ORIGINAL ARTICLE

Is myocardial repolarization duration associated with repolarization heterogeneity?

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Funding information

This work was supported by the National
Institutes of Health [grant number
5K12HL109068]. The content is solely the
responsibility of the authors and does not
necessarily represent the official views of the
National Heart, Lung, and Blood Institute or
the National Institutes of Health

Background: Dispersion of repolarization is theorized as one mechanism by which myocardial repolarization prolongation causes lethal torsades de pointes, (TdP). Our primary purpose was to determine whether prolongation of myocardial repolarization as measured by the heart rate-corrected J-to-T peak interval (JTpkc), is associated with repolarization heterogeneity as measured by transmural dispersion, defined as the median duration from the peak to the end of the T wave (TpTe).

Methods: A retrospective cohort study was performed at a single urban tertiary ED from July 2011–September 2012. Inclusion criteria included all consecutive ED patients with ECG based on QTc and QRS intervals. Automated measurements of all intervals were performed. The association of JTpkc with the dependent variable TpTe was assessed after adjustment for QRS and RR interval durations with a multiple linear regression model. A secondary analysis included a similar adjusted assessment of the association of JTpkc with QT dispersion, QTd. Finally, we constructed two multiple regression models to assess the association of clinical causative factors of TdP with TpTe and JTpkc.

Results: Eight hundred seventy-four cases were included: 186 with QTc <500 ms, 118 with QTc ≥500 and QRS ≥120 ms, and 570 with QTc ≥500 and QRS <120 ms. The coefficient for association of JTpkc with TpTe was −0.10 (95%CI −0.15 to −0.05), and for JTpkc with QTd was 0.03 (95% CI −0.01 to 0.06). Clinical causative TdP factors were associated more with JTpkc than TpTe.

Conclusion: Repolarization duration as measured by JTpkc is not positively associated with dispersion of repolarization as measured by TpTe or QTd. Dispersion of repolarization may not be a critical mechanistic link between QTc prolongation and TdP.

KEYWORDS

cohort studies, dispersion, QT interval, repolarization, torsades de pointes

1 | INTRODUCTION

The median ECG interval from the peak to the end of the T wave (TpTe) may reflect the degree of transmural repolarization heterogeneity in the ventricular myocardium. QT dispersion (QTd) is defined as the difference between the longest and shortest duration QT interval on the 12 lead ECG. QTd may partly reflect heterogeneity

in repolarization across the left ventricular myocardium, although it may also be largely due to geometric considerations from ECG lead placement. Some evidence and theory implicate increased repolarization heterogeneity in the genesis of ventricular dysrhythmias including torsades de pointes (TdP) (Said, Wilson, Jeyaraj, Fossa, & Rosenbaum, 2012; Shimizu, Ohnishi, Inoue, & Yokoyama, 2001), and these tachydysrhythmias can lead to sudden cardiac

death (Cuddy, Halli, & Tate, 2009; Mänttari, Oikarinen, Manninen, & Viitasalo, 1997; Panikkath et al., 2011; Rosenthal et al., 2015). Current understanding of the causative relationship between heart rate-corrected QT interval (QTc) prolongation and TdP is incomplete, and predicting the occurrence of TdP is important but difficult.

If TpTe and QTd increase with the duration of repolarization as measured by the heart rate-corrected J point to T-wave peak interval (JTpkc), then this could provide a partial explanation why QTc prolongation causes TdP, and it could represent an additional means to assess risk for TdP. Conversely, if repolarization heterogeneity is not integral to the development of TdP, then prolongation of the depolarized state as measured by JTpkc might best predict the risk of TdP. The primary aim of this study is to assess the association of JTpkc duration with TpTe. Secondary aims include assessment of JTpkc with QTd, and a multivariate assessment of the association of clinical factors known to cause TdP with JTpkc and TpTe. These factors include amiodarone or sotalol antidysrhythmic treatments. These medicines both prolong QTc but have different propensities to cause TdP (Hii et al., 1992; van de Loo, Klingenhoben, & Hohnloser, 1996; Milberg et al., 2004).

2 | METHODS

2.1 | Study design

A single-center retrospective cohort study of Emergency Department (ED) patients who had an ECG was performed after Partners Healthcare institutional review board approval with waiver of informed consent.

2.2 | Study setting and population

The setting was a 900 bed urban hospital with annual ED census of 100,000. Three separate groups of consecutively collected ED patients were included (Figure 1): (1) ECG with QTc < 500 ms (2) ECG with QTc ≥ 500 ms, (3) ECG with QTc ≥ 500 ms and QRS < 120 ms. The third group was added after initiation of the study because the second group was heavily comprised of patients with QRS > 120 ms, and delayed depolarization as a cause of QTc prolongation was not the condition of primary interest. For comparison in Table 1, patients in the second group with QRS < 120 ms were moved to the third group to provide three mutually exclusive groups. A 500 ms threshold was chosen to yield a sample enriched with QTc substantially above normal with increased TdP risk.

FIGURE 1 Flowchart of recruitment, exclusions, inclusions, and missing data

TABLE 1 Patient characteristics: mean values (standard deviation) or number of cases (% of *n*)

Patient characteristics	Excluded from QT Guard Analysis	Included			Total
		QTc<500 ms	QTc>=500 ms & QRS>=120 ms	QTc>=500 ms & QRS<120 ms	
n (except where noted)	136	186	118	570	874
Patient age (years)	65.1 (17.7)	59.2 (18.5)	73.8 (13.2)	61.0 (18.0)	62.3 (18.1)
Males	66 (48.5%)	97 (52.2%)	70 (59.3%)	270 (47.4%)	437 (50.0%)
LVEF < 35%	13 (9.6%)	4 (2.2%)	27 (22.9%)	50 (8.8%)	81 (9.3%)
Hemodialysis	4 (2.9%)	2 (1.1%)	6 (5.1%)	36 (6.3%)	44 (5.0%)
Hypothermia (<90 deg F)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (0.9%)	5 (0.6%)
Antidysrhythmic therapy					
Amiodarone	9 (6.6%)	1 (0.5%)	18 (15.3%)	23 (4.0%)	42 (4.8%)
Sotalol	6 (4.4%)	1 (0.5%)	1 (0.9%)	7 (1.2%)	9 (1.0%)
Other	3 (2.2%)	0 (0.0%)	0 (0.0%)	4 (0.7%)	4 (0.5%)
Methadone	4 (2.9%)	1 (0.5%)	0 (0.0%)	25 (4.4%)	26 (3.0%)
Known QT-prolonging meds (mean #)	0.02 (0.15)	0.01 (0.1)	0.02 (0.1)	0.03 (0.2)	0.02 (0.2)
Possible QT-prolonging meds (mean #)	0.2 (0.5)	0.2 (0.4)	0.1 (0.3)	0.2 (0.5)	0.2 (0.5)
Conditional QT-prolonging meds (mean #)	0.3 (0.6)	0.2 (0.4)	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)
Newly classified QT-prolonging meds (post November 2011) (mean #)	0.1 (0.4)	0.07 (0.3)	0.08 (0.3)	0.1 (0.3)	0.1 (0.3)
ECG acquisition hour of the day	13.7 (6.2)	12.1 (6.2)	12.6 (6.5)	13.0 (6.9)	12.8 (6.7)
Heart rate	114.0 (32.5)	78.4 (18.4)	78.7 (15.3)	86.6 (19.1)	83.8 (18.8)
Atrial fibrillation	47 (34.6%)	9 (4.8%)	18 (15.3)	42 (7.4)	69 (7.9%)
QRS interval duration (ms)	96.7 (24.2)	94.7 (20.2)	157.3 (26.3)	93.9 (12.4)	102.6 (27.3)
QTc (ms) (Marquette)	535.5 (24.2)	435.7 (27.9)	527.9 (25.0)	523.1 (27.8)	505.1 (45.4)
QTc (ms) (QT Guard)	–	439.2 (27.7)	528.9 (26.9)	519.7 (29.5)	503.8 (44.4)
JTpkc (ms)	–	216.6 (28.4)	207.8 (32.9)	270.4 (47.1)	250.5 (50.1)
Repolarization heterogeneity					
QTd (ms)	–	13.1 (12.3)	30.7 (26.9)	19.9 (26.6)	19.9 (24.9)
TpKTe (ms)	–	102.2 (14.3)	127.2 (29.8)	119.8 (37.9)	117.0 (34.1)
LVH (Sokolow or Cornell criteria)	23 (16.9%)	28 (15.1%)	18 (15.3%)	129 (22.6%)	175 (20.0%)
Serum sodium (Na) (mmol/L)	137.4 (4.9)	137.5 (4.3)	136.9 (4.1)	136.5 (5.2)	136.8 (4.9)
Serum potassium (K) (mmol/L)	3.7 (0.8)	3.9 (0.5) (n = 184)	4.2 (0.9)	3.6 (0.7)	3.8 (0.7) (n = 872)
Serum bicarbonate (HCO ₃) (mmol/L)	24.8 (5.0)	25.9 (3.1)	25.9 (4.5)	24.8 (6.3)	25.2 (5.6)
Serum creatinine (mg/dl)	1.3 (1.5)	1.0 (0.6)	1.8 (2.0)	1.7 (2.2)	1.5 (1.9)
Serum glucose (mg/dl)	142.4 (63.3)	121.2 (51.9)	141.6 (73.0)	150.3 (105.4)	142.9 (93.1)
Serum magnesium (Mg) (meq/L)	1.7 (0.3) (n = 132)	1.7 (0.2) (n = 165)	1.8 (0.3) (n = 116)	1.7 (0.3) (n = 549)	1.7 (0.3) (n = 830)
Serum calcium (Ca) (mg/dl)	9.2 (1.0) (n = 135)	9.5 (0.6)	9.3 (0.7) (n = 117)	8.9 (0.9) (n = 568)	9.1 (0.9) (n = 871)
Toxicologic testing	50 (36.8%)	47 (25.3%)	15 (12.7%)	234 (41.1%)	296 (33.9%)
Non-ST elevation MI (NSTEMI)	4 (2.9%)	0 (0.0%)	7 (5.9%)	20 (3.5%)	27 (3.1%)
ST elevation MI (STEMI)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.7%)	4 (0.5%)
Ischemic cerebrovascular accident (CVA)	3 (2.2%)	2 (1.1%)	0 (0.0%)	15 (2.6%)	17 (1.9%)

(Continues)

TABLE 1 (Continued)

Patient characteristics	Excluded from QT Guard Analysis	Included			Total
		QTc<500 ms	QTc>=500 ms & QRS>=120 ms	QTc>=500 ms & QRS<120 ms	
Intracranial hemorrhage (ICH)	2 (1.5%)	9 (4.8%)	4 (3.4%)	44 (7.7%)	57 (6.5%)
Overdose of QT-prolonging medicine	3 (2.2%)	0 (0.0%)	0 (0.0%)	11 (1.9%)	11 (1.3%)
Known or suspected genetic LQTS	0 (0.0%)	0 (0.0%)	1 (0.9%)	4 (0.7%)	5 (0.6%)
Hospital admission					
ED Observation Unit	10 (7.4%)	26 (14.0%)	12 (10.2%)	29 (5.1%)	67 (7.7%)
Hospital ward or stepdown unit	86 (63.2%)	77 (41.4%)	76 (64.4%)	321 (56.3%)	474 (54.2%)
ICU	25 (18.4%)	9 (4.8%)	13 (11.0%)	133 (23.3%)	155 (17.7%)
OR or cardiac cath laboratory	1 (0.7%)	4 (2.2%)	3 (2.5%)	12 (2.1%)	19 (2.2%)
TdP during ED care or admission	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.7%)	4 (0.5%)
Mortality during ED care or admission	10 (7.4%)	0 (0.0%)	2 (1.7%)	45 (7.9%)	47 (5.4%)

*Median absolute difference in days between ECG acquisition and measurement of LVEF was 31 (IQR 1,195) for all cases.

Ms, milliseconds; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LQTS, long QT syndrome; ED, emergency department; ICU, intensive care unit; OR, operating room; TdP, torsades de pointes.

2.3 | Study protocol

We used a written study protocol, and data collection manual and instrument to guide data abstraction. One investigator who was not blinded to the study objectives inspected all ECGs and collected data from all included cases. One hundred of the first 720 cases were randomly selected for data abstraction reliability analysis. A second investigator blinded to the study goals abstracted data for these cases. Both investigators are practicing board-certified emergency physicians.

All automated QTc measurements made by the bedside Marquette ECG recorders using the 12SL algorithm (GE Healthcare, Milwaukee, WI) were checked for accuracy by one author using manual measurement and calculation of the QTc on the electronically viewed magnifiable ECG after uploading to the central MUSE ECG server. We preferentially used the automated measurement to remove bias. However, if the automated measurement was grossly incorrect, then we used the manual precordial measurement. The same author decided to include or exclude a patient based solely on ECG review prior to opening any other documents. If the patient was included, then he reviewed the complete medical record.

All ECG source code files were downloaded and run as a single automated batch in GE QT Guard Plus (GE Healthcare) for repolarization measurements. The program will not perform the measurements if there is an unsatisfactory signal or excessive lead noise.

2.4 | Measurements

We recorded acute historical data including: the chief complaint reported to the triage nurse, and patient age and sex. We recorded past cardiologic history including: any dysrhythmias, personal or family history of long QT syndrome, pacemaker or implantable cardioverter

defibrillator implantation, coronary artery disease including MI, percutaneous cardiac stent placement or balloon angioplasty, or coronary artery bypass grafting, and measured left ventricular ejection fraction (LVEF).

We recorded the LVEF measured closest temporally within 6 months before the ED visit, the date of the study, and the measurement modality. If no LVEF was measured within 6 months before the ED visit, then the closest before or after the ED visit was recorded.

We recorded medicines administered at an outside facility prior to patient transfer or in our ED prior to ECG acquisition. All chronic oral or parenteral medicines were recorded based primarily on the admitting service admission note, or the ED physician notes if the patient was discharged. We relied primarily on these notes because we believed they most accurately reflected true patient usage before the visit. Inhaled, ophthalmologic, transdermal, and as needed (PRN) medicines were not recorded. Medicines of particular interest including Vaughan Williams class I and III antidysrhythmics and methadone were noted. Other QT-prolonging medicines were classified according to the Arizona CERT website (Woosley & Romero, 2016) into three categories as of November 2011, or in a category indicating new listing since that time.

We recorded vital signs closest to the time of ECG acquisition. ECG data recorded included: date and time of acquisition, and automated heart rate, QRS, QT, and QTc interval measurements with manual confirmation. We manually assessed cardiac rhythm, QRS morphology including bundle branch block or electrical pacing, and left ventricular hypertrophy based on Sokolow or Cornell criteria or right ventricular hypertrophy.

QT Guard Plus software was used for automated measurement of: QRS, QT, QTd, and median TpTe (Andersen et al., 2007; Morin et al., 2012). The algorithm identifies the T-wave's peak (Tp) using a composite of measurements from all individual leads. JTpKc was calculated using Bazett's formula by subtracting QRS and TpTe from QT and dividing by

the square root of the RR interval. As a secondary sensitivity analysis, JTpkc was also calculated as above but by dividing by the cubed root of the RR interval using Fridericia's formula. Cases were excluded and noted if: QT Guard Plus was unable to provide measurements, or if QTc measured by QT Guard Plus was at least 10% greater or less than QTc measured by the bedside Marquette system, suggesting inaccuracy. Cases were excluded from QTd analysis if QTd was zero, indicating the QT interval could not be measured in some leads. All ECG analysis was

performed from the same beats in a single 10 second ECG tracing for each subject.

We recorded serum chemistries obtained closest temporally to ECG acquisition within 24 hr including: sodium, potassium, bicarbonate, creatinine, glucose, magnesium, calcium, and serum or urine toxicologic screen. If the specimen was hemolyzed, then the next closest available nonhemolyzed specimen results were used for the first five elements listed above.

FIGURE 2 Transmural dispersion of repolarization (TpTe) and QT dispersion (QTd) as unadjusted functions of repolarization duration (JTpkc)

We reviewed the complete record for any evidence of TdP. Final diagnoses from the ED if discharged or the hospital if admitted were recorded.

2.5 | Data analysis

All analyses including construction of multiple linear regression models were performed using SPSS 24 (IBM, Armonk, NY). Reliability of data abstraction of interval measurements was assessed with the intra-class correlation coefficient (ICC) using two way random models. The primary outcome measure was the independent variable JTpkc coefficient in a multiple linear regression model with dependent variable TpTe. Other independent variables included in this model were QRS duration and RR interval (1/HR). A secondary sensitivity analysis of the primary outcome was performed by constructing the same model using JTpkc calculated with Fridericia's formula for QT correction. Bazett's correction formula was otherwise used throughout the study. Another secondary outcome included the independent variable JTpkc coefficient in a similar model with dependent variable QTd instead of TpTe.

Other secondary outcomes included the coefficients in two multiple linear regression models developed to assess the linear relationship of JTpkc and TpTe with major clinical variables associated with TdP occurrence. A two piecewise linear spline with inflection point knot at 3.9 mmol/L was used to model potassium dependence based on our previous investigation (Marill & Miller, 2017). These two models included coefficients for amiodarone and sotalol treatments as dummy binary independent variables. Finally, we investigated the repolarization characteristics of those patients who developed TdP. LVEF was treated as a binary variable with threshold 35% due to its relatively lower measurement reliability. For patients with no measurement of LVEF, it was imputed as >35%.

3 | RESULTS

A total of 1,010 cases were available for repolarization analysis. Thirteen (1.3%) ECG's required manual over-read of the automated Marquette QTc measurement. Reliability of data collection for the 100 cases abstracted by two reviewers yielded ICC 0.95 or greater for all interval variables except HCO3. HCO3 ICC was 0.48 due to a single gross data entry error.

QT Guard Plus did not compute results for 76 cases. QTc differed by >10% by the two measurement programs for 60 cases. These cases were excluded leaving 874 cases for analysis (Figure 1, Table 1). QTd was zero for an additional 173 cases which signifies inability of the QT Guard program to read the QT interval in all necessary leads. These cases were excluded from the QTd dependent variable model.

Case characteristics are tabulated in Table 1. Mean TpTe was 117.0 ms (SD 34.1), QTd was 19.9 ms (SD 24.9), and JTpkc was 250.5 ms (SD 50.1). The results do not suggest meaningful positive correlation between JTpkc and TpTe or QTd by univariate (Figure 2) or multivariate (Table 2) analyses. The regression coefficients in the tables can be viewed as the slopes of the lines estimating the adjusted

TABLE 2 (A) TpTe as an adjusted function of JTpkc; (B) QTd as an adjusted function of JTpkc

	Coefficient	95% CI lower bound	95% CI upper bound
(A)			
Constant	103.28	84.61	121.95
JTpkc (ms)	-0.10	-0.15	-0.05
QRS interval (ms)	0.04	-0.05	0.14
RR interval (ms)	0.05	0.03	0.06
$R^2 = 0.07$			
(B)			
Constant	-20.22	-33.88	-6.56
JTpkc (ms)	0.03	-0.01	0.06
QRS interval (ms)	0.14	0.07	0.21
RR interval (ms)	0.03	0.02	0.04
$R^2 = 0.06$			

association of each predictor variable with the outcome, TpTe or QTd. Sensitivity analysis using Fridericia's formula yielded a coefficient of -0.34 (95% CI -0.39 to -0.29) for the association of JTpkc with TpTe. This is qualitatively similar to the primary result, -0.10 (Table 2A).

The coefficients in two multiple linear regression models constructed with independent variables that were clinical factors associated with TdP occurrence and dependent variable TpTe or JTpkc are listed in Table 3. Potassium terms in the model are calculated as (K-3.9), thus the negative terms for K < 3.9 suggest TpTe and JTpkc increase as potassium decreases below this value.

Four patients developed TdP. Mean values for these four patients were: TpTe 143 ms, QTd 5 ms, and JTpkc 345 ms.

4 | DISCUSSION

Our primary purpose is to determine if increased duration of myocardial repolarization among ED patients is associated with increased heterogeneity of repolarization. If true, repolarization heterogeneity could be a mechanistic link between QTc prolongation and TdP, and could represent an additional metric to help assess the risk of TdP. We found no substantial evidence that depolarization duration is positively associated with repolarization heterogeneity as measured by TpTe and QTd. Factors known to increase risk of TdP such female sex, genetic LQTS, QT-prolonging medicines such as oral sotalol, and serum hypokalemia or hypocalcemia are all associated with JTpkc, but not necessarily TpTe (Table 3).

We are confident in the veracity of our results. We collected detailed contemporaneous data on a large number of cases, confirmed reliability of data abstraction using a second blinded abstractor, and emphasized automated ECG analysis using state-of-the-art software to minimize potential investigator measurement bias.

We did find a small negative association of JTpkc with TpTe. This could be due to a small artifactual bias because JTpkc is calculated in

TABLE 3 Multiple regression coefficients for clinical predictors of TdP with: Model A: TpTe as dependent variable ($R^2 = 0.06$); Model B: JTpkc as dependent variable ($R^2 = 0.16$)

	Unstandardized coefficients		95.0% confidence interval for B		Significance
	B	Std. error	Lower bound	Upper bound	
Model A					
(Constant)	97.87	14.02	70.36	125.39	0.00
Gender (female)	3.64	3.07	-2.39	9.67	0.24
LQTS known or thought to be genetic	-25.70	15.24	-55.61	4.22	0.09
Amiodarone*	19.82	5.54	8.95	30.69	0.00
Sotalol	7.52	11.42	-14.89	29.94	0.51
Known long QT causing medicine (#)	2.45	7.76	-12.79	17.69	0.75
Possible long QT causing medication (#)	-1.56	2.62	-6.71	3.58	0.55
Conditional long QT causing medication (#)	-0.44	2.04	-4.45	3.57	0.83
New long QT medicine (#)	5.13	3.68	-2.09	12.35	0.16
Methadone (Y,N)	20.27	7.05	6.44	34.10	0.00
Serum potassium (K) if <3.9 (mmol/L)	-16.15	4.37	-24.72	-7.57	0.00
Female sex * K < 3.9 (mmol/L)	6.26	5.57	-4.66	17.19	0.26
Serum potassium (K) if >3.9 (mmol/L)	6.26	2.76	0.84	11.68	0.02
Serum magnesium (meq/L)	-4.69	4.01	-12.57	3.19	0.24
Serum calcium (mg/dl)	2.09	1.37	-0.61	4.78	0.13
Overdose of QT-prolonging agent (Y,N)	-3.14	10.47	-23.68	17.40	0.76
Model B					
(Constant)	344.82	19.19	307.14	382.49	0.00
Gender (female)	14.77	4.21	6.51	23.03	0.00
LQTS known or thought to be genetic	81.11	20.87	40.15	122.07	0.00
Amiodarone	2.42	7.59	-12.47	17.31	0.75
Sotalol	30.71	15.64	0.02	61.41	0.05
Known long QT causing medicine (#)	3.91	10.63	-16.96	24.78	0.71
Possible long QT causing medication (#)	0.35	3.59	-6.69	7.39	0.92
Conditional long QT causing medica- tion (#)	5.22	2.80	-0.26	10.71	0.06
New long QT medicine (#)	-1.05	5.04	-10.93	8.84	0.84
Methadone (Y,N)	31.98	9.65	13.04	50.91	0.00
Serum potassium (K) if <3.9 (mmol/L)	-15.81	5.98	-27.55	-4.07	0.01
Female sex * K < 3.9 (mmol/L)	-10.65	7.62	-25.61	4.31	0.16
Serum potassium (K) if >3.9 (mmol/L)	3.47	3.78	-3.94	10.89	0.36
Serum magnesium (meq/L)	5.55	5.50	-5.24	16.34	0.31
Serum calcium (mg/dl)	-13.56	1.88	-17.25	-9.87	0.00
Overdose of QT-prolonging agent (Y,N)	12.27	14.33	-15.86	40.40	0.39

(Y,N) signifies the change in TpTe or JTpkc associated with the presence of the predictor. The presence or absence of the predictor is coded with a dummy variable equal to 1 (predictor present) or 0 (absent).

(#) refers to the change in QTc (ms) associated with ingestion of each medicine in that category. Some patients may have been taking more than one medicine in the category.

Units such as (mmol/l) refer to the change in QTc (ms) for each 1 mmol/L change in the predictor.

Plasma potassium is coded as the observed value minus 3.9, either above or below. Thus, values below 3.9 are coded as negative. Female sex * K < 3.9 is an interaction term multiplying 1 if the patient is female times (plasma K - 3.9) if less than 3.9.

*The mean heart rates in patients treated with amiodarone and sotalol were 77.6 (SD 15.2) and 67.2 (SD 11.5) beats per minute, respectively.

LQTS = long QT syndrome.

part by subtracting TpTe from QT. We specifically did not use QTc to assess repolarization duration because TpTe is a component of the QT interval and this could lead to a positive bias, and recent data point to the emerging clinical importance of JTpkc as compared to QTc (Vicente et al., 2015).

Data to assess the effects of amiodarone and sotalol were limited, but the point estimates demonstrated the reverse of the effect that might be expected if sotalol caused increased repolarization dispersion as compared to amiodarone in concert with its known increased propensity to cause TdP (Table 3A) (Cui, Sen, Sager, Uppal, & Singh, 1994). There was a trend toward greater JTpkc prolongation associated with sotalol as compared to amiodarone, and this could be due to primary IKr (HERG) channel block due to sotalol versus multichannel block due to amiodarone (Johannesen et al., 2014). The data for TdP cases were too limited to draw conclusions, but TpTe was mildly prolonged and JTpkc was moderately prolonged in these four cases as compared to the group means.

A lack of positive association between repolarization duration and repolarization heterogeneity has not previously been shown for acquired QT prolongation. A report by Zareba and Moss demonstrated patients with genetic LQTS have greater repolarization dispersion as measured by JTd as compared to patients with coronary artery disease or without heart disease, but there was no significant association of QTc with JTd within each group (Zareba & Moss, 1995). Vicente, et al. did find an association between QTc and TpTe in normal subjects treated with QT-prolonging antidysrhythmics (Vicente et al., 2015). Bhuiyan, et al. found TpTe increased proportionally to QT after treatment (Bhuiyan et al., 2015). While these were small but precise studies focusing on the effects of specific ion channel blocking agents, the etiology of repolarization prolongation in our study is undoubtedly variable involving an unknown mixture of ion channel and ion concentration derangements.

Increased RR interval and thus decreased heart rate were associated with mildly increased measures of repolarization heterogeneity in our study (Table 2). This is in contrast to the absence of association observed in a sample of healthy subjects (Haamark et al., 2010). The pathophysiologic significance of our observation, if any, is unknown.

QTc, which includes the QRS, JTpkc, and TpTe segments, is currently the primary clinical factor used to assess for TdP risk. QRS duration is not associated with TdP and our data suggest that TpTe is not a critical factor either. This suggests, as previously supposed, JTpkc may be a more precise and preferred predictor of TdP risk (Johannesen et al., 2014). This awaits further confirmation.

4.1 | Limitations

This is a retrospective study of only patients who received ECGs, and it may be subject to a variety of biases from obtaining, documenting, and abstracting patient histories. The relationship between repolarization duration and measures of repolarization dispersion may be subject to unknown confounding factors. We have created parsimonious models correcting for the other important ECG intervals QRS and RR

duration, but there may be other unknown confounding ECG metrics and clinical factors.

We used two measures for dispersion of repolarization, TpTe and QTd, but the ideal measure remains uncertain. Furthermore, dispersion of repolarization is only a proxy for dispersion of refractoriness, which could be the more important mechanistic factor. Unfortunately, dispersion of refractoriness is not readily measurable on the resting ECG.

JTpkc was derived by subtracting the QRS and TpTe values from the QT interval and then correcting for heart rate. QT Guard Plus does not provide a direct measurement. The derived value may have lower accuracy and reproducibility due to possible compounded error from multiple measurements.

Despite using software specifically developed to assess repolarization characteristics (Andersen et al., 2007; Xue, 2011), repolarization metrics were challenging to measure, particularly in patients with prolonged repolarization. This led to exclusions due to inability to measure intervals or incorrect results which could cause bias. Excluded cases had a higher heart rate and proportion of atrial fibrillation. This included a substantial portion of patients treated with sotalol, and thus limited results and conclusions regarding this agent. Our results illustrate the challenge of implementing automated repolarization measurements in an unselected sample of patients with variably noisy clinical ECGs acquired outside of a controlled lab setting. Nevertheless, all included cases had an automated measured QTc within 10% of the manually checked value.

Bazett's formula is most commonly used to correct the QT interval for heart rate, and we used it to correct the JTpkc interval. However, it can over and under correct at high and low heart rates, respectively (Sagie, Larson, Goldberg, Bengtson, & Levy, 1992). Therefore, we performed a sensitivity analysis of the primary outcome using Fridericia's formula with similar results obtained.

LVEF was imputed as greater than 35% if no measurement was identified. This was a simplifying assumption that may have rarely been incorrect. In general, the threshold for echocardiography or other cardiologic imaging is low in our hospital to investigate further patients with any suggestion of heart disease.

5 | CONCLUSIONS

Repolarization duration as measured by JTpkc is not positively associated with dispersion of repolarization as measured by TpTe. Clinical factors known to cause TdP were most strongly associated with JTpkc as opposed to TpTe. No trend was observed suggesting increased dispersion of repolarization in patients treated with sotalol as compared to amiodarone. Dispersion of repolarization may not be a critical mechanistic link between QT prolongation and TdP.

ACKNOWLEDGMENT

The authors are grateful to Dr. Clif Callaway for many thought-provoking discussions and suggestions.

AUTHORS' CONTRIBUTIONS

PD, AH, and KM contributed primarily to the acquisition of data. ESM acquired and assisted with analysis of data. JX contributed to study design, developed analytic software, and assisted with study analysis. KAM conceived the study, and was primarily responsible for its execution and reporting.

CONFLICTS OF INTEREST

There are no disclosures or conflicts of interest pertaining to this work.

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How to cite this article: Marill KA, Dorsey P, Holmes A, Muthal K, Miller ES, Xue J. Is myocardial repolarization duration associated with repolarization heterogeneity? *Ann Noninvasive Electrocardiol*. 2018;23:e12519. <https://doi.org/10.1111/anec.12519>