15 minutes before the echocardiographic exam. All the scans were recorded to both echo machine and external hard drive (Toshiba STOR.E ALU2; 3.5”; 1,5TB of data). Measurements were performed on 3 consecutive beats and an average of these was calculated. Parasternal long-axis view was used to obtain the following M-mode parameters: left atrial diameter (LAD), left ventricular end-diastolic diameters (LVEDD), LV end-systolic diameters (LVESD), diastolic interventricular septal thickness (IVSd), systolic interventricular septal thickness (IVSs), diastolic posterior wall thickness (PWd), systolic posterior wall thickness (PWs), LVFS and LVEF (calculated by the Teicholz method). LV mass (LVM) was calculated as $1.04 \times [(\text{LVED} + \text{IVSd} + \text{PWd})^3 - (\text{LVED})^3] \times 0.8 + 0.6$ while LVM index (LVMi) was calculated as LVM/body surface area. End systolic left atrial dimensions were measured in the parasternal axis view from the trailing edge of the posterior aortic–anterior left atrial complex.

The left ventricular outflow tract (LVOT) was measured in the parasternal long-axis view according to standard criteria. Cardiac index (CI, liters per minute per square meter) was calculated as the product of LVOT area index, LVOT pulsed Doppler velocity-time integral and heart rate. Apical four chamber view was used to measure: LV end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were calculated from the apical 2- and 4-chamber views using a modified Simpson’s method. LV ejection fraction was calculated as ejection fraction \( \frac{(\text{LVEDV} - \text{LVESV})}{\text{LVEDV}} \times 100 \). Pulsed-wave Doppler imaging was performed by placing the sample volume at the tip level of the mitral and tricuspid leaflets in the apical four chamber view, obtaining in this way peak inflow early diastolic velocity (E), late diastolic atrial filling velocity (A), their ratio (E/A) and E-wave deceleration time (EDT). Isovolumic relaxation time (IVRT) was obtained
by placing the cursor of CW Doppler in the LVOT to simultaneously display the end of aortic ejection and the onset of mitral inflow. Color M-mode Vp and peak E velocity to Vp ratio (E/Vp) was performed in the apical 4-chamber view, using color flow imaging with M-mode scan line placed through the center of the LV inflow blood column from the mitral valve to the apex, with baseline shift to lower the Nyquist limit so that the central highest velocity jet is blue. MAPSE (mitral annular plane systolic excursion) and TAPSE (tricuspid annular plane systolic excursion), an index of LV and RV systolic function, was measured with M-mode in apical four-chamber view, placing the examination beam on the lateral mitral and tricuspidian annulus (mm).

The tissue Doppler-based myocardial performance index of the left ventricle (Tei index) was calculated according to the formula: (a-b)/b, where a represents the time interval between the end and onset of atrioventricular valve annular diastolic velocities, and b is the duration of annular systolic velocity.

Pulsed-wave Tissue Doppler Imaging (TDI) was performed with a variable frequency, phased-array transducer, bypassing the high-pass filter to display tissue velocities. Gains were minimized to allow a clear tissue signal with minimal background noise aligning the echo image to the annular motion. From the apical four-chamber view, the Doppler sample volume (20-mm axial length) was placed at the lateral tricuspid annulus as well as at the septal and lateral mitral annulus obtaining peak systolic myocardial velocity (Sm), early (Em) and late (Am) diastolic myocardial velocities. The Nyquist limit was adjusted to a velocity range of 1.5–15cm/s. The monitor sweep speed was set at 50–100mm/s to optimize the spectral display of myocardial velocities. In cases having tricuspid regurgitation (TR), the RV systolic pressure (RVSP) was estimated from the peak TR velocity.

Speckle tracking echocardiography (STE)

The four-chamber apical plane was acquired for the assessment of LV longitudinal strain, while the short-axis plane at the papillary muscle level was acquired for the assessment of LV radial and
circumferential strain. Using customized QLab software version 8.1 (Philips Healthcare, Bothell, WA, USA), a speckle tracking region of interest was defined. Real time tracking of natural acoustic markers within the region of interest throughout the cardiac cycle allows derivation of the two-dimensional strain and strain-rate (SR). The LV free wall and ventricular septum were respectively divided into three segments, while the LV short-axis plane was divided into six segments for quantification of regional myocardial deformation. The narrowest possible image sector angle was used to achieve the maximum color Doppler frame rate. The frame rates ranged from 84 to 112 fps. Strain rate was expressed as 1/ s. The strain data were expressed as negative % values and measured from systolic strain curves. All TDI and strain measurements were calculated from 3 consecutive cycles and an average of 3 measurements was recorded and stored on echo machine and external hard drive. The intraobserver and interobserver variability for strain was 5.1%, respectively 4.7%. The total time for one exam had an average of 24 minutes/patient for conventional echo and 38 minutes/patient for advanced echo, including software analysis.

Magnetic resonance imaging

All CMR exams were performed in Pisa, Italy, at MRI Laboratory of the Institute of Clinical Physiology using a 1.5-T MRI scanner (GE Signa CV/I; General Electric, Milwaukee, WI, USA). A four-element cardiac phased-array receiver surface coil with breath-holding in expiration and ECG-gating was used for signal reception. For the measurements of myocardial T2*, a fast-gradient-echo multi-echo sequence was used with electrocardiogram triggering. Three parallel short-axis views (basal, median, and apical) of the LV were obtained.

To evaluate myocardial fibrosis contrast delayed enhanced (DE) images were acquired in the same view used for cine MRI from 10 to 18 minutes, after Gadobutrol (1.0 mol/L) (0.2 mmoli/Kg) administration, using an inversion recovery segmented gradient-echo sequences. The images acquired were analyzed using custom-written software (Hippo Miot IFC-CNR©)
developed in the IDL 6.0 environment (International Patent PCT/IB2006/000880 13 April 2006).

**Statistical analysis**

The data analysis was made with statistical software (SPSS version 13 for Windows, Chicago, IL), using descriptive analysis and correlation analysis. Descriptive analysis was made in order to test the normality of variables distribution. Correlation analysis was applied to study the strength of a linear relationship between two or more quantitative variables. Continuous variables were expressed as mean±/standard deviation. Student t-test was used for comparison of parametric values. Correlation analysis was performed with Pearson correlation analysis. Linear regression analysis was modeled to determine the independent determinants of indexed LV mass (LVMi) and LA, SR and TDI parameters. A p value <0.05 was considered statistically significant.
3. Results

The study groups consisted in a 41 controls subjects, aged 31.3+/−8.3 years, 21 males and 41 thalassemic patients, aged 33.2+/−9.4 years, 21 males. Patients with TM had lower body surface areas (1.62+/−0.2 m² vs. 1.72+/−0.19 m², p=0.009). There were no significant differences between groups regarding systolic and diastolic blood pressure and heart rate. Patients with TM had iron overload with elevated serum ferritin levels (mean value = 1636+/−1943 ng/ml) and haemoglobin levels at 10 days after transfusion 9.9+/−1.02 g/dl. Mean NT-pro BNP levels was 131+/−248 pg/dl. The T2* value, evaluated by CMR imaging with Hippo-MIOT software was 29+/−10.7 msec, with 8 patients (20%) having a T2* < 20msec. The T2* values < 10 ms are associated with the development of heart failure\textsuperscript{13}.

Conventional and Tissue Doppler echocardiographic parameters

All subjects had normal ejection fraction and other parameters of systolic and diastolic function. Although average values were within normal range, patients with TM had significantly higher LVEDD, LV mass, LVMi, LA volume, mitral and tricuspidal A velocity, EDT, systolic pulmonary artery pressure (PAPs), septum Sm, and lower EF, LVEDV, LVESV, mitral and tricuspid E/A ratio and IVRT (Table 2).

STE parameters

Left ventricular myocardial deformation parameters are presented in Figure 2 and 3. The LV circumferential systolic strain was similar between groups, excepting the anterior and infero-septal walls (p=0.001 and 0.003 respectively), while longitudinal and radial systolic strain was different between controls and TM patients, being lower in the thalassemia group, almost for all segments of the left ventricle. Regarding strain rate (SR), when comparing the groups, the major difference was between radial SR at the level of the antero-septal, infero-lateral and antero-lateral walls (p=0.033, respectively 0.01 and 0.035). The cardiac T2* correlated only with radial SR at the level of the
infero-septal wall (p=0.009). The EF and FS measured with echo and CMR correlates well with T2* (p=0.001 and 0.002 for echo, respectively 0.026 and 0.007 for CMR). There were no differences between 2 groups divided using a T2* cut-off value of 20 msec.

The longitudinal and circumferential global systolic strain was similar between control and thalassemic group (20.06+/-1.53% vs. 20.8+/-2.66%, p=0.09 and 19.9+/-2.08% vs. 18.96+/-2.72%, p=0.11) while radial global systolic strain was significantly lower in thalassemic patients (27.9+/-4.53% vs. 21.5+/-7.9%, p<0.001).
4. Conclusions

Heart disease is the primary determinant of prognosis and survival in beta-thalassemia major. Myocardial iron deposition seems to be the trigger for the development of heart failure in thalassemia major.

IOC is a potentially lethal, but curable disease when diagnosed and treated early in its course. Iron studies, cardiac MRI with T2* measurement, echocardiographic assessment, and plasma BNP levels are all important diagnostic and prognostic tools to evaluate patients with iron-overload cardiomyopathy. Once heart failure develops, the prognosis is usually poor with precipitous deterioration and death, despite intensive chelation.

Myocardial iron toxicity is attributed to free radical damage, and the role of NTBI has been demonstrated. In asymptomatic thalassemia patients with normal myocardial mass, diastolic dysfunction has been found to be an early event, even while the systolic function is only mildly impaired. Traditional diagnostic tools (i.e: electrocardiography, 24-hour tracings, echocardiography, nuclear studies), although routinely used, are not predictive of subsequent cardiac dysfunction.

Echocardiography, on the other hand, is the examination of choice for routine heart evaluation. The role of ultrasound on a regular basis in cardiac monitoring is undoubtedly of great importance. Conventional echo measures of systolic and diastolic dysfunction are insensitive for detecting early myocardial iron overload from their dependence on loading conditions and heart rate\(^{14}\). However, in TM patients, unlike MRI, ultrasound can only depict the complications of cardiac iron overload, not the iron accumulation itself\(^{15-17}\).

Thalassemia patients have early regional systolic and/or diastolic dysfunction even if they do not have overt heart failure, thus the necessity of precocious diagnosis of cardiac involvement. Acoustic densitometry using ultrasonic backscatter techniques was reported to be effective in early detection of myocardial dysfunction in asymptomatic thalassemic patients\(^{18,19}\). Later, echo analysis of echo diastolic parameters were useful in cardiac evaluation of thalassemic patients, followed by
TDI parameters and strain analysis\textsuperscript{20}. Nowadays, myocardial deformation techniques (2D strain) and rotational dynamics showed great results.

Strain rate imaging (SRI) is a way of defining local wall thickening and thinning leading to a better description of regional myocardial function and is helpful in early detection and quantitative assessment of left ventricular (LV) longitudinal systolic functions in thalassemic patients and may provide additional data for management of thalassemic patients suspected of iron-mediated cardiomyopathy. Speckle tracking echocardiography (STE), a new echocardiographic technique, is a promising tool which can diagnose early stages of regional systolic or diastolic dysfunction of either ventricle before conventional echo parameters are abnormal and can be used for quantitative assessment of myocardial function. STE permits an angle-independent assessment of the magnitude and rate of deformation in the longitudinal, radial and circumferential dimensions as they are strong indices of ventricular systolic and diastolic function\textsuperscript{21-25}. Myocardial mechanics, including rotational mechanics (LV twist), is a more sensitive marker of myocardial dysfunction than traditional echocardiography and offers a simple alternative to cardiac MRI for assessing significant myocardial iron deposition\textsuperscript{26}. Echocardiographic measurements of myocardial mechanics accurately detect the degree of myocardial iron deposition assessed by CMR T2* values\textsuperscript{27}.

Conventional echo parameters do not provide enough informations for early ventricular dysfunction\textsuperscript{28}. 2D strain imaging is one of the latest techniques and may provide additional data for management of thalassemic patients suspected of iron cardiomyopathy.

The main finding of our study was that multiple cardiac abnormalities, detectable only using new diagnostic tools such as 2D strain, occur in patients with beta-thalassemia major requiring long-term blood transfusions and undergoing iron chelation therapy despite the absence of significant myocardial iron overload and structural cardiovascular changes. Our study group had significantly higher values of LVEDD, LV mass, LVMi, LA volume, mitral and tricuspid A velocity, EDT, systolic pulmonary artery pressure (PAPs) and septum Sm, similar to those found by Henry et al and attributed by an increased cardiac output caused by chronic anaemia\textsuperscript{29}. 
In our study, all the patients had normal conventional echo parameters of systolic and diastolic function. However, the advanced echo parameters of speckle tracking echocardiography showed significantly differences between control and thalassemic patients, especially regarding the radial and longitudinal strain, indicating the presence of regional dysfunction. Also, we found a good correlation between T2* and infero-lateral radial SR, underlying the hypothesis of regional iron deposits. Further studies are necessary to confirm this.

Previous articles showed that impaired longitudinal and circumferential strain and radial strain rates have been found in patients with significant myocardial iron overload. However, early abnormalities of LV myocardial function also have been observed in well chelated patients with TM.

The major advantage of 2D strain over conventional echo parameters is its superiority in detecting the subclinical cardiac involvement and the fact that is not affected by age and volume load and being not angle-dependent.

Our data have confirmed these findings, because we observed an impairment in LV radial and longitudinal deformation in patients without significant myocardial iron overload, suggesting that even a mild myocardial iron deposition could be responsible for the cardiac abnormalities and that radial strain may be useful to detect those patients with possible cardiac iron loading who may then have a CMR for further assessment.

Longitudinal strain is mainly driven by deformation of the subendocardial fibers, circumferential strain results from the mid- or subepicardial fibers, and radial strain from the transmural deformation of all myocardial fibers. It is known that subendocardial fibers are the most vulnerable to myocardial damage, including hypoxemia due to anemia, and, thus, the earliest to be affected at the onset of myocardial involvement, preceding the abnormalities of circumferential and radial deformation. This could be an explanation for the wide variation of LV longitudinal and radial strain values obtained in our study. The assessment of myocardial deformation could be valuable in the early detection of cardiac involvement and, eventually, in the adjustment of iron-chelating
therapy in these patients. For this purpose, 2D strain, as already shown for other diseases, will be more accurate and reproducible than standard echocardiography and tissue Doppler imaging in the identification of subclinical myocardial abnormalities in these patients. Furthermore, the TM patients will benefit from a close follow-up with advanced echocardiography for an early diagnosis of iron overload cardiomyopathy.

The limitation of the study is the small sample size in a relatively defined population of thalassemic patients. The new development in the field of strain, the 3D strain, can be useful in the near future for the assessment of these patients. Also, the extension of deformation analysis to the right ventricle and left atrium may be of interest, knowing that iron deposits are heterogeneous and the fact that the iron has been reported to be absent from the right ventricular subendocardium in some patients with cardiac iron overload. Problems with software analysis, vendor dependent, still remain a challenge.
References:


Echocardiography. 2010 Mar;27(3):253-9


29) Henry WL, Nienhuis AW, Wiener M, Miller DR, Canale VC, Piomelli S.
Figure 1: Flow chart of the inclusion criteria for thalassemic patients

Total patients (n=154) → Patients regularly followed (n=149) → NOT under transfusions (n=9) → Patients regularly followed (n=140) → Other types of haemoglobinopathies (n=33) → Patients with TM and transfusions (n=107) → NOT meeting inclusion criteria (n=55) → Eligible patients (n=52) → Poor echo window (n=6) Complete refuse of the exam (n=5) → Included patients (n=41) → Control group (n=41)
Figure 2: Circumferential (left panel), radial (right panel) and longitudinal (lower panel) systolic strain in thalassemia patients (red) and controls (yellow). *p<0.05 vs control.
Figure 3: Circumferential (left panel), radial (right panel) and longitudinal (lower panel) systolic strain rate in thalassemia patients (red) and controls (yellow). *p<0.05 vs control
Table 1: Demographic, haematological and biochemistry parameters of the study population

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Thalassemic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td><strong>M/F</strong></td>
<td>21/20</td>
<td>21/20</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>31.3+/-.8.3</td>
<td>33.2+/-.9.4</td>
</tr>
<tr>
<td><strong>Body surface area (m²)</strong></td>
<td>1.72+/-.0.19</td>
<td>1.62+/-.0.2</td>
</tr>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td>73.43+/-.7.18</td>
<td>69.56+/-.6.80</td>
</tr>
<tr>
<td><strong>Hemoglobin (g/dL)</strong></td>
<td>13.1+/-.0.8</td>
<td>9.9+/-.1.02</td>
</tr>
<tr>
<td><strong>NT-proBNP (pg/mL)</strong></td>
<td>97+/-.21</td>
<td>131+/-.248</td>
</tr>
<tr>
<td><strong>T2⁺ (msec)</strong></td>
<td></td>
<td>29+/-.10.7</td>
</tr>
</tbody>
</table>
Table 2: Conventional and Tissue Doppler echocardiography parameters of the thalassemia patients and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=41)</th>
<th>TM patients (n=41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LVEDD (mm)</strong></td>
<td>41 ± 5</td>
<td>46.39 ± 5.31</td>
<td>0.035</td>
</tr>
<tr>
<td><strong>LV mass (g)</strong></td>
<td>88 ± 27</td>
<td>127.25 ± 40.05</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>LV mass indexed (g/m²)</strong></td>
<td>54.4 ± 16.1</td>
<td>77.11 ± 19.98</td>
<td>0.022</td>
</tr>
<tr>
<td><strong>EF Teicholtz (%)</strong></td>
<td>67 ± 4</td>
<td>62.90 ± 5.42</td>
<td>0.034</td>
</tr>
<tr>
<td><strong>FS (%)</strong></td>
<td>36.8 ± 3.3</td>
<td>34.40 ± 4.32</td>
<td>NS</td>
</tr>
<tr>
<td><strong>LVEDV (ml)</strong></td>
<td>123.08 ± 26.48</td>
<td>98.74 ± 30.53</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>LVESV (ml)</strong></td>
<td>41.05 ± 14.59</td>
<td>20.90 ± 18.43</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>EF – Simpson (%)</strong></td>
<td>66.87 ± 6.39</td>
<td>61.67 ± 6.20</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>LA area (cm²)</strong></td>
<td>18.2 ± 2.4</td>
<td>17.37 ± 4.45</td>
<td>NS</td>
</tr>
<tr>
<td><strong>LA volume (ml)</strong></td>
<td>37 ± 15</td>
<td>48.11 ± 18.4</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>RA area (cm²)</strong></td>
<td>15.5 ± 2.3</td>
<td>15.59 ± 5.38</td>
<td>NS</td>
</tr>
<tr>
<td><strong>RA volume (ml)</strong></td>
<td>41 ± 13</td>
<td>42.4 ± 27.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Mitral inflow Doppler indexes**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=41)</th>
<th>TM patients (n=41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E veloc (cm/s)</strong></td>
<td>98 ± 11</td>
<td>99.95 ± 18.10</td>
<td>NS</td>
</tr>
<tr>
<td><strong>A veloc (cm/s)</strong></td>
<td>52 ± 8</td>
<td>61.78 ± 14.33</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>E/A ratio</strong></td>
<td>1.92 ± 0.33</td>
<td>1.69 ± 0.50</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>EDT (msec)</strong></td>
<td>199 ± 37</td>
<td>210.29 ± 44.35</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>IVRT (msec)</strong></td>
<td>78 ± 4.9</td>
<td>66.22 ± 11.01</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>TEI Index</strong></td>
<td>0.37 ± 0.06</td>
<td>0.40 ± 0.06</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Tricuspid inflow Doppler indexes**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=41)</th>
<th>TM patients (n=41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E veloc (cm/s)</strong></td>
<td>67 ± 11</td>
<td>65.42 ± 10.89</td>
<td>NS</td>
</tr>
<tr>
<td><strong>A veloc (cm/s)</strong></td>
<td>33 ± 5</td>
<td>49.12 ± 10.16</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>E/A ratio</strong></td>
<td>2.38 ± 0.2</td>
<td>1.35 ± 0.21</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>RV end-diastolic area (cm²)</strong></td>
<td>15 ± 2</td>
<td>13.33 ± 3.31</td>
<td>NS</td>
</tr>
<tr>
<td><strong>PAPs (mmHg)</strong></td>
<td>25.2 ± 3.6</td>
<td>29.88 ± 6.48</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**TDI velocities (cm/s)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=41)</th>
<th>TM patients (n=41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Septum S</strong></td>
<td>9.66 ± 1.39</td>
<td>10.75 ± 2.50</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Septum Em</strong></td>
<td>9.98 ± 2.50</td>
<td>16.19 ± 3.77</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>Septum Am</strong></td>
<td>7.38 ± 1.86</td>
<td>9.06 ± 2.61</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Septum E/Em</strong></td>
<td>6.62 ± 2.39</td>
<td>6.38 ± 1.73</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Tricuspid S</strong></td>
<td>12.47 ± 1.86</td>
<td>13.69 ± 2.17</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Tricuspid Em</strong></td>
<td>11.62 ± 2.51</td>
<td>12.47 ± 3.03</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Tricuspid Am</strong></td>
<td>10.62 ± 2.60</td>
<td>12.72 ± 3.57</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Tricuspid E/Em</strong></td>
<td>6.77 ± 2.17</td>
<td>7.05 ± 1.54</td>
<td>NS</td>
</tr>
</tbody>
</table>