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Electrocardiographic consequences of cardiac iron overload in thalassemia major

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Abstract

Background—Iron cardiomyopathy is a leading cause of death in transfusion dependent thalassemia major (TM) patients and MRI (T2*) can recognize preclinical cardiac iron overload, but, is unavailable to many centers.

Design and Methods—We evaluated the ability of 12-lead electrocardiography to predict cardiac iron loading in TM. 12-lead electrocardiogram and cardiac T2* measurements were performed prospectively, with a detectable cardiac iron cutoff of T2*less than 20 ms. Patients with and without cardiac iron were compared using two-sample statistics and against population norms using age and gender-matched Z-scores.

Results—45/78 patients had detectable cardiac iron. Patients having cardiac iron were older and more likely female but had comparable liver iron burdens and serum ferritin. Increased heart rate (HR) and prolonged corrected QT interval (QT_c) were present, regardless of cardiac iron status. Repolarization abnormalities were the strongest predictors of cardiac iron, including QT/QT_c prolongation, left shift of T-wave axis, and interpretation of ST/T-wave morphology. Recursive partitioning of the data for females using T-axis and HR and for males using QT, HR and T-axis produced algorithms with AUROC's of 88.3 and 87.1 respectively.

Conclusions—Bradycardia and repolarization abnormalities on 12-lead electrocardiography were the most specific markers for cardiac iron in thalassemia major. Changes in these variables

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Authorship

Contribution: J.W. was the principal investigator. He recruited patients, interpreted cardiovascular studies, performed statistical analysis and wrote the paper. L.N. coordinated the study personnel and patients and reviewed the paper. P.H. recruited patients for the study and reviewed the paper. T.C. recruited patients for the study and reviewed the paper. Y.B.C. supervised ECG interpretation and reviewed the paper. F.D. provided statistical support and reviewed the paper. J.D. interpreted ECG data, performed statistical analyses, and wrote the paper.

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may be helpful to stratify cardiac risk when cardiac MRI is unavailable. However, diagnostic algorithms need to be vetted on larger and more diverse patient populations and longitudinal studies are necessary to determine reversibility of the observed abnormalities.

Keywords

Electrocardiogram; Thalassemia Major; Cardiac Iron; MRI

Introduction

Thalassemia is the most common hereditary disease in the world[1, 2]. Transfusion therapy, for thalassemia major prevents many of the complications introduced by ineffective erythropoiesis but produces toxic iron accumulation in the endocrine glands and heart. Congestive heart failure is the leading cause of morbidity and mortality in this population but sudden cardiac death can also occur, even in the absence of known cardiac dysfunction[1, 3, 4]. Monitoring cardiac function with echocardiography is the standard of care for TM patients, however, diastolic and systolic dysfunction are later signs of iron overload[5, 6]. Monitoring for rhythm disturbances is done using electrocardiography (ECG) and ambulatory Holter monitoring, however many changes seen are considered non-specific[7, 8].

MRI evaluation of iron overload using T2* imaging has given the clinician the ability to quantify iron loading, prior to clinical manifestations, in all organ systems, including the heart[9–12]. Once present, cardiac iron deposits are difficult to clear, having a half life of more than 19 months even with optimal therapy[13]. Thus prevention of cardiac iron accumulation is a key goal of iron chelation therapy. Maintenance of low serum ferritin and liver iron concentration are important therapeutic goals in their own right but do not convey complete cardiac protection [14, 15]. As a result, some thalassemia centers routinely screen their patients with cardiac MRI to detect preclinical cardiac iron deposition. A cardiac T2* lower than 20 ms is indicative of cardiac iron and a T2* below 10 ms conveys significant prospective risk for cardiac dysfunction[16]. As a result, cardiac T2* has become standard of care for the evaluation of pre-clinical cardiac iron load, at institutions capable of making the measurements.

Unfortunately, many centers still lack the ability to perform cardiac T2* measurements. Disease burden is heaviest in regions with significant economic barriers to routine MRI use. Thus the goal of this study was to determine whether standard 12 lead electrocardiogram analysis could be used to “predict” cardiac iron deposition. Specifically, we hypothesized that many of the nonspecific changes observed in electrocardiograms from thalassemia major patients would be relatively more common in those with cardiac iron overload.

Methods

Patient Selection

Patients with a diagnosis of Thalassemia Major were enrolled in a prospective NIH funded study to determine the ability of standard cardiovascular assessments to predict cardiac iron loading. The institutional review boards at Children’s Hospital Los Angeles and Children’s Hospital Oakland approved this study. Inclusion Criteria for study participants was: current chronic transfusion therapy defined as greater than 8 transfusions per year, patients greater than 7 years of age. Exclusion Criteria for study participants was: contraindication to MRI, including MRI incompatible metal implants, pacemakers, and intractable claustrophobia; pregnancy; patients, who in the judgment of their referring physicians or principal investigator, are too ill to participate; history of successful bone marrow transplantation.

Patients underwent MRI cardiac iron (T2*) measurements and standard 12 lead electrocardiogram during a single study visit. Instrumentation difficulties sometimes prevented simultaneous acquisition but average time delay between the two studies was 3.0 +/- 8.3 days [range 0 to 45]. Examinations were performed between 3 and 10 days following their prior transfusion.

ECG

Standard 12-lead ECG's were performed using a GE MAC 550 ECG machine with software version 9, revision A. All intervals, axes, and heart rates were taken from the standard ECG software. The QRS-T axis angle was calculated using the frontal plane measurements from the standard ECG software as described in Zhang et al., spatial QRS-T axis angle in three dimensions was not used.[17] All ECG interpretations were over-read by a cardiologist, not familiar with the patients in the study and screened from the patients' MRI results. Long QT was defined as a corrected QT interval > 450 ms in males and >460 ms in females[18]. Sinus bradycardia was defined as a resting heart less than 60 in an adult and below the 2.5% percentile for pediatric patients.

MRI

All cardiac MRI examinations were performed using a 4-element torso phased array coil and a 1.5 Tesla General Electric CVi scanner running system 9.1 Cardiac T2* measurements were performed using a validated multiecho gradient-echo sequence with 8 echoes spaced between 2 and 17.6 ms. Images were fit, pixelwise, to a monoexponential decay plus a constant offset[19–21]. Cardiac function measurements were measured using steady state free precession acquisition in the short axis plane. Left ventricular volumes and ejection fractions were calculated from 15 contiguous slices using MASS 4.0 (Medis, The Netherlands). Using this software package, a left ventricular ejection fraction < 56% is considered abnormal unlike higher values observed with CMR Tools software.

Statistics

Since our primary goal was to identify ECG parameters that predict cardiac iron deposition, patients were separated into two groups based upon a T2* greater than 20 (no detectable cardiac iron) or T2* ≤ 20 ms (detectable cardiac iron). To account for potential age and gender bias between the groups, age and gender matched Z scores were created for ECG based on a large population study of normal individuals[22]. Norms for P and T wave axis could not be obtained from the literature. To compensate, P and T wave axis Z-scores were estimated in the patients lacking detectable cardiac iron, using linear regression with respect to age; in our data, sample size was too small to correct for gender as well. Z-scores for patients having T2* less than 20 ms were then calculated by subtracting the predicted value divided by the mean-squared error of the regression. Student's T-test was used to compare continuous data with a normal distribution and Mann Whitney Rank Sum Test was used to compare data with a non-normal distribution. One-sample T-test was used to determine whether average Z-scores were abnormal.

The physician's narrative interpretation of the ECG was also logged and sensitivity, specificity, negative predictive value and positive predictive value of predicting cardiac iron were determined based on those narratives versus T2*.

Multivariate logistic regression was done to determine which ECG parameters were associated with cardiac iron overload. Multiple regression tree analyses were then created using recursive partitioning to determine the relationship of those ECG parameters found on multivariate logistic regression.

Results

79 patients with Thalassemia Major were enrolled in the study ranging from ages 9 years to 47 years. Ethnic background reflected the diversity of the American West Coast, 20 Chinese, 16 non-Chinese Far East, 14 Indian/Pakistani, 16 Mediterranean, and 13 other assorted backgrounds. Genotypes were not available in all subjects, but were predominately beta thalassemia major, with a few E-beta thalassemia patients and two known alpha thalassemia patients. All patients were clinically well, with no history of heart failure or arrhythmias in the previous year and none were on cardiac medications. Transfusion and chelation duration were 18.1 ± 9.0 years and 22.2 ± 8.7 years, respectively. Median transfusion interval was three weeks, with no patient transfused less frequently than every four weeks. Half of the patients were taking deferoxamine and half had switched to deferasirox when it became available in 2003. One patient was taking deferiprone and two were taking combination deferiprone and deferoxamine. Iron burdens were independent of chelation treatment. One patient was excluded because the MRI and ECG studies were more than 6 months apart. There were 45 patients with cardiac T2* values less than 20 ms, indicating MRI-detectable cardiac iron overload, and 33 patients with cardiac T2* greater than 20 ms (Table 1). Patients with cardiac iron were an average of five years older and more likely to be female. Age and gender were interdependent; there were no living male patients older than 30 years with cardiac iron compared with 13 females, raising the possibility of a survival bias[4, 23].

Both groups were heavily iron overloaded but liver iron, ferritin and serum iron were not significantly different between the two groups. High sensitivity CRP, a non-specific marker of systemic inflammation was increased in patients having cardiac iron overload. Patients having low risk hs-CRP, by American Heart Association classification (<1.0 mg/L), had normal heart rate (Z-score 0.02 ± 0.84), while patients with higher hs-CRP had heart rates nearly one standard deviation above average values for the reference population (Z-score 0.90 ± 0.97 , $p < 0.0002$). Twenty four hour mean HR on Holter recording was correlated with HR on the resting ECG ($r^2 = 0.32$, $p < 0.0001$) but an average of 7 beats per minute faster ($p < 0.0001$); mean HR was also increased in patients with elevated hs-CRP. Cardiac systolic function was not significantly different between the two patient groups. However LV dysfunction (MRI LVEF less than 56%) was observed in 6 patients; 5 out of 6 had severe iron deposition (T2* less than 10 ms). The hemoglobin levels were similar between both groups of patients.

Table 2 shows the ECG characteristics between patients with Thalassemia Major and iron overload (T2* less than 20 ms) versus those without iron overload (T2* greater than 20 ms). Since cardiac function and hemoglobin were similar, ECG changes between the two groups most likely represented preclinical effects of cardiac iron. Repolarization indices were the most sensitive discriminators. QT interval was greater in patients having cardiac iron deposition (Figure 1A). ROC analysis demonstrated an AUROC of 0.68 for the presence of cardiac iron with an optimal cutoff of 407 ms (horizontal line). The group differences persisted after correcting the QT for heart rate by two validated methods (Bazzett's & Fridericia method) but discrimination was worse. Ten patients had QTc prolongation (450 ms for men, 460 ms for women) but only seven had cardiac iron ($p = 0.39$). Figure 1b demonstrates the interaction between QT interval and beat-to-beat (RR) interval; horizontal line indications the 407 ms cutoff and curved lines represent power-law fits to the QT-RR relationship for both patient groups. Repolarization appears to prolong to a greater extent at low heart rate (long RR) in patients having cardiac iron, although curve-fit parameters were not statistically different from one another.

The T wave axes were left shifted in patients having cardiac iron. Figure 2 demonstrates T-wave axis as a function of cardiac T2*; the curve is somewhat similar to previously published T2*-LVEF relationships[24]. ROC analysis yielded an AUROC of 0.72 and optimal cutoff of 43 degrees (horizontal line).

Table 3 summarizes age and gender corrected Z scores for HR, axis, and intervals between the two groups. No significant gender differences in Z-scores were noted, indicating good correction by the population norms. As a group, TM patients had tachycardia and lengthening of the corrected QT interval, regardless of cardiac iron status, although the magnitude of QT increase was significantly greater in patients having cardiac iron. In contrast, leftward shift of the T-axis was only observed in patients with cardiac iron. Neither QT prolongation, nor left shift of the T-axis was correlated with left ventricular ejection fraction.

Cardiologist ECG interpretations are summarized in Table 4. Cardiologist morphologic assessment was consistent with observed changes in axis and intervals. Although tachycardia and various forms of conduction abnormalities were observed, they were not associated with cardiac iron. The most common abnormalities associated with cardiac iron were non-specific ST-T wave changes (n = 19), prolonged QTc (n=10), inferior lead T wave inversions (n=5), sinus bradycardia (n=4). LVH was equally distributed in both groups (3/33 versus 5/45). Taking the specific metrics together (simple Boolean “OR” operation) yielded a sensitivity and specificity of 73% and 82%, respectively, for the presence of detectable cardiac iron. Overlap between the qualitative and quantitative assessments of abnormal repolarization was incomplete allowing them to be used together. Combining a criteria of QT greater than 407, or T-wave axis less than 43, or abnormal reading (nonspecific ST-T wave changes, prolonged QTc, inferior lead T wave inversions, bradycardia) yielded a sensitivity of 89% and a specificity of 70%. The combined metric yielded a positive predictive value of 80% and a negative predictive value of 70%.

Univariate logistic regression analysis was performed using cardiac iron overload as the outcome variable. Subsequently we performed several multivariate stepwise logistic regression analyses in order to determine a small subset of variables that were most strongly associated with cardiac iron overload. In addition a further subset analysis revealed that the relationships clearly depended on gender, and in order to simplify the results, all subsequent analyses were stratified by gender. These analyses indicated that QT, QTc, T-axis, and HR, along with gender, were most strongly associated with cardiac iron overload. In order to account for the observed (and physiologically predictable) interactions between these variables a regression tree analysis (recursive partitioning) was performed to clarify the interactions between the variables in the model and the presence of cardiac iron. For both males and females these results could be collapsed into 3 subsets of patients with increasing risk of cardiac iron overload. T-axis and heart rate best-stratified risk in females, while QT and heart rate best stratified risk in males. While there are many statistical models that could be used to represent these relationships, and these results may not generalize exactly to other populations, these results clearly demonstrate in a parsimonious way that iron influences repolarization in a rate-dependent manner. If we consider high and highest risk ECG's as diagnostic for cardiac iron, these partition trees yielded AUROC's of 88.3 and 87.1 for females and males, respectively.

Discussion

Thalassemia major has known complications of congestive heart failure (CHF), sudden cardiac death (SCD) and arrhythmias. These conditions are multifactorial, resulting from iron cardiotoxicity, chronically elevated cardiac output secondary to anemia, coexisting

metabolic and endocrine derangements as well as increased cardiac afterload because of accelerated vascular aging.

Electrocardiogram abnormalities, similar to those observed in our present study, have been well documented in both the pre and post chelation era [25–30]. Previously, these changes could not be correlated with cardiac iron status. We found that a number of reported abnormalities, such as tachycardia, QT prolongation, and interventricular conduction delays were common in TM patients regardless of current cardiac iron status. While tachycardia is generally thought to represent physiologic compensation for anemia, we found that it was much more strongly associated with vascular inflammation (assessed by HS-CRP). HS-CRP, in turn, was independently correlated with increasing ferritin (or liver iron) and patient age, suggesting both the intensity and duration of iron overload contributed to systemic inflammation. Observed QT prolongation and conduction delays may be secondary to compensatory ventricular dilation, other myocardial stressors such as increased circulating oxidative species like labile plasma iron, or derangements in electrolytes, vitamins, or trace minerals[31]. Patients with thalassemia major have ventricular dimensions that are 10–15% larger than age and gender-matched controls, even when there is no detectable cardiac iron present [32]. Many of these patients were also on deferasirox; however we did not observe any independent effect of chelator type on QT interval. Furthermore, deferasirox did not prolong QT interval in a large, prospective study[33].

In contrast, iron loaded hearts were characterized by repolarization abnormalities, such as, ST and T wave abnormalities and additional prolongation of QT and QTc interval; bradycardia was also observed. The changes in repolarization are consistent with impairment of delayed rectifier potassium channels observed in animal models of iron overload[34], but many other electrophysiologic targets undoubtedly exist. Repolarization abnormalities such as prolonged QT, QTc and T wave abnormalities are known risk factors for sudden death in patients with coronary heart disease and congestive heart failure. ST/T wave changes, QT interval prolongation and leftward shift of the T wave axis were the most sensitive metric of iron loading.

Bradycardia was a relatively rare but specific indicator for cardiac iron. It is somewhat surprising given patient anemia, but has previously been described in animal models of iron overload[30]. Atrial iron deposition does occur in thalassemia but whether the observed changes represent direct sinus nodal toxicity or increased cardiac vagal tone are unknown, but impaired heart rate variability observed in TM patients makes the latter explanation unlikely[35, 36]. The observation that absolute QT was a better marker of cardiac iron than corrected QT interval indicates that interaction between heart rate and QT interval is abnormal in iron overload. Both temporal and spatial dispersion in QT interval are abnormal in beta thalassemia patients and appear to predict of cardiac morbidity and mortality[37, 38].

Overall, the changes in electrocardiographic parameters associated with cardiac iron represented subtle shifts within the normal range, limiting specificity. We evaluated several strategies using corrected and uncorrected QT interval, T wave axis and heart rate to determine whether we could characterize a cardiac iron “fingerprint” with sufficient sensitivity and specificity to serve as a screening tool in locations where cardiac MRI is limited. While our algorithms demonstrated some potential, there are many inherent biases that limit generalizability. The use of uncorrected QT in any diagnostic algorithm will be vulnerable to changes in resting HR. However the success of this metric in our study, compared to QTc, suggests that iron-mediated repolarization abnormalities may be rate-dependent; further work is needed to test this hypothesis.

Our study was compromised by its relatively small size, cross-sectional nature, and inherent selection bias. Some potentially important metabolic markers, such as vitamin D and serum calcium, were not measured in these patients. Hypocalcemia is associated with QT prolongation and vitamin D deficiency is common in our population[39]. We did not have sufficient patient numbers to generate a separate validation group, independent of our training set; performance in such a set would be expected to be lower. In particular, recursive partitioning might not generalize perfectly because the algorithm “matches” itself to the study population.

Some parameters used in this study, most notably T-wave axis, did not have appropriate age and gender corrected Z scores from large, healthy cohorts, forcing us to derive norms from patients lacking cardiac iron. However, the most sensitive discriminating statistics did not rely on Z-scores, allowing quick bedside assessment. Determination of QT interval can be subjective when U-waves (a normal late-repolarization phenomenon) are present. Although all ECG's in this study were read by an electrophysiologist, we purposely relied upon interval and axis values generated from standard ECG software to eliminate any observer bias in these parameters. In contrast, cardiologist interpretations represent standard clinical practice, rather than machine-generated interpretations, so these were used in the final algorithm. In fact, cardiologist and machine interpretation were concordant greater than 90% of the time. Thus, even a completely unsupervised ECG recording could potentially be used by hematologists as a screening tool. While automated ECG analysis programs yield fair consistent results with respect to intervals and duration, inter-program reproducibility of T-wave assess has not been adequately studied and could limit the proposed approach.

We cannot comment whether the observed changes are reversible once iron is cleared from the heart. Given the long half-life of cardiac iron clearance, this would represent a challenging study to perform. A study by Pepe et al suggests that ECG changes are associated with microvascular scarring[40]; one would expect ECG changes to be irreversible if this mechanism is true. We did not perform delayed gadolinium hyperenhancement in our MRI assessments.

Lastly, our study population contained uncorrectable selection/survival bias. Patients with cardiac iron overload had a prevalence of 58% suggesting that this population may have been enriched because of known prior noncompliance with medication or other concerns for their cardiac status. The near absence of middle aged men with cardiac iron most likely represents a survival bias, given their known vulnerability to iron cardiomyopathy [4]. These data will need to be replicated in other study populations because thresholds and sensitivities may depend on local transfusion and chelation practices.

In summary, electrocardiogram abnormalities are common in thalassemia, but some changes are more strongly associated with iron overload than others. We found that bradycardia and repolarization abnormalities including: QT interval prolongation, leftward shift of the T-wave axis, and generalized ST/T wave changes were most sensitive and specific for cardiac iron overload. Further, multicenter studies will be necessary to determine whether combinations of these parameters can be used to form robust screening algorithms but the present work highlights likely strategies.

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Figure 1.

A) Plot QT interval and T axis versus cardiac T2*. Patients with cardiac iron (located left of the vertical line at T2* of 20 ms) exhibit longer QT values. Horizontal line at a QT interval of 407 ms represents the optimal cutoff by ROC analysis. B) QT interval as a function of RR interval for patients with (filled circles) and without (open circles) cardiac iron. Curved lines indicate best power-law fit between QT and RR.

Figure 2. Plot of T axis versus cardiac T2*. MRI detectable cardiac iron was associated with leftward shift of the T-wave axis (less than 43 degrees, horizontal line).

Table 1
Demographics, laboratory data, and MRI findings in patients with and without detectable cardiac iron

Data are expressed as mean $\pm$ one standard deviation. BSA = body surface area, SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, CO = cardiac output, LVEF = left ventricular ejection fraction, RVEF = right ventricular ejection fraction, LVMES = left ventricular mass at end systole

Parameter	T2* greater than 20	T2* less than 20	p Value
Male	21	14	0.004
Female	12	31	0.004
Age (years)	21.6 $\pm$ 8.7	26.1 $\pm$ 8.2	0.026
BSA (m ²)	1.49 $\pm$ 0.25	1.54 $\pm$ 0.23	0.417
Hemoglobin (g/dl)	11.9 $\pm$ 1.9	11.8 $\pm$ 1.5	0.77
Ferritin (μ g/L)	2701 $\pm$ 2511	4170 $\pm$ 4491	0.07
Iron (μ g/dL)	212.1 $\pm$ 77.2	219.8 $\pm$ 100.1	0.71
BNP (ng/L)	14.1 $\pm$ 17	31.4 $\pm$ 43.0	0.063
LDH (U/L)	456.4 $\pm$ 299.1	386.5 $\pm$ 220.7	0.32
hs-CRP (mg/L)	1.1 $\pm$ 1.1	2.9 $\pm$ 4.9	0.023
HR at MRI (bpm)	79 $\pm$ 9.5	78 $\pm$ 10.6	0.53
SBP (mmHg)	107.4 $\pm$ 11.6	107.9 $\pm$ 10.2	0.85
DBP (mmHg)	63.5 $\pm$ 10.2	67.5 $\pm$ 9.2	0.084
MAP (mmHg)	82.0 $\pm$ 10.7	83.7 $\pm$ 9.4	0.47
MRI CI (L/min/m ²)	4.1 $\pm$ 0.6	3.8 $\pm$ 0.9	0.06
MRI LVEF (%)	63.1 $\pm$ 4.9	61.2 $\pm$ 6.4	0.15
MRI RVEF (%)	60.7 $\pm$ 6.5	61.0 $\pm$ 6.6	0.87
MRI LVMESi (g/m ²)	64.6 $\pm$ 20.7	64.3 $\pm$ 18.9	0.91
Liver Iron Content (mg/g)	11.1 $\pm$ 12.9	14.1 $\pm$ 9.8	0.26

Values expressed as (mean $\pm$ standard deviation)

Table 2
ECG findings of TM patients with and without detectable cardiac iron

Data are expressed as mean $\pm$ one standard deviation.

ECG Parameter	T2* greater than 20	T2* less than 20	<i>p</i> Value
PR (ms)	147.1 $\pm$ 14.4	151 $\pm$ 22.5	0.36
Pduration (ms)	96.6 $\pm$ 10.6	93.3 $\pm$ 9.1	0.31
QRS (ms)	87.1 $\pm$ 10.6	90.4 $\pm$ 9.1	0.167
QT (ms)	375.8 $\pm$ 22.5	397 $\pm$ 34.5	0.0018
QTcB (ms)	415.7 $\pm$ 22.8	435.6 $\pm$ 24.0	0.0005
QTcF (ms)	408.9 $\pm$ 20.6	429.1 $\pm$ 23.1	0.0002
ECG HR (bpm)	74 $\pm$ 10.1	74 $\pm$ 12.7	0.85
P Axis (degrees)	47.8 $\pm$ 17.6	46.8 $\pm$ 18.2	0.81
QRS Axis (degrees)	60.0 $\pm$ 22.7	50.8 $\pm$ 25.7	0.105
T Axis (degrees)	50.3 $\pm$ 17.3	36.0 $\pm$ 21.0	0.0018
QRS to T axis angle difference	17.6 $\pm$ 13.5	27.6 $\pm$ 23.2	0.021

ECG Values expressed as (mean $\pm$ standard deviation)

Table 3
Age and gender corrected electrocardiographic Z scores

All patients are separated according to their cardiac iron status. Asterisks demarcate parameters that differ significantly ($p < 0.05$) from the reference population. P values in the right hand column describes the differences between patients with and without detectable cardiac iron.

ECG Parameter Z-score	All TM Patients	T2* greater than 20	T2* less than 20	p value
PR	0.1 ± 0.9	0.0 ± 0.7	0.1 ± 1.1	0.69
QRS	-0.1 ± 0.9	-0.3 ± 1.0	0.0 ± 0.9	0.162
QT	0.3 ± 1.1	0.0 ± 0.8	$0.5 \pm 1.2^*$	0.02
QTcB	$1.1 \pm 1.2^*$	$0.7 \pm 1.1^*$	$1.4 \pm 1.2^*$	0.003
QTcF	$1.4 \pm 1.3^*$	$0.9 \pm 1.0^*$	$1.7 \pm 1.3^*$	0.002
HR	$0.4 \pm 1.0^*$	0.4 ± 1.0	$0.4 \pm 1.0^*$	0.8
QRS	0.1 ± 0.9	0.2 ± 0.8	-0.1 ± 0.9	0.12
T Axis	NA	0 ± 1	$-0.8 \pm 0.9^*$	0.012

Z-Scores reported as (mean $\pm$ standard deviation)

* represents statistical significance ($p < 0.05$) with respect to the reference population

p values in the right hand column represent between-group differences

Table 4
Cardiologist interpretation of the electrocardiogram

Sensitivity and specificity for each parameter in predicting detectable cardiac iron (T2* less than 20 ms) are listed in the right two columns. The final three rows of the table list the sensitivity and specificity of various logical parameter combinations.

Cardiologist ECG Reading	T2* greater than 20	T2* less than 20	specificity	sensitivity
Left Atrial Hypertrophy	0	1	100 %	2 %
Left Ventricular Hypertrophy	3	5	91 %	11 %
Right Axis deviation	0	2	100 %	4 %
Right Ventricular Hypertrophy	1	0	97 %	0 %
Sinus Bradycardia	0	4	100 %	9 %
Sinus Tachycardia	1	1	97 %	2 %
Long QT interval	3	14	91 %	31 %
Symmetric T-Wave Inversions	0	5	100 %	11 %
Low Voltage QRS	0	2	100 %	4 %
Nonspecific ST/T wave changes	4	19	88 %	42 %
Left Anterior Hemiblock	1	0	97 %	0 %
Right Bundle Branch Block, interventricular conduction delay	2	0	94 %	0 %
ST Segment, QT prolongation, T- wave Abnormalities	6	29	82 %	64 %
ST Segment, QT prolongation, T- wave Abnormalities, Bradycardia	6	33	82 %	73 %
ST Segment, QT prolongation, T- wave Abnormalities, Bradycardia, QT greater than 404, T axis < 43°	10	40	70 %	89 %