Electrocardiographic repolarization abnormalities and increased risk of life-threatening arrhythmias in children with dilated cardiomyopathy

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BACKGROUND Life-threatening arrhythmia events (LTEs) occur in ~5% of children with dilated cardiomyopathy (DCM). While prolonged QRS duration has been shown to be associated with LTEs, electrocardiographic (ECG) repolarization findings have not been examined.

OBJECTIVE We sought to determine the associations between ECG repolarization abnormalities and LTEs in children with DCM.

METHODS A single-center retrospective review of children with DCM was performed. LTEs were defined as documented ventricular tachycardia or fibrillation requiring medical intervention. Three pediatric cardiologists, blinded to clinical events, evaluated ECGs obtained at the time of initial referral. Kaplan-Meier survival and Cox proportional hazards analyses were used to evaluate time to LTEs.

RESULTS A total of 137 patients (mean age 7.8 ± 6.7 years; 75 (55%) male patients) with DCM (mean ejection fraction 35% ± 16%) were included; 67 patients (49%) had a corrected JT (JTc) interval of ≥340 ms, 72 (53%) had a corrected QT (QTc) interval of ≥450 ms, and 41 (30%) had abnormal T waves. LTEs occurred in 15 patients at a median of 12 months (interquartile range 3–36 months) after the initial ECG. Patients with LTEs had a longer JTc interval (371 ± 77 ms vs 342 ± 41 ms; $P = .02$) and a longer QTc interval (488 ± 96 ms vs 453 ± 44 ms; $P = .01$). In survival analysis, a JTc interval of ≥390 ms (hazard ratio [HR] 4.07; 95% confidence interval [CI] 1.12–14.83; $P = .03$), a QTc interval of ≥510 ms (HR 6.95; 95% CI 1.53–31.49; $P = .01$), abnormal T-wave inversion (HR 11.62; 95% CI 2.75–49.00; $P = .001$), and ST-segment depression (HR 6.91; 95% CI 1.25–38.27; $P = .03$) were associated with an increased risk of LTEs, even after adjusting for QRS duration and amiodarone use.

CONCLUSION Repolarization abnormalities are common in children with DCM. Certain ECG repolarization abnormalities, such as significantly prolonged JTc and QTc intervals, may be useful in identifying patients at risk of LTEs.

KEYWORDS Pediatric; Dilated cardiomyopathy; ECG; Repolarization; Life-threatening events

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Introduction

Dilated cardiomyopathy (DCM) is the most common cause of heart failure in children with structurally normal hearts.[1] Life-threatening arrhythmia events (LTEs) occur in up to 5% of children with DCM.[2–4] Several large series[3–6] of children with DCM have identified demographic and echocardiographic characteristics, such as age and left ventricular end-diastolic dimension (LVEDD), as risk factors for serious adverse events. Some electrocardiographic (ECG) findings in children with DCM have also been associated with poor outcome.[3–8] In a recent study[4] from our institution, QRS prolongation was identified as a risk factor for LTEs in children with DCM. Several studies[9–15] in adults have demonstrated an association between corrected QT (QTc) interval prolongation and mortality in certain high-risk groups, such as those with coronary disease, hypertension, and hypertrophic cardiomyopathy, as well as in the general adult population. Compared with the adult literature, there are much fewer studies[3,7,8,16] examining ECG repolarization in children with DCM.

The primary objective of this study was to characterize ECG repolarization abnormalities in children with DCM. Since QRS duration has previously been shown to be associated with arrhythmias in children with DCM, we specifically focused on the corrected JT (JTc) interval, which does not include QRS duration. Our hypothesis was that the JTc interval would be prolonged in children with LTEs than in those without LTEs.

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Methods

This was a single-center retrospective cohort study. Children younger than 18 years with a clinical diagnosis of DCM followed at Lucile Packard Children's Hospital Stanford were identified. DCM was defined as LVEDD z score ≥2 and ejection fraction <55%.[3] Patients with hypertrophic or restrictive cardiomyopathy, arrhythmia-induced DCM, or ventricular pacing were excluded. The study was approved by the Stanford University Institutional Review Board.

Medical records were reviewed for all patients meeting inclusion criteria. ECGs, 24-hour Holter reports, and ambulatory event monitor reports were collected. Our primary outcome variable was an LTE, defined as an episode of ventricular fibrillation or ventricular tachycardia that resulted in syncope or hypotension (defined as <5th percentile of systolic blood pressure according to age and height[17]) and required intervention (ie, medical or electrical shock). Organ death, defined as death or heart transplantation, was a secondary outcome variable.

Three pediatric cardiologists (S.C., S.R.C., and K.S.M.), blinded to clinical events, reviewed all initial 12-lead ECGs obtained at the first presentation to our institution. Using TraceMaster (version C.02.01.03, Philips, Andover, MA), manual measurements were made with digital calipers according to the 2009 expert consensus guideline on ECG interpretation.[18] Measurements were made in lead II, or if there was significant artifact or indiscernible intervals in lead II, measurements were made in lead V_5. If lead V_5 was unclear, then measurements were made in lead V_4 or V_6. The QT and JT intervals were measured from the onset of the Q wave and the end of the S wave, respectively, to the return of the T wave to baseline, or if the end of the T wave was not easily discernible to the intersection of the isoelectric baseline with the tangent of the T-wave downslope. U waves greater than half the height of the T wave and contiguous to the T wave were included in the QT interval, while U waves clearly separated from the T wave or less than half the height of the T wave were not included. The PR interval, QRS duration, and RR interval of the preceding beat were measured. Early repolarization was defined according to published criteria.[19] For calculating dispersion, QT and JT intervals were measured in all 12 leads, and dispersion was defined as the maximum minus the minimum interval.[16] T-wave flattening was defined as the absence of discernible deviation from baseline after the QRS complex in the lateral or inferior leads. Abnormal T-wave inversions were noted on the basis of age-appropriate criteria.[20] If sinus arrhythmia was noted, the average of measurements made over 3 beats was used.[18] QTc and JTc intervals were calculated using the Bazett formula ($QTc = QT/\sqrt{RR}$ and $JTc = JT/\sqrt{RR}$).[21] Prolonged QTc and JTc intervals were defined as ≥450 and ≥340 ms, respectively.[22,23] Significantly prolonged QTc and JTc intervals were defined as the 90th percentile of our study population (510 ms for the QTc interval and 390 ms for the JTc interval). Prolonged QT dispersion and JT dispersion were defined as ≥100 ms.[24] ST-segment depression or elevation (>1 mV and in 2 contiguous leads) and Q waves (>3 mV and >0.10 ms) were noted.

To assess the reliability of manual measurements, all 3 cardiologists interpreted 10 randomly selected ECGs and the intraclass correlation coefficient (ICC) was calculated for the JTc interval. The Bland-Altman method was used to determine the mean difference and limits of agreement (defined as the mean difference ± 1.96 standard deviations) between reviewers.[25] As the Bland-Altman method allows for a comparison only between 2 reviewers, we performed multiple Bland-Altman analyses (reviewer 1 vs reviewer 2, reviewer 1 vs reviewer 3, and reviewer 2 vs reviewer 3) and then averaged the mean differences and limits of agreement between the 3 reviewers.

Data were collected and managed using the Research Electronic Data Capture (REDCap) electronic data tool hosted at the Stanford Center for Clinical Informatics.[26] Variables were described as mean ± standard deviation for parametric variables and median (interquartile range or 25th–75th percentile) for nonparametric variables. A 1-sample t test was used to compare QTc and JTc intervals with published normative values for children.[22,23] Characteristics were compared between patients with and without LTEs using the Student t test for parametric continuous variables, the Wilcoxon rank-sum test for nonparametric continuous variables, and the Fisher exact test for categorical variables. Kaplan-Meier survival analyses with Cox proportional hazards models were used to examine time to primary and secondary outcomes. Given the small number of outcomes (n = 15), analyses with more than 2 covariates were not performed. Statistical analysis was performed on STATA/IC 13 (StataCorp LP, College Station, TX). P values <.05 were considered significant.

Results

Between January 1, 2005, and April 30, 2014, we identified 178 patients with DCM meeting the inclusion criteria. Thirty-six patients did not have an ECG in our medical record system and 5 patients had initial presentations with LTEs and thus did not have baseline ECGs for review. The remaining 137 patients were included in our study analysis. Baseline characteristics of these patients are summarized in Table 1. The median age was 6.5 years (interquartile range [IQR] 0.8–13.7 years), 75 (55%) were male patients, 79 (58% were nonwhite, and 58 (42%) had idiopathic or familial DCM. The median ejection fraction was 34% (IQR 21%–46%), and the LVEDD z score was 4.15 (IQR 2.15–6.32). Over a median follow-up period of 1.0 years (IQR 0.4–3.2 years), 15 patients (12%) had an LTE. Baseline characteristics between patients with and without LTEs were not significantly different, except that more patients with LTEs were on digoxin and amiodarone.

ECG findings

The initial ECG at the time of first presentation to our institution was reviewed for all 137 patients. The ICC for the