Relationship of Magnetic Resonance Imaging Estimation of Myocardial Iron to Left Ventricular Systolic and Diastolic Function in Thalassemia

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OBJECTIVES We sought to evaluate whether echocardiographic diastolic function indices correlate with myocardial iron and systolic function in patients with transfusion-dependent thalassemia (TDT) who are at risk for cardiomyopathy.

BACKGROUND In thalassemia syndromes, there is an important clinical need to risk stratify patients for the development of iron-overload cardiomyopathy so that chelation therapy can be adjusted and cardiac morbidity averted. This purpose may be served by measuring the magnetic resonance imaging (MRI)-derived parameter T2*, which varies inversely with tissue iron concentration but has limited availability. As diastolic dysfunction may precede systolic dysfunction, we sought to directly compare more readily available echocardiographic indices of diastolic function to myocardial T2* and ejection fraction (EF).

METHODS We identified 47 paired echocardiography and MRI examinations in 24 patients with TDT. Echocardiographic measurements of transmitral flow velocities (E, A), tissue Doppler velocities (E′), and left ventricular volume and EF were compared with MRI measurements of myocardial T2*, ventricular volume, and EF.

RESULTS All patients had a restrictive filling pattern (E/A ≥1.5 and deceleration time <140 ms) and normal relaxation. There was no significant correlation between E/E′ or the Tei index versus EF. Although E/A and E′ had statistically significant correlations with EF, the relationships were weak with all correlation coefficients <0.52. The parameters E/A, E′, E/E′, and the Tei index did not significantly correlate with myocardial iron concentration as assessed by MRI T2*. Increased myocardial iron as measured by T2* was strongly associated with lower left ventricular EF, with a T2* <9 ms having a sensitivity of 100% and specificity of 89% for MRI EF <50%.

CONCLUSIONS In patients with TDT, echocardiographic diastolic function parameters correlated poorly with EF and myocardial T2* and were thus not well-suited for risk stratification. Myocardial T2* had a strong relationship with EF and appears to be a promising approach for predicting the development of heart failure and for iron chelator dose adjustment.   (J Am Coll Cardiol Img 2008;1: 572–8) © 2008 by the American College of Cardiology Foundation

Although treatment with chronic blood transfusions and chelation therapy has improved survival in patients with thalassemia major, mortality remains high with heart failure caused by transfusion iron overload accounting for up to 71% of all deaths from this disease (1–5). Deterioration in left ventricular (LV) systolic function is often rapid and unpredictable in this condition, and once heart failure has developed, the prognosis is poor (6). There is thus an important clinical need to reliably risk stratify patients for the development of heart failure and arrhythmia so that chelation therapy can be intensified and cardiac morbidity averted.

One promising approach to this challenge has been the development of magnetic resonance imaging (MRI) techniques to noninvasively quantify myocardial iron content to detect pre-clinical evidence of potentially toxic levels within the myocardium. The MRI-derived relaxation time parameter, T2*, varies inversely with iron concentration because iron interferes with local magnetic field homogeneity. Elevated myocardial iron levels by T2* have been shown to be associated with depressed LV ejection fraction (EF) (7) and improve in concert with LV function during recovery (3,8,9). Nevertheless, the clinical impact of T2* assessment will likely be limited by the availability and cost of MRI examinations in much of the developing world where thalassemia is quite prevalent.

Left ventricular diastolic function might be a more sensitive marker of the adverse effects of excess myocardial iron overload than systolic function, as has been shown in ischemic heart disease. Diastolic function can be assessed by echocardiographic techniques, which are more readily available and less expensive than MRI. We therefore sought to directly compare echocardiographic indices of diastolic function to myocardial T2* and EF in a cohort of transfusion-dependent thalassemia (TDT) patients.

METHODS

Study population. A retrospective database review identified all patients with TDT who underwent both echocardiography and MRI T2* assessment at Children's Hospital Boston. All patients had been regularly transfused since early childhood to maintain hemoglobin levels above 10 g/dl. All patients were prescribed chelation therapy with deferox-amine typically beginning before the age of 7 years. The conventional chelation treatment was subcutaneous infusion of deferoxamine in a daily dose 30 to 50 mg/kg, 5 to 6 times per week. Chelation therapy was monitored by frequent estimation of ferritin. A serum ferritin level below 2,000 ng/ml was considered to be an indicator of successful treatment with deferoxamine. None of the patients were in heart failure at the time of imaging assessment, although some patients had a prior history of heart failure. Permission for a database and medical record review was granted by the Children's Hospital Boston Committee on Clinical Investigation.

MRI techniques and data analysis. Magnetic resonance imaging examinations were routinely performed within 10 days of transfusion. Iron in the myocardium was quantified by measuring T2* (1/R2*), a MR relaxation parameter that has been shown to vary inversely with tissue iron concentration (7,10,11). This technique has high reproducibility and inter-MRI scanner agreement (7,12–14). Magnetic resonance imaging measurements were performed using a 1.5-T clinical MRI scanner (initially a General Electric TwinSpeed, General Electric Medical Systems, Waukesha, Wisconsin; more recently a Philips Achieva, Philips Medical System, Best, the Netherlands) and a torso surface coil. Myocardial T2* was assessed from a single mid-papillary ventricular short-axis slice using a cardiac-gated, segmented, multiecho gradient echo sequence obtained in a single breath-hold, similar to the technique described by Westwood et al. (13). Eight echoes with a minimum echo time (TE) of 2.0 ms, an echo spacing of 2.2 ms, and a repetition time of 19.1 ms were obtained.

The T2* values were calculated using custom-written software developed in MATLAB (The MathWorks, Natick, Massachusetts) by Dr. John C. Wood and adapted by Dr. Yansong Zhao. A region of interest was manually defined encompassing the ventricular septum. The signal decay of each pixel within the region of interest was fit to a monoexponential decay with a constant offset [$S = S_0 \exp(-TE \times R2^*) + C$]. The mean value was used as the R2* for that region and its reciprocal was taken to yield T2*.

Measurements of ventricular EF were made using standard MRI techniques. A stack of 12 short-axis slices positioned to cover the entire ventricle were obtained using an ECG-gated, segmented

ABBREVIATIONS AND ACRONYMS

DT = deceleration time

EF = ejection fraction

IVRT = isovolumic relaxation time

LV = left ventricular

MRI = magnetic resonance imaging

TDT = transfusion-dependent thalassemia

breath-hold steady-state free precession cine sequence. Ventricular volumes were measured off-line using commercially available software (MASS, Leiden, the Netherlands) with manual identification of myocardial borders and a summation of disks algorithm. Systolic LV dysfunction was defined as mild if the EF was 41% to 55%, moderate if 31% to 40%, and severe if ≤30%.

Echocardiography. Complete 2-dimensional, Doppler, and tissue-Doppler echocardiography was performed, using Sonos 5500 or 7500 Philips ultrasound systems (Philips Medical Systems, Andover, Massachusetts). Left ventricular end-diastolic and end-systolic volumes were calculated using a modified Simpson's algorithm based on long- and short-axis images, and the EF was calculated. Systolic LV dysfunction was defined as mild if the EF was 41% to 55%, moderate if 31% to 40%, and severe if ≤30%. Left ventricular diastolic function was assessed using pulsed-Doppler samples of mitral inflow and pulsed-tissue Doppler at the level of the lateral wall of the mitral annulus. Standard diastolic indices were recorded, including early (E) and late (A) transmitral peak flow velocities, early deceleration time (DT), and LV isovolumic relaxation time (IVRT). Deceleration time was measured as the time between the peak E velocity and the point where the velocity returns to 0. The peak velocities (cm/s) of the myocardial systolic wave and of the early (E′) and late (A′) diastolic tissue Doppler signals were measured and the E/E′ ratio was calculated. The pattern of LV filling was classified as restrictive if E/A >1.5 and DT <140 ms, as impaired relaxation if E/A ≤0.75, and as pseudonormal if (0.75 < E/A ≤1.5 and DT >140 ms and E/E′ ≥10) (15). The IVRT, LV ejection time (ET), and duration of mitral closure (DMC) were measured from pulsed-Doppler samples as the time from the end of antegrade flow across the LV outflow tract to the onset of the diastolic mitral inflow signal, the duration of antegrade flow across the LV outflow tract, and the time from the termination to the onset of the diastolic mitral inflow signal, respectively. Isovolumetric contraction time (IVCT) was calculated as DMC − (ET + IVRT). The Tei index was calculated as (IVCT + IVRT)/(ET) (16).

Statistical analysis. Correlations between the myocardial T2* and the indices of LV systolic and diastolic function were calculated using least-square linear regression. A p value of <0.05 was considered statistically significant. The sensitivity and specificity of T2* for ventricular dysfunction on

MRI or echocardiography were evaluated using receiver operating characteristic curve analysis.

RESULTS

Patients. A total of 24 patients (15 male, mean age 28 ± 10 years, age range 11 to 48 years) were identified with TDT who underwent both echocardiography and MRI T2* assessment. Mean pre-transfusion hemoglobin level was 9.1 ± 1.9 g/dl (range 6.1 to 12.1), and the average serum ferritin level was 2,380 ± 2,002 ng/ml (range 79 to 7,727 ng/ml).

Echocardiography findings. There were 80 echocardiograms available in this cohort. The mean LV end-diastolic volume, end-systolic volume, and EF were, respectively, 158 ± 65 ml, 77 ± 51 ml, and 53 ± 12%. The mean E/A, E/E′, and E′ were, respectively, 2.4 ± 0.69, 7.3 ± 5.44, and 15 ± 5 cm/s. The mean Tei index was 0.56 ± 0.15. All patients had a restrictive filling pattern (E/A ≥1.5 and DT <140 ms) and normal relaxation. The echocardiographic EF had a significant negative correlation with E/A (r = 0.27, p < 0.05) and a significant positive correlation with E′ (r = 0.38, p < 0.01) but was not significantly correlated with E/E′ (r = 0.08, p = 0.59) or the Tei index (r = 0.22, p = 0.23). No threshold effects were observed.

There were 47 paired echocardiograms and MRI examinations in the 24 patients within 1 month of each other and the comparison between echocardiography and MRI was restricted to this subset. The results for this subset of echocardiographic examinations were similar to the overall results with a mean LV end-diastolic volume, end-systolic volume, and EF of 156 ± 57 ml, 72 ± 44 ml, and 55 ± 12%, respectively. Systolic function as measured by echocardiographic EF was classified as normal in 32 cases, mild dysfunction in 9 cases, moderate dysfunction in 4 cases, and severe dysfunction in 2 cases.

MRI findings. There were 47 MRI examinations in the 24 patients that were performed within 1 month of an echocardiogram. The mean LV end-diastolic volume, end-systolic volume, and EF derived from MRI were 172 ± 62 ml, 79 ± 46 ml, and 56 ± 11%, respectively. Systolic function as measured by EF was classified as normal in 33 cases, mild dysfunction in 7 cases, moderate dysfunction in 6 cases, and severe dysfunction in 1 case.

Myocardial T2* was obtained in all but 2 examinations. Among the 24 patients, T2* on the first MRI study was abnormal (<20 ms) (13) in 13 patients

with 7 of them having a T2* <10 ms. There was a significant correlation between 1/T2* and EF by MRI (r = 0.58, p < 0.001) and between 1/T2* and EF by echocardiography (r = 0.62, p < 0.001). As shown in Figure 1, the relationships between T2* and EF were highly nonlinear with a threshold effect clearly evident. Receiver operating characteristic analysis was used to explore the sensitivity and specificity of threshold values of T2* for ventricular dysfunction, and the results of this analysis are presented in Figure 2. Using a T2* threshold value of 9 ms, sensitivity = 1 and specificity = 0.89 for a MRI EF <50%, sensitivity = 0.77 and specificity = 0.87 for a MRI EF <55%, sensitivity = 1 and specificity = 0.83 for echocardiographic EF <50%, and sensitivity = 0.71 and specificity = 0.84 for an echocardiographic EF <55%. There was a significant correlation between myocardial 1/T2* and serum ferritin (r = 0.45, p < 0.01). The correlation between myocardial 1/T2* and age was not significant (r = 0.13, p = 0.41).

Comparison between MRI and echocardiography. Magnetic resonance imaging EF had a significant negative correlation with E/A (r = 0.52, p = 0.002) and a significant positive correlation with E′ (r = 0.39, p = 0.03), but was not significantly correlated with E/E′ (r = 0.11, p = 0.54) or the Tei index (r = 0.42, p = 0.06). In contrast, myocardial 1/T2* was not significantly correlated with E/A (r = 0.15, p = 0.42), E/E′ (r = 0.27, p = 0.15), E′ (r = 0.21, p = 0.26), or the Tei index (r = 0.06, p = 0.78).

Left ventricular size and function measurements by MRI and echocardiography were compared in the 47 instances with paired studies. End-diastolic and end-systolic volumes by the two techniques had fairly good agreement (mean difference ± standard deviation 14.6 ± 22.1 ml) with MRI volumes being on average 14% higher than those obtained by echocardiography. Ejection fraction was highly correlate with no significant difference between the 2 modalities (mean difference ± standard deviation 0.5 ± 5.1%). Classification of severity of dysfunction (as defined in the Methods section) by echocardiography and MRI agreed in 39 of 47 instances and was different by no more than 1 category in all instances.

DISCUSSION

This study compared echocardiographic indices of diastolic function to myocardial T2* and EF in a cohort of 24 TDT patients. We found that all
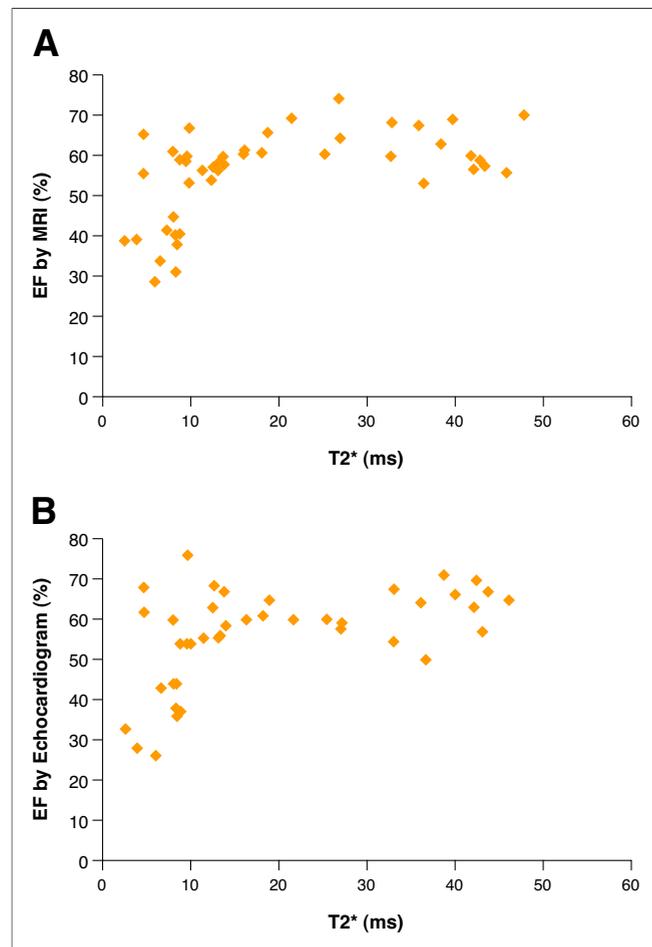

Figure 1. Relationship Between EF and Myocardial T2*

Among 24 subjects with transfusion-dependent thalassemia, there were 47 paired echocardiograms and magnetic resonance imaging (MRI) examinations performed within 1 month of each other. Left ventricular ejection fraction (EF) was measured with both echocardiography and MRI. Myocardial T2*, a parameter that varies inversely with tissue iron concentration, was measured by MRI and T2* <20 ms indicates an elevated iron level. The figure shows the relationship between myocardial T2* and percent EF measured by MRI **(A)** and by echocardiogram **(B)**. Note that all patients with a depressed EF (<50%) by either modality have evidence of elevated myocardial iron but that not all patients with elevated myocardial iron have a depressed EF.

patients had a restrictive filling pattern (E/A ≥1.5 and DT <140 ms) and normal relaxation. There was no significant correlation between E/E′ or the Tei index versus LVEF (measured by either MRI or echocardiography). Although E/A and E′ had statistically significant correlations with EF, the relationships were weak (all correlation coefficients <0.52). The parameters E/A, E′, E/E′, and the Tei index did not correlate with myocardial iron concentration (1/T2*). In contrast, we found that increased myocardial iron as measured by T2* was strongly associated with lower LVEF, with a T2*
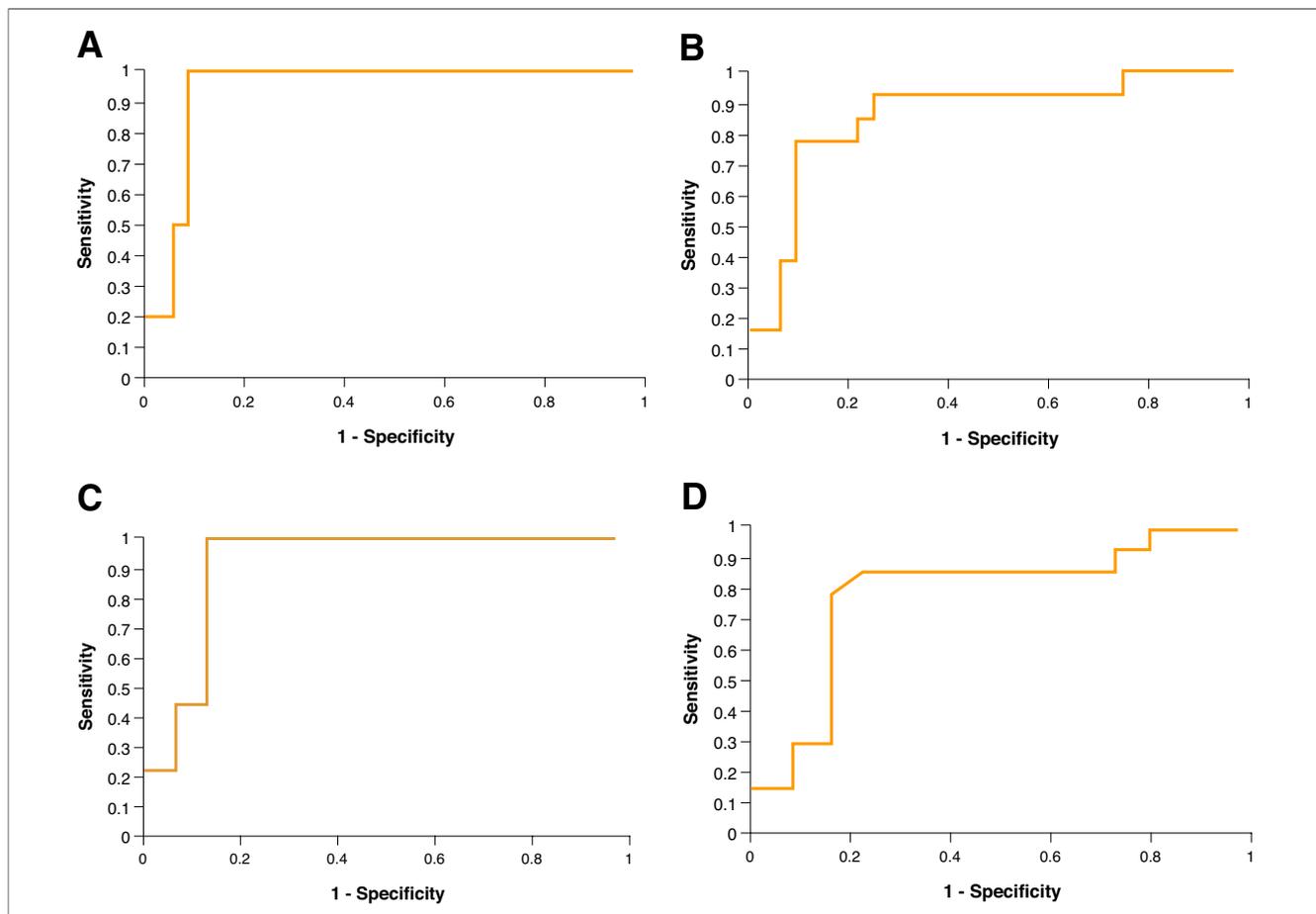
Figure 2. Receiver-Operating Characteristic Curve Analysis

A receiver operating characteristic curve analysis was used to explore the sensitivity and specificity of threshold values of myocardial T2* for left ventricular dysfunction. Using a T2* threshold value of 9 ms, sensitivity = 1 and specificity = 0.86 for a MRI EF <50% **(A)**, sensitivity = 0.77 and specificity = 0.85 for a MRI EF <55% **(B)**, sensitivity = 1 and specificity = 0.83 for echocardiographic EF <50% **(C)**, and sensitivity = 0.71 and specificity = 0.84 for an echocardiographic EF <55% **(D)**. Thus myocardial T2* had a strong relationship with EF and appears to be a promising approach for predicting the development of heart failure and for iron chelator dose adjustment. Abbreviations as in Figure 1.

<9 ms having a sensitivity of 100% and specificity of 89% for a MRI EF <50%.

The principal goal of a cardiac surveillance program in patients with TDT is to allow optimal titration of iron chelator medications to prevent the development of cardiac dysfunction and arrhythmia while avoiding chelator-associated toxicities. Periodic monitoring of systolic function is not adequate for this task because of the rapid deterioration in systolic function that is commonly observed (inadequate sensitivity) (6). Left ventricular diastolic dysfunction precedes the onset of systolic dysfunction in ischemic cardiomyopathy. Therefore, some researchers have proposed that LV diastolic function may be more sensitive as an early marker of myocardial iron overload and thus serve as a guide for adjusting chelator therapy. Several noninvasive techniques have been used in clinical practice to

assess LV diastolic function in TDT, including radionuclide ventriculography (17), Doppler echocardiography of transmitral flow, and tissue-Doppler imaging (17–19). Although the presence of abnormalities of diastolic function is often noted in the absence of systolic dysfunction, as we also found in this study, the clinical significance of these abnormalities remains unclear. The potential clinical utility of subclinical diastolic functional abnormalities is the identification of patients at high risk for systolic dysfunction and clinical heart failure. The ability of diastolic function indices to identify TDT patients who are at risk for heart failure has not been shown by others (17–19) and is not supported by our data. We found that diastolic function indices were abnormal in this cohort, regardless of systolic function. Although we did identify a statistically significant relationship be-

tween several of the echocardiographic indices of diastolic function and LVEF, the correlations are too weak for this to be a clinically useful method for adjusting chelator dose. An important potential confounder in this regard is the pre-load dependence of these diastolic indices, because the periodic variation in blood volume associated with development of anemia and the regular administration of blood transfusions in TDT have a significant effect on pre-load. Although tissue-Doppler imaging has been shown to be less pre-load dependent than mitral valve Doppler in assessing diastolic function (20,21), this dependence is not eliminated.

Another approach to assessing the potential utility of diastolic function parameters in TDT is to compare them with myocardial MRI T2* measurements. Myocardial T2* has been shown to correlate well with biopsy-derived iron concentration in the heart (10,22–24), and myocardial T2* values <20 ms (indicating elevated iron) were found to be associated with LV dysfunction (7,25) and improve in concert with LV function during recovery (3,8,9). Our data are in agreement with these prior studies and showed a strong association between T2* values <9 ms and depressed LVEF. However, we failed to identify a significant correlation between the diastolic function parameters E/A, E′, and E/E′ and myocardial T2*, suggesting that these are a poor reflection of myocardial iron concentration. There are only few other reports comparing echocardiographic diastolic function indices with myocardial T2*. Aessopos et al. (26) related a variety of parameters including E, A, and E/A but not tissue-Doppler indices to myocardial T2*. They found statistically significant correlations between A and E/A versus T2* but these were not strong (r < 0.5) and lacked discriminatory power to identify patients with myocardial iron overload yet normal systolic function. Vogel et al. (18) found that although abnormal tissue-Doppler measurements were more common in thalassemia patients with myocardial iron overload, they were also present in 35% of patients with a normal T2*,

yielding a specificity of only 65% to detect abnormal iron loading. Westwood et al. (27) used MRI-derived ventricular volume-time curves to measure early and atrial peak filling rates and found that diastolic parameters were weakly correlated with myocardial iron loading. These reports are in agreement with our findings in that they identify that abnormal diastolic function indices are frequently present in TDT patients but have insufficient specificity to identify patients who are at risk for developing systolic dysfunction.

Study limitations. The principal limitation of our study is its relatively small sample size, which diminishes its power to detect associations between diastolic parameters and EF and myocardial T2*. Nevertheless, there were a sufficient number of patients and range of LV function to allow identification of a strong relationship between myocardial T2* and LV function. In addition, the application of standard adult criteria for defining a restrictive filling pattern to a patient group with chronic and cyclical volume overload may have limitations. The clinical implications of a restriction in this setting may not be the same as in patients with other causes of cardiomyopathy.

CONCLUSIONS

None of the echocardiographic diastolic function parameters examined in this study were found to be suitable for cardiac surveillance in TDT patients. Myocardial T2* measured by MRI, in contrast, had a strong relationship with LVEF and appears to be a promising approach for cardiac risk stratification and iron chelator dose adjustment in patients with TDT. Longitudinal studies are needed to evaluate the utility of echocardiographic and MRI parameters to predict cardiac events.

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Key Words: thalassemia ■ myocardial T2* ■ diastolic function ■ cardiac siderosis.