Longitudinal Analysis of Heart and Liver Iron in Thalassemia Major

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Introduction: Conclusions regarding the relationship between heart and liver iron in patients with thalassemia major have been inconsistent. High hepatic iron concentration (HIC) is associated with heart disease caused by cardiac iron overload [1-3]. However, quantitative measures of heart and liver iron taken at the same time have no significant linear relation [4,5]. Since there clearly seemed to be a relation between HIC and cardiac iron (R2*), we explored whether representing the relation of cardiac R2*, a measure of cardiac [Fe] to HIC as a function of time would uncover a hidden relation.

Methods: A retrospective review of medical records from 38 patients with thalassemia major followed at Childrens Hospital Los Angeles was done for dates between 2002 and 2007. The eligible subjects underwent three or more MRIs to estimate their heart and liver iron content. The mean age of the patients was 20.6 ± 8.9 (range: 5.4 to 43.8). The average cardiac R2* at the beginning of analysis was 80.1 ± 94.5 Hz and the average HIC was 14.7 ± 11.9 mg/g dry weight liver. The average time between a patient's first and last MRI was 3.1 ± 1.2 years (range: 0.9 to 4.9 years). All patients were on chronic transfusions and on standard iron chelation for their iron overload. HIC was estimated by using liver R2 and R2* measurements. Liver R2 and R2* as well as cardiac R2* were determined by previously validated methods [6, 7]. For cardiac R2* measurements, echo times of 2, 3, 4, 6, 9, 12, 15, and 18 msec, and a fixed repetition time of 21 msec were used [6]. Liver R2* was measured using echo times automatically stepped at 0.25-msec intervals from 0.8 to 4.8 msec, and a fixed repetition time of 25 msec [7]. Liver R2 was measured using echo times of 3.5, 5, 8, 12, 18, and 30 msec, and a repetition time of 300 msec [7]. We determined the trajectory of cardiac iron change with respect to liver iron change by plotting R2* against HIC at each time point of longitudinal measures. Figure 1 is a schematic showing how hysteresis is measured for each trajectory by finding the center of mass of each trajectory and the area of each slice formed by connecting two adjacent points on the curve to the center of mass. Depending on whether the slice runs clockwise or counterclockwise with respect to the center of mass, it is given either a negative or positive area, respectively. The sum of the slices gives an overall negative or positive area that represents the amount and direction (clockwise or counterclockwise) of hysteresis for a trajectory.

Figure 1

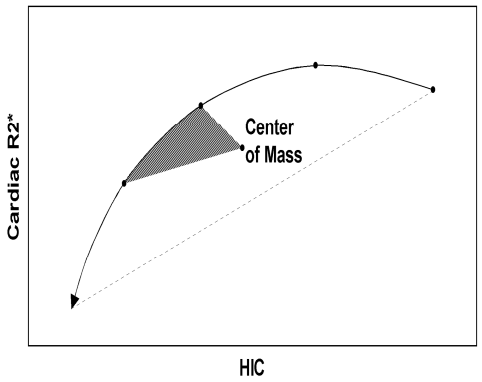
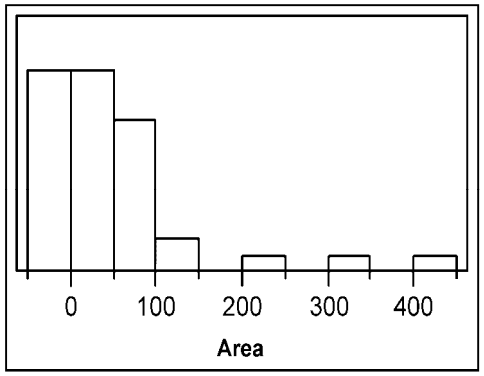


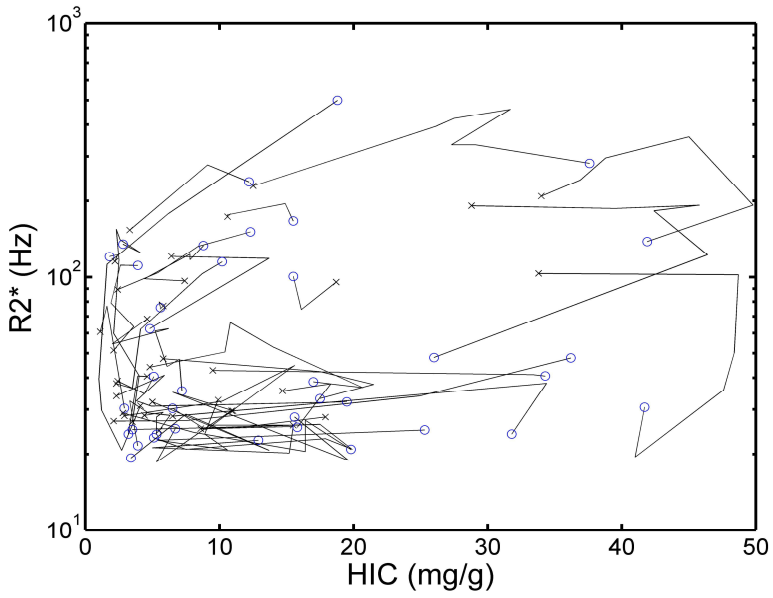
Figure 2



Results: Figure 2 is a histogram showing the distribution of the areas calculated for 38 trajectories. The distribution is positively skewed (mean=50.98; median=25.85), which indicates that there is more counterclockwise than clockwise movement when looking at all 38 trajectories. Figure 3 shows the relationship between HIC and cardiac R2* for the population of subjects. Each trajectory represents a patient's longitudinal HIC and cardiac R2* measurements. In each trajectory, the blue circle represents the initial HIC and R2* measurement and each following point represents a chronological measurement. Based on the results from figure 2, the general direction of the 38 trajectories in figure 3 is counterclockwise.

Discussion: Current population studies suggest that there is no relation between HIC and cardiac iron. While it is true that there is no linear relation between HIC and cardiac R2* measurements made at the same time, the data and analysis presented here suggests that a clear relation exists if a third variable, time, is included in the analysis. For this reason, longitudinal monitoring of liver and heart iron appears to better define the complex relationship between HIC and cardiac R2*. When HIC is plotted against cardiac R2* over time for individual patients, the trajectories form a counterclockwise hysteresis loop. This indicates a lag in the loading and unloading of iron in the heart with respect to the liver. The fact that it is counterclockwise (positive) suggests that the direction of change in R2* is the same as the direction of change in the previous HIC measurement. This time-lagged relation explains why cardiac disease is related to HIC and the direct relation between HIC and cardiac iron is not linear in population studies where cardiac iron and HIC are compared at the same point in time. This information can help predict the course of iron in the heart when the liver iron burden is known. Furthermore, if the warning signs of cardiac iron overload are better understood, it may be possible to prevent iron related heart complications.

Figure 3



Acknowledgements: GCRC (RR00043-43), NIH (1 R01 HL75592-01A1)

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