Characterization of chelation therapies in thalassemia patients by longitudinal analysis of MRI-assessed cardiac and hepatic iron overload

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Introduction. To date the gradient echo multiecho T2* MRI technique is the most robust method for the sensitive, fast, and reproducible quantification of cardiac and hepatic iron overload in thalassemia patients [1]. It has been demonstrated that longitudinal analysis of liver and heart T2* values during time could assess a lag between cardiac and liver iron burden changes [2]. The aim of this study was to extend the analysis to identify the relationship between different chelation regimes and liver and heart iron overload dynamic.

Materials and methods. Among the 193 thalassemia patients enrolled in the Myocardial Iron Overload in Thalassemia (MIOT) network [3] who underwent three or more MRIs we selected 55 patients that maintained the same chelation therapy among all the scans and who had at the first examination pathological liver and global heart T2* values (T2*<15.8 ms and T2*<26 ms, respectively) [4]. Liver T2* values were converted in LIC (liver iron concentration) by using the calibration curve presented in [5]. A 2-D plot with global heart R2* values (1000/T2*) in the vertical axis and LIC values in the horizontal axis was constructed, each point in the plot representing a MRI examination [2]. For each patient a trajectory was defined joining all the scans in chronologic order. The area under the curve (AUC) and the direction were measured for each trajectory. A positive area indicated that cardiac R2* changes lagged LIC changes.

Results. The mean time between two consecutive MR scans was 1.4 ± 0.4 years (range: 0.8-2.2 years).
Figure 1 shows the 55 obtained trajectories, the global trajectory for each group of patients under the same chelation therapy (desferoxamine: N=11, deferiprone: N=6, deferasirox: N=10, sequential desferoxamine-deferiprone: N=12, and combination desferoxamine+deferiprone: N=16) and the global trajectory for the whole patient population.
Figure 2 shows the relative changes in global heart R2* and LIC values. The desferoxamine and the deferasirox induced very similar changes. Combination and sequential treatments demonstrated the greatest changes in cardiac iron relative to changes in liver iron. In fact, combination therapy was the only therapy that had negative cardiac iron balance in the presence of neutral or positive hepatic iron balance. Deferiprone, alone, did not do this. This suggests an interaction between the two agents or an interaction between initial liver iron and change in R2*
Figure 3 shows the distribution of area under the curve measured for each of the trajectories. The magnitude of the positive area was higher than the magnitude of the negative area (89.1 vs -49.4; P=0.0001). The overall distribution, as well as the distribution within each single group had a positive skewness. 31 trajectories (56.4%) had a positive area and 24 (43.6%) had a negative area, suggesting the prevalence of a temporal delay between iron loading changes in liver and heart. The number of positive areas was not significantly different among the groups (desferoxamine: 9 (81.8%), deferiprone: 3 (50%), deferasirox: 5 (50%), sequential: 7 (43.8%), combination: 6 (18.8%); P=0.378), but the delay was more commonly associated with the use of desferoxamine.

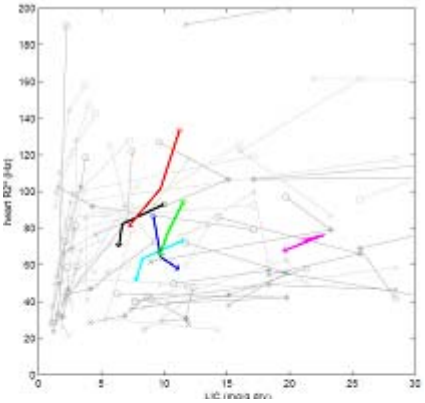

Figure 1

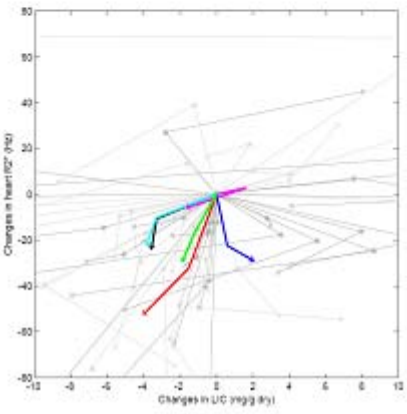

Figure 2

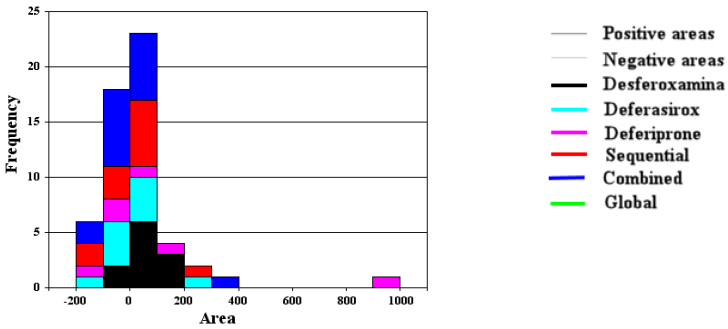

Figure 3

Conclusion. Longitudinal analysis of cardiac and hepatic iron overload by the proposed approach allows the characterization of chelation therapies efficacy and mechanism in thalassemia patients.

References: [1] Wood JC and Ghugre N. Hemoglobin 2008;32:85-96. [2] Noetzli L et al. Blood 2008;112:2973-2978. [3] Meloni A et al. Int J Med Inform 2009;78(8):503-512. [4] Ramazzotti A et al. JMRI 2009 ;30(1) :62-68. [1] Wood JC et al. Blood 2005;106:1460-1465.