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Atrial dysfunction as a marker of iron cardiotoxicity in thalassemia major

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Abstract

We measured left atrial size and function from biplane MRI data in 62 adults with thalassemia major. Age-adjusted left atrial ejection fraction was depressed in 7 out of 20 subjects having T2* < 10 ms. Left atrial size, left ventricular size and cardiac output fell with cardiac iron loading, representing increased cardiac or peripheral vascular stiffness.

Keywords

thalassemia; diastolic function; systolic function; iron overload; MRI

Diastolic dysfunction precedes systolic function in many systemic diseases and leads to left atrial dilation and impaired atrial contraction.[1-4] We postulated that left atrial dilation and dysfunction would be earlier markers of iron cardiotoxicity than depressed ventricular function in thalassemia major subjects.

Study subjects

Sixty-two subjects with thalassemia major, age >18 years, underwent CMR at the Children's Hospital Los Angeles for assessment of hepatic and myocardial iron overload. Permission for retrospective data analysis was approved by the Committee for Clinical Investigation at the Children's Hospital of Los Angeles to retrieve cardiac MRI examinations performed from 1/3/2003 to 3/13/2007.

Magnetic resonance imaging

CMR scans were performed asynchronously with the transfusion cycle. All scans were performed using a torso coil on a 1.5 T General Electric CVi scanner. Left atrial volumes were calculated using the biplane area-length method,[2] using tools available on the Synapse PACS system. Left ventricular volumes were calculated as previously described.[5] All volumes were normalized to body surface area. Cardiac T2* measurements before 2006 were collected using a multiple breath-hold gradient-echo technique as previously described[6] and using a single breath-hold multiecho gradient echo technique thereafter. Cross-validation of these techniques in 27 subjects demonstrated a correlation coefficient of 0.96.[7]

Statistical analysis

Thalassemia-specific normative atrial data was obtained from subjects with no detectable cardiac iron (T2* >20 ms). Linear regression was performed to remove physiologic changes

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due to normal aging, yielding age and disease-specific Z-scores. A Z-score was considered abnormal if its absolute value was greater than or equal to 2. The effect of cardiac iron on Z-score was assessed by simple linear regression and by discrete stratification. Cardiac T2* values between 10 ms and 20 ms were categorized as intermediate-risk while T2* less than 10 ms were categorized as high-risk.

A total of 62 subjects had examinations suitable for atrial volume measurements. Average liver iron concentrations was 12.4±12.0 mg/g and mean cardiac R2* was 94.8±94.4 Hz. Patient genders were well-matched in subjects with no detectable cardiac iron (14 males, 12 females). However, cardiac iron loading was more than 2.5 times more common in women (26 *vs.* 10, p=0.05) reflecting either selection or survival bias.[8]

In subjects without detectable cardiac iron (T2* >20 ms), left atrial ejection fraction (LAEF) declined with age (r=0.54, *data not shown*) and indexed left atrial end-diastolic volume (LAEDVI) rose with age (r=0.49) consistent with physiologic decreases in ventricular compliance.[1]

Z-scores derived from these non-iron overloaded subjects were used to evaluate the effects of cardiac iron. Figure 1A demonstrates the downward drift in LAEF Z-score with increasing cardiac R2* (r=−0.4). Average Z-score in high-risk (T2* <10 ms) subjects was −1.39 (p<0.05) or 1.39 standard deviations below the predicted value for age.

LAEF was a more sensitive marker of cardiotoxicity than left ventricular ejection fraction (LVEF). Figure 1b compares LAEF and LVEF Z-scores. LAEF and LVEF are uncorrelated with one another. LAEF was depressed in both subjects who exhibited left ventricular dysfunction, but was also decreased in 5 high-risk subjects and 2 intermediate-risk subjects (10 ms <T2* <20 ms). In total, 7 out of 20 high-risk (T2* <10 ms) subjects had abnormal LAEF and 2 others were borderline (Z-score <−1.95), for a sensitivity of 35-45% for the detection of dangerous cardiac iron levels. LAEF Z-score did not vary with age for either intermediate or high-risk subjects.

Although one might expect left atrial dimensions to increase with ventricular iron deposition, the opposite phenomenon was observed (Figure 2). Z-scores for LAED-VI fell with increasing cardiac iron (top) and with age (bottom), suggesting that iron toxicity represents a combination of the intensity and duration of iron loading. Left atrial volume index was correlated with left ventricular end-diastolic volume index (r^2=0.57, *data not shown*), and with cardiac index (r^2=0.16, *data not shown*).

This study demonstrates that atrial volume and function are decreased by cardiac iron overload. Decreased atrial ejection fraction probably represents a combination of increased atrial afterload (through ventricular stiffening) as well as direct poisoning of the atrial muscle. Autopsy studies suggest greater iron deposition in the ventricles, compared with the atria, but the thin walls and relative muscular paucity of the left atrium may make it more vulnerable to even small amounts of tissue iron.[9] Regardless of the mechanism, depressed left atrial ejection fraction was 2.5-3.5 times more sensitive than depressed ventricular ejection fraction in identifying subjects with heavy cardiac iron burden. The practical implication of this observation is fairly clear. Most areas of the world do not have the means to assess cardiac iron burden by MRI, relying primarily on echocardiographic indices of cardiac volume and function. The biplane area-length metrics of atrial volume used in this paper were originally defined for and applied to two-dimensional echocardiography. Therefore, atrial ejection fraction may serve as a valuable marker of pre-clinical cardiac dysfunction in the developing world. LAEF assessments may also serve to complement T2* and LVEF measurements for risk stratification in centers routinely using cardiac MRI.

Decreased ventricular compliance is typically associated with left atrial dilation. Indeed, this was demonstrated with aging in subjects with a normal cardiac T2*. By contrast, cardiac iron led to lower atrial volumes than predicted. There are two possible explanations: (i) cardiac iron directly stiffens atrial walls, preventing their dilation in response to increased ventricular filling pressures, or (ii) cardiac iron lowers cardiac output through peripheral vasoconstriction. Since atrial volumes were correlated with ventricular volumes and cardiac output, we believe the latter explanation to be correct. Furthermore, cardiac T2* has already been shown to correlate with endothelial dysfunction.[10]

Our study was limited by its retrospective approach, relatively small patient numbers and restrictive cross-sectional analysis. Derivation of Z-scores from subjects having T2* < 20 ms, although controlling for the abnormal preload, afterload, and oxidative stress experienced by thalassemia subjects, was compromised by the small sample size.

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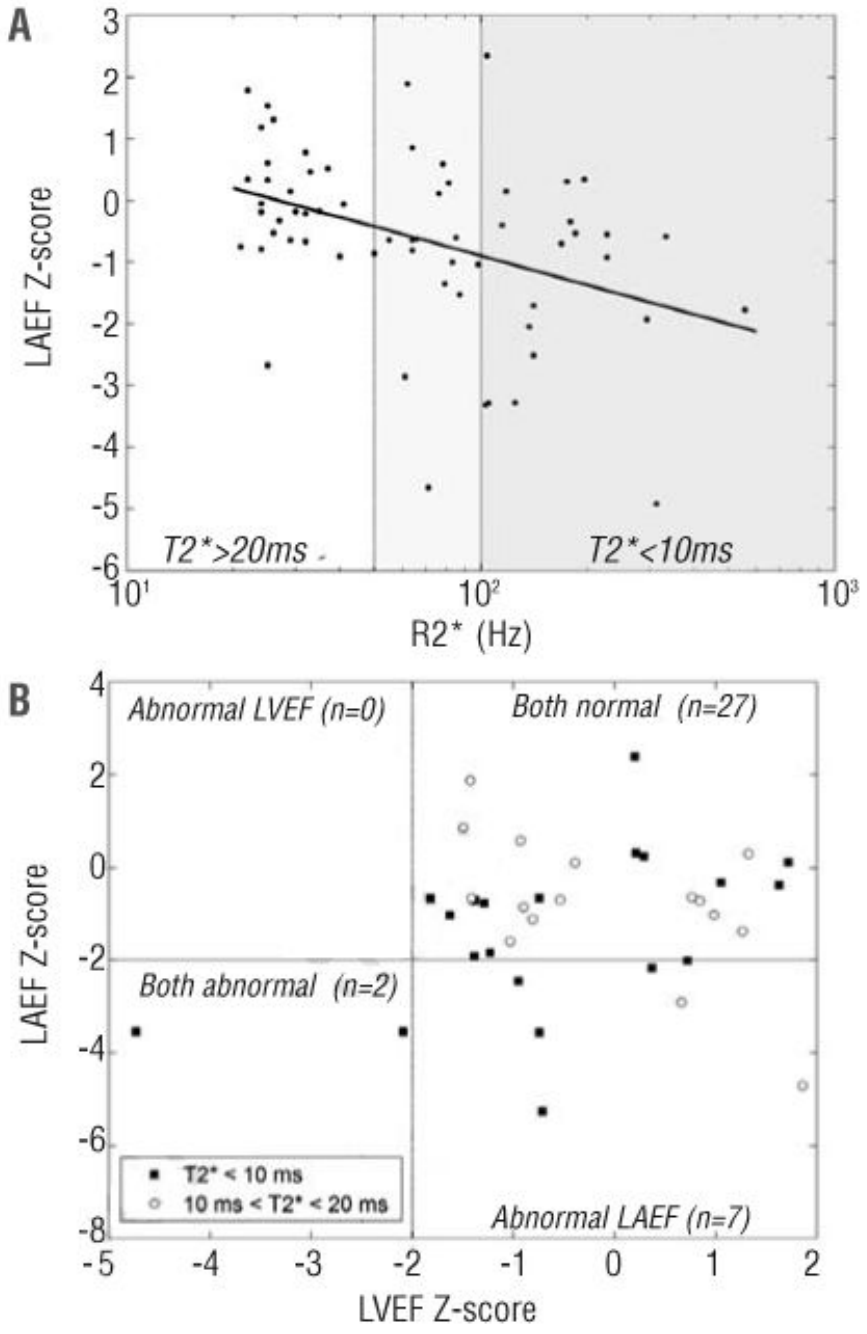

Figure 1.
Left atrial ejection fraction of iron overloaded thalassemia major patients: (A) comparison of LAEF Z-score and cardiac R2* (note the log scale); (B) comparison of LAEF and LVEF Z-scores.

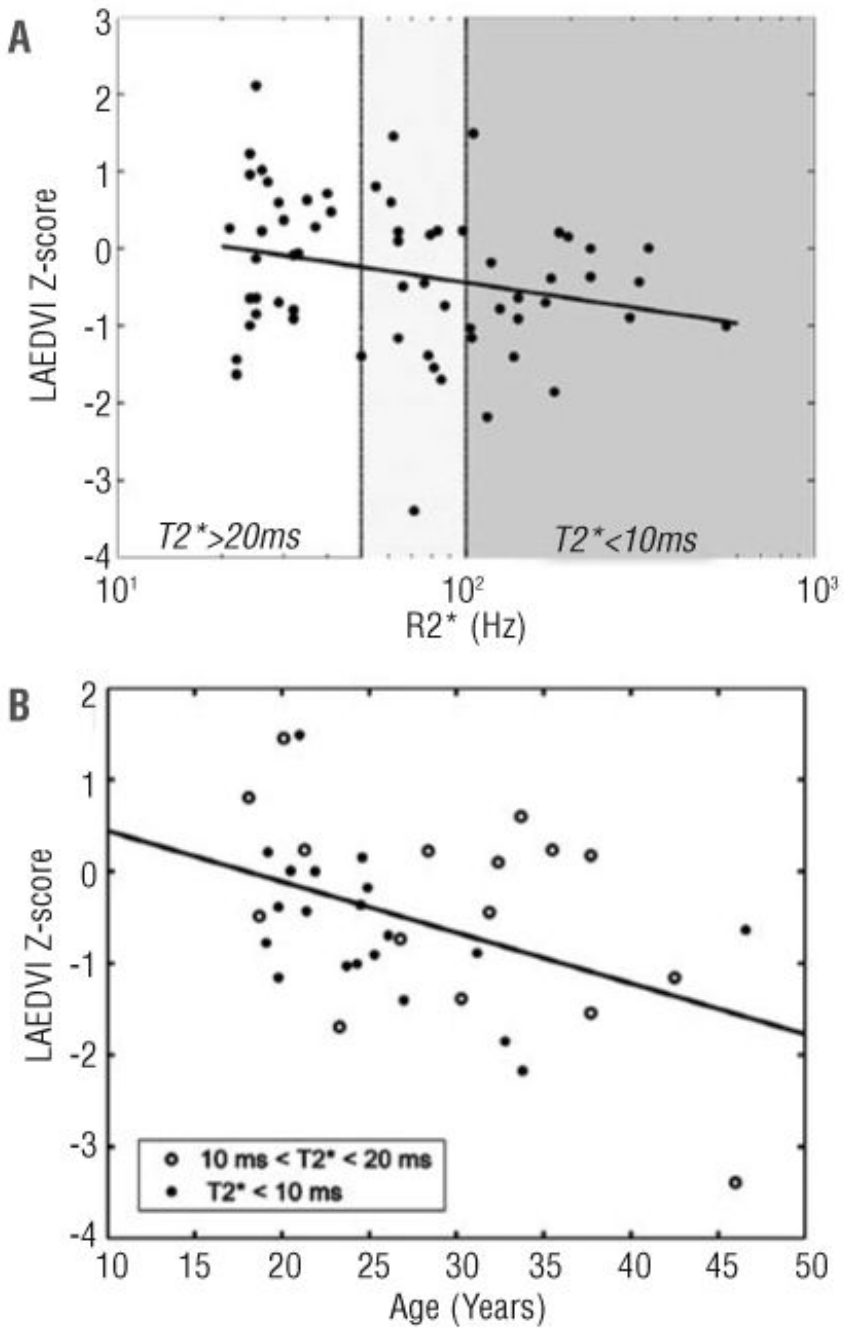

Figure 2.
Left atrial end-diastolic volume index of iron overloaded thalassemia major patients: (A) comparison of LAEDVI and cardiac R2* (note the log scale); (B) left atrial end-diastolic volume index Z-score of iron overloaded thalassemia major patients compared with age.