Assessment of diastolic function with Cardiac Magnetic Resonance (CMR) in patients affected by #-thalassemia: a pilot study.

Poster No.: C-1015
Congress: ECR 2014
Type: Scientific Exhibit
Authors: M. Falcione¹, M. la Torre¹, G. Restaino², M. Missere², G. Sallustio², L. Bonomo¹, ¹Rome/IT, ²Campobasso/IT
Keywords: Cardiac, MR, Diagnostic procedure, Haematologic diseases
DOI: 10.1594/ecr2014/C-1015

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Aims and objectives

In #-thalassemia major patients are affected by severe anemia due to ineffective erythropoiesis and extravasal hemolisis, frequently requiring a regular transfusion program in order to ensure patient’s survival. However, patients needing regular transfusions may suffer from several side effects due to iron overload and iron toxicity.

Consequently, iron chelation therapy is often needed in order to lower body iron load and toxicities due to iron accumulation in several organs, such as heart, liver and endocrine glands. In particular, cardiac failure still represents the major cause of death in patients affected by #-Talassemia; in fact it has been clearly demonstrated that cardiac siderosis leads to systolic dysfunction and heart failure.

However, several authors\textsuperscript{1,2} have echocardiographically assessed diastolic function in #thalassemia patients, concluding that a ventricular diastolic dysfunction also exists, which appears earlier in patient’s life than systolic dysfunction and failure.

Cardiac Magnetic Resonance (CMR) represents a standardized and reproducible method which can be used to evaluate myocardial siderosis using T2$^*$ imaging, aiding in the detection of iron overload. CMR can also be used to obtain a morphological assessment of the atrial and ventricular chamber volumes, as well as myocardial wall thickness and myocardial mass. CMR is also able to provide information about diastolic function with several techniques, among which the most commonly used are the analysis of the transmitral flow with phase-contrast technique and the analysis of the ventricular filling through the measurement of quantitative parameters from the time-volume curve.

Since 2007, our Institution is involved in the MIOT (Myocardial Iron Overload in Thalassemia) project, a multi-center Italian study for the monitoring of #-Thalassemia patients using CMR with assessment of myocardial and hepatic iron load using T2$^*$-based sequences, measurement of cardiac function with b-SSFP sequence and assessment of myocardial fibrosis with late enhancement technique.

On the basis of this background, our aim has been to evaluate diastolic function in patient affected by #thalassemia involved in MIOT program with Cardiac Magnetic Resonance.
Methods and materials

Study samples

57 thalassemia patients (both major and intermedia), treated with transfusion and chelation therapy, were consequently studied from 2012 july to 2013 july, as part of the MIOT (Myocardial Iron Overload in Thalassemia) research study protocol to evaluate the myocardial and hepatic iron overload.

2 of the 57 patients were excluded due to the absence of the sequence Phase Contrast MRI in the survey, 5 were excluded due to poor quality of the scan and MRI lack of reliable functional measurements, 1 patient was excluded due to inability to obtain reliable data on the type of thalassemia disease.

The actual sample of the study was represented by 49 patients, including 43 with thalassemia major (TM), F:M =24:19, mean age 32.2 ± 10.7 years; 6 patients with thalassemia intermedia (TI) F:M = 3:3, mean age 34.8 ± 5.6 years.

The study was conducted in accordance with the principles of the Declaration of Helsinki and with the approval of the Ethics Committees of all institutions involved. All patients gave a written informed consent for voluntary participation in the research protocol both at the Reference Center for Thalassemia both at our institution on the day of the MR.

MRI technique

For all patients was employed the same 1.5 T MR scanner (GE Signa Excite HD, Milwaukee, WI) with phased-array 8-channel surface coil dedicated for cardiac imaging.

The sequences used for the evaluation of diastolic function and myocardial iron overload (integrated in the protocol MIOT) were:

GRADIENT ECHO multiecho (3 slices in the short axis) 10 images at increasing TE each, useful for the measurement of myocardial T2* (to estimate iron overload)

"FIESTA" - b - SSFP (balanced - Steady State Free Precession), for the analysis of volumes and function

PHASE CONTRAST (it is a gradient echo with flip angle of 25° and 20 stages of acquisition) useful for the assessment of transmitral flow

The technical parameters of the scans are shown in Table 1.
Iron overload analysis

The myocardial iron load was assessed by measurement of myocardial T2* evaluated with HippoMIOT dedicated software (IFC-CNR, Pisa, Italy). The software is able to extract a decay curve by calculating the average signal intensity obtained at different echo times. The decay curve was approximated to an exponential equation according to the formula:

\[ S = S_0 e^{-\frac{TE}{T2^*}} + C \]

ROIs were drawn manually by outlining the endocardial and epicardial contours of the left ventricle on short-axis images obtained at three levels: basal, mid-ventricular and para-apical levels. The results provided by the software include the value of T2* in msec for each of the 16 LV segments according to the conventional description of the AHA (except for the 17th segment, the apex), the global myocardial T2* and the average septum T2*.

The correlations between myocardial T2* and systolic and diastolic function were evaluated only for the 43 patients with thalassemia major.

Transmitral flow analysis

For the transmitral flow analysis we used the "CV Flow" Advantage Workstation software on the PC QF mitral Vasc Cine sequence comprising 20 MR images for the assessment of transmitral flow.

By outlining manually the mitral valve in all the phases of the cardiac cycle the software calculates a flow curve, whence, using algebraic proportions, we extrapolated the values of E-wave and A-wave velocity (Fig. 1) and the MDT value (mitral deceleration time, representative of the slope of the cE-wave projected on the horizontal axis and expressed in ms), adjusted for the duration of the RR interval.

We also measured the E/A ratio, and from the trans mitral flow curve, the area under the velocity curve (DVI), the area under the E-wave (Ea) and the A-wave (Aa) curves and their relationships (Ea/FVI, Aa/FVI and Ea/Aa).

Finally, we calculated the E/FVI ratio that expresses left ventricular diastolic function independently from the heart rate or the preload.

Systolic function and left ventricular filling analysis

In order to measure cardiac volumes and indices of systolic and diastolic function (EDV -end-diastolic volume-, ESV -end-systolic volume-, SVI -stroke volume index-, EDVI -end-diastolic volume indexed to body surface area, ESVI -end-systolic volume indexed to body surface area-, EF -ejection fraction-, HR -heart rate-, CI -cardiac index-, PER -peak emptying rate- and PFR -peak filling rate-), we used the LV_analysis Advantage
software, that allows the semi-automatic delineation of the endocardial and epicardial contours of the left ventricle in all slices and in all phases of the cardiac cycle.

**Statistical Analysis**

Software used: SPSS version 16.0.

The correlation analysis was performed using the Spearman test.

For comparison between means was used t-test for unpaired data.

It was considered statistically significant $P < 0.05$. 
Table 1: MRI sequences and plains used in the study

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Fig. 1

Results

Volumes and systolic function analysis

The LV volumes values are within normal limits (EDVI: 77 ± 15 ml; ESVI: 23 ± 8 ml), as well as cardiac output and cardiac index (6 ± 2 l/min, 3.8 ± 0.8 l/min/m²). The comparison between TM patients and TI patients showed statistically significant differences regarding the EDV, ESV, the EDVI, the ESVI, the CO and the CI, with all values higher in the group with TI.

All patients included in the study showed normal systolic function, with EF average of 70% (±6). The data are summarized in table 2.

Diastolic function analysis

The transmitral flow analysis showed a 2.1 mean value of the E/A ratio, higher than the usual; considering also the deceleration time (DT), in 23/49 patients (47 %) we observed a diastolic dysfunction pattern of restrictive type (DT <160 msec + E/A > 1.5); the TM group showed this pattern in 20/43 patients (47 %) while in the TI group this feature was found in 3/6 patients (50 %).

One TM patient showed a pattern of impaired relaxation type (DT > 240 msec).

None of these parameters showed statistically significant differences between the two groups of patients.

The values of Ea/DVI and Ea/Aa were above the normal range only in patients with TM, but the values of E/FVI were normal in both groups.

The PFR analysis showed average values of 636 ± 173 ml and PFR/EDV values of 5.1 ± 1.1, within normal limits. Only the PFR was significantly higher in the group of patients with TI compared to those with TM.

The data are summarized in Table 3.

Correlation between diastolic function and iron overload

The measurement of myocardial T2* detected an abnormal global T2* (<20 msec) in 9/49 patients (18%) all suffering from Thalassemia Major, 6 of which were females.
The correlation performed on the entire study population between myocardial T2* values and parameters of diastolic function (E, A, E/A and PFR/EDV) showed no significance values (Figures 2-4).

Considering only the patients with abnormal myocardial T2* (<20 msec) the correlation with the main parameters of diastolic dysfunction (E/A, PFR/EDV and E/FVI) was contradictory: a good correlation was found between the PFR corrected for EDV and T2* ($R^2 = 0.48$) and between the E/A ratio and T2* ($R^2 = 0.32$), with values directly proportional with increasing of the early myocardial iron overload (Figures 5-6) while it was detected no significant correlation between the value of E/FVI and myocardial T2* (Figure 7).

In the group of TM patients, the comparison between patients with pathological myocardial T2* and those with normal myocardial T2* showed no statistically significant differences regarding volumes and global systolic function of the left ventricle (Table 4).

Regarding the parameters of diastolic dysfunction, the comparison between the two groups (Table 5) showed values of E/A and Ea/FVI higher in the group with iron overload, albeit with p values still not significant (respectively $p = 0.14$ and $p = 0.09$) and value of Aa/FVI higher in the group without overload, also in this case without statistical significance ($p = 0.09$).

Statistically significant difference was instead observed for the parameter Ea/Aa, higher in the group with myocardial iron overload. The value of E/FVI, which expresses the extent of diastolic dysfunction, regardless of the heart rate and preload, showed no difference between the two groups ($p = 0.63$), similarly to PFR/EDV ($p = 0.57$), parameter of similar meaning.
Table 2: LV volumes and systolic function in patients with TM and TI

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<tr>
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<th>TI</th>
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<td>EDV (ml)</td>
<td>127±32</td>
<td>123±31</td>
<td>153±36</td>
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<td>ESV (ml)</td>
<td>39±15</td>
<td>37±15</td>
<td>51±14</td>
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<tr>
<td>SVI (ml)</td>
<td>88±20</td>
<td>87±19</td>
<td>102±23</td>
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<td>EDVI (ml/m³)</td>
<td>77±15</td>
<td>75±14</td>
<td>93±15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ESVI (ml/m³)</td>
<td>23±8</td>
<td>22±8</td>
<td>31±7</td>
<td>0.02</td>
</tr>
<tr>
<td>EF %</td>
<td>70±6</td>
<td>71±6</td>
<td>67±3</td>
<td>0.17</td>
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<tr>
<td>HR (bpm)</td>
<td>70±9</td>
<td>70±10</td>
<td>71±8</td>
<td>0.64</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>6±2</td>
<td>6±1</td>
<td>7.3±2</td>
<td>0.048</td>
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<tr>
<td>CI (l/min/m²)</td>
<td>3.8±0.8</td>
<td>3.7±1</td>
<td>4.4±1</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Table 3: Parameters of LV diastolic function in patients with TM and TI.
**Fig. 2:** Correlation between myocardial T2 * and the E value
Fig. 3: Correlation between myocardial T2 * and the E/A ratio

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**Fig. 4:** Correlation between myocardial T2* and PFR/EDV ratio

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![Graph showing correlation between myocardial T2* and PFR/EDV](image)

**Fig. 5:** Correlation between myocardial T2* and PFR/EDV in Patients with myocardial iron overload

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Fig. 6: Correlation between myocardial T2* and E/A ratio in Patients with myocardial iron overload.

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Fig. 7: Correlation between myocardial T2* and E/FVI ratio in Patients with myocardial iron overload.

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<tr>
<td>EDVI</td>
<td>74 ± 15</td>
<td>76 ± 15</td>
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<tr>
<td>SV</td>
<td>87 ±21</td>
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<tr>
<td>EF</td>
<td>69 ± 5</td>
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<tr>
<td>HR</td>
<td>72 ± 10</td>
<td>71 ± 9</td>
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<tr>
<td>CI</td>
<td>3.6 ± 0.7</td>
<td>3.7 ± 0.8</td>
<td>0.69</td>
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Table 4: Correlation between myocardial iron overload and LV systolic function

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<th>Parameters</th>
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<th>$T2^* \geq 20\text{ msec}$</th>
<th>$p$</th>
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<tbody>
<tr>
<td>PFR (ml/sec)</td>
<td>627 ± 223</td>
<td>617 ± 142</td>
<td>0.87</td>
</tr>
<tr>
<td>PFR/EDV (sec)</td>
<td>4.9 ± 1</td>
<td>5.1 ± 1.1</td>
<td>0.57</td>
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<tr>
<td>E (cm/sec)</td>
<td>79 ± 15</td>
<td>73 ± 12</td>
<td>0.23</td>
</tr>
<tr>
<td>A (cm/sec)</td>
<td>36 ± 9</td>
<td>39 ± 9</td>
<td>0.42</td>
</tr>
<tr>
<td>E/A</td>
<td>2.4 ± 0.9</td>
<td>2 ± 0.5</td>
<td>0.14</td>
</tr>
<tr>
<td>DT (msec)</td>
<td>155 ± 12</td>
<td>152 ± 37</td>
<td>0.84</td>
</tr>
<tr>
<td>Ea/FVI</td>
<td>0.69 ± 0.1</td>
<td>0.65 ± 0.1</td>
<td>0.09</td>
</tr>
<tr>
<td>Aa/FVI</td>
<td>0.20 ± 0.1</td>
<td>0.24 ± 0.1</td>
<td>0.09</td>
</tr>
<tr>
<td>Ea/Aa</td>
<td>3.98 ± 1.9</td>
<td>2.95 ± 1</td>
<td>0.03</td>
</tr>
<tr>
<td>E/FVI</td>
<td>4.16 ± 0.5</td>
<td>4.02 ± 0.9</td>
<td>0.63</td>
</tr>
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</table>

**Table 5:** Correlation between myocardial iron overload and LV diastolic function

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Conclusion

Our study about MRI evaluation of diastolic heart function in patients with thalassemia major and intermedia showed some interesting results.

Regarding the comparison between patients with TM and TI our study has confirmed what has already been observed by other echocardiographic studies documentong volumes and cardiac output significantly greater in the group of patients with TI.

There are only few information available in the literature about the cardiac involvement in patients with TI, often limited to the description of case reports. However, it is reasonable to expect a cardiac involvement in patients with TI, caused by following factors, known for a role in the pathogenesis of the so-called thalassemic cardiomyopathy: chronic anemia, resulting in a state of high flow rate, and cardiac overload of iron, more late compared to the accumulation in other organs.

The larger volumes of LV, the greater stroke volume and the higher cardiac index observed in the TI group are probably supported by the presence of chronic anemia, associated with increased blood volume due to the expansion of the bone marrow. The reduced ability of blood to carry an adequate amount of oxygen to peripheral tissues in these patients is offset by the increase in cardiac output. The venous return is increased and the significant volume overload is compensated through the Frank-Starling mechanism and a increased heart rate, which was observed in both groups.

Regarding the diastolic function in patients with thalassemia major and intermediate, our results are in line with those of the literature; in the work of Aessopos et al published in Chest in 2005, in which cardiac function was studied by echocardiography in 205 patients with TM and TI, the authors found the prevalence of diastolic restrictive pattern in 44% of patients with TM and 37% of those with TI; our values are respectively 47% and 50%. We believe that the discrepancy regarding the patients with TI is explained by their small number in our study sample (only 6). Like the literature data, in this study we didn't detect any significant difference regarding the DT.

In a recent work by Leonardi B et al., performed on 24 patients with transfusion-dependent thalassemia, the percentage of restrictive pattern is even 100%.

The meaning and the interpretation of the high prevalence of restrictive pattern observed in both groups studied (in agreement with previous literature) are not completely clear and could depend on different reasons.
The restrictive diastolic dysfunction is known to be associated with iron overload cardiomyopathy and some authors have suggested the use of the E/A ratio as a marker of early functional impairment of a LV with normal systolic function. However, the values of high preload and high cardiac output affect echocardiographic indices of diastolic function and MRI. Thus, the prognostic significance of echo findings on diastolic function has been questioned even in patients with TM.

Waldes-Cruz et al demonstrated abnormalities of LV systolic and diastolic function in children with asymptomatic beta-thalassemia using computer-assisted echocardiography. On the contrary, Bosi G et al found, in their echocardiographic study of 197 young adults with asymptomatic thalassemia, that the LV compliance of such patients is normal and the increased speed and integrals of the curve of transmitral flow can be explained by the condition of elevated cardiac output.

**Diastolic function and myocardial iron overload**

To our knowledge, only one work has compared the parameters of diastolic function measured by MRI with myocardial iron overload estimated through the measurement of myocardial T2*. In this work on 67 patients with TM, Westwood et al come to similar results to ours about the absence of significant correlation between parameters of diastolic dysfunction (PFR) and T2* in the entire study population. However, limiting the evaluation to the patients with myocardial iron overload (46 (69%) in their study), they also detect inverse correlation between values of PFR and T2*, weaker compared to our experience (r = -0.20). In our study, although the absolute number and percentage of patients with myocardial iron overload are much lower (9 patients, 18% of the sample), we observed a similar, but much more robust, negative correlation between the two indices (R2 = 0.48). The possible explanation may lie in the small size of our sample, but also in the fact that we have not considered the absolute value of the PFR, but the PFR/EDV value, as suggested in the literature to reduce the influence of preload on that parameter of diastolic dysfunction.

We also observed another correlation, less robust but undeniable, between myocardial T2* and E/A ratio (R^2 = 0.32), in agreement with the findings of Aessopos et al published in 2007.

Unlike these results, we didn't observe any correlation between iron overload and the E/FVI ratio (another parameter of diastolic dysfunction independent from heart rate and preload). We hope that future analysis on a larger sample may help to clarify the significance of this discrepancy.
There are only a few other studies of echocardiographic evaluation of diastolic function correlated with myocardial T2*. Leonardi B. et al, exactly like Westwood, didn’t found any significant correlation in their 2008 study.

In the study of Aessopos et al\textsuperscript{23}, published in 2007, a relatively high statistical correlation between E/A and myocardial iron overload measured with MRI (r = 0.48, p <0.0001) was demonstrated, but similar alteration of this index is also observed in patients without myocardial iron overload, suggesting that this parameter is not a specific characteristic of iron deposition rate, and that, perhaps, the state of high cardiac output has an impact on these values.

Vogel et al\textsuperscript{24} in 2002 (and even more recent works\textsuperscript{25,26}), showed good correlation between dysfunctional LV alterations measured with tissue Doppler and myocardial iron overload evaluated with T2*, even in patients with normal global systolic function.

The limitation of our study is certainly represented by the low number of patients and the low percentage of patients with myocardial iron overload, thanks to the excellent treatment received in the respective centers of Hematology. The analysis of a larger patient population will certainly reduce this limit and give our observations greater strength and significance.

The evidence, recently tested with cardiac CE-MRI\textsuperscript{27,28}, of the existence of areas of myocardial scar in thalassemia patients with iron overload opens a new chapter not yet investigated about the possible correlation between these foci of fibrosis and diastolic left ventricular dysfunction, as it has been demonstrated in patients with hypertrophic cardiomyopathy\textsuperscript{29}.

Our study has confirmed the presence of diastolic functional changes in young adult with both thalassemia major and intermedia and with normal systolic function.

Our results on the correlation between these diastolic dysfunction and extent of myocardial iron overload are conflicting, consistently with the existing literature on the subject.

Although the small size of our study sample does not allow conclusions supported by statistical significance, a trend of correlation between extent of myocardial iron overload and diastolic dysfunction seems to exist.
Personal information

M. Falcione, M. la Torre, L. Bonomo
Department of Bioimaging and Radiological Sciences.
Catholic University of Sacred Heart, Policlinico Universitario A. Gemelli, Largo Agostino Gemelli 8, 00168, Rome, Italy.

G. Restaino, M. Missere, G. Sallustio
Imaging Department
Catholic University of Sacred Heart, Fondazione di Ricerca e Cura Giovanni Paolo II, 86100 Campobasso, Italy

mail to: falcione.matteo@gmail.com
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