Does the Magnitude of the Electrocardiogram QT Interval Dispersion Predict Stroke Outcome?

Yitzchok S. Lederman, MD,* Clotilde Balucani, MD, PhD,* Leah R. Steinberg, MD,* Charles Philip, DO,† Jason M. Lazar, MD,† Jeremy Weedon, PhD,‡ Gautam Mirchandani, MD,§ Sarah Z. Weingast, BA,* Giovanna Viticchi, MD,‖ Lorenzo Falsetti, MD,¶ Mauro Silvestrini, MD,‖ James J. Gugger, MD, PharmD,* David Aharonoff, MD,* Pirouz Piran, MD,* Zachary Adler, BS,* and Steven R. Levine, MD*,#

Background: QT dispersion, maximal interlead difference in QT interval on 12-lead electrocardiogram (ECG), measures cardiac repolarization abnormalities. Data are conflicting whether QT dispersion predicts adverse outcome in acute ischemic stroke (AIS) patients. Our objective is to determine if QT dispersion predicts: (1) short-term clinical outcome in AIS, and (2) stroke location (insular versus noninsular cortex). *Methods:* Admission ECGs from 412 consecutive patients with acute stroke symptoms from 2 university-based stroke centers were reviewed. QT dispersion was measured. A neuroradiologist reviewed brain imaging for insular cortex involvement. Favorable clinical outcomes at discharge were modified Rankin Scale (mRS) score of 0-1, discharge National Institutes of Health Stroke Scale (NIHSS) score less than 2, and discharge to home. Multiple logistic regressions were performed for each outcome measure and to determine the association between insular infarct and QT dispersion. *Results:* Of 145 subjects in the final analysis, median age was 65 years (interquartile range [IQR] 56-75), male patients were 38%, black patients were 68%, median QT dispersion was 78 milliseconds (IQR 59-98), and median admission NIHSS score was 4 (IQR 2-6). QT dispersion did not predict short-term clinical outcome for mRS score (odds ratio [OR] = 1.001, 95% confidence interval [CI] .99-1.01, P = .85), NIHSS at discharge (OR = .994, 95% CI .98-1.01, P = .30), or discharge disposition (OR = 1.001, 95% CI .99-1.01, P = .81). Insular cortex involvement did not correlate with QT dispersion magnitude (OR = 1.009, 95% CI .99-1.02, P = .45). *Conclusions:* We could not demonstrate that QT dispersion is useful in predicting short-term clinical outcome at discharge in AIS. Further, the magnitude of QT dispersion did not predict insular cortical stroke location.

Key Words: QT dispersion—ECG—acute ischemic stroke—prognosis

From the *Department of Neurology, Stroke Center, State University of New York (SUNY) Downstate Medical Center, Brooklyn, New York; †Division of Cardiovascular Medicine, SUNY Downstate Medical Center, Brooklyn, New York; ‡School of Public Health, SUNY Downstate Medical Center, Brooklyn, New York; §Department of Radiology, SUNY Downstate Medical Center, Brooklyn, New York; ‖Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy; ¶Internal and Subintensive Medicine Department, Azienda Ospedaliero Universitaria "Ospedali Riuniti", Ancona, Italy; and #Department of Emergency Medicine, Kings County Hospital Center, Brooklyn, New York.

Received July 24, 2018; accepted September 2, 2018.

Financial Disclosure: None.

Address correspondence to Steven R. Levine, MD, Department of Neurology, Stroke Center, State University of New York (SUNY) Downstate Medical Center, 450 Clarkson Avenue, Box 1213, Brooklyn, NY 11203. E-mail: steven.levine@downstate.edu

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.09.006

Introduction

QT interval dispersion (QTd), defined as the difference between the maximal and minimal leads on a 12-lead electrocardiogram (ECG), is an expression of cardiac repolarization abnormalities. In a variety of clinical settings, including acute stroke, multiple studies have suggested that an increase in QTd places patients at increased risk to develop ventricular arrhythmias and adverse clinical outcomes.[1-4] We sought to determine if admission QTd predicts short-term clinical outcome in patients with acute ischemic stroke (AIS) as well as to investigate if an AIS in the insular cortex region has a greater effect on QTd than strokes in other areas of the brain, as insular cortical involvement has been associated with increased sympathetic nervous system activity including arrhythmias.[5]

Methods

Subjects

After institutional review board approval, medical records from 412 consecutive patients admitted for acute stroke symptoms from 2 university-based stroke centers were reviewed. Patients were admitted between January 2010 and December 2010. The following data elements were systematically abstracted from each chart: stroke type, age, gender, admission and discharge National Institutes of Health Stroke Scale (NIHSS) score,[6] history of cardiovascular disease (CVD), history of stroke, stroke risk factors (hypertension, diabetes, hyperlipidemia, and cigarette smoking), discharge modified Rankin Scale (mRS) score,[7] and discharge disposition (home versus rehabilitation unit, skilled nursing facility, or death).

Only acute ischemic stroke patients were included in the final analyses. A neuroradiologist (GM) reviewed the neuroimaging of each patient to confirm an ischemic infarct and determine insular cortex involvement, blinded to ECG data. Patient's records confirming hemorrhagic stroke or transient ischemic attack (TIA) were excluded.

ECG Data

Admission ECGs were retrieved and 2 independent, trained investigators blinded to the clinical data manually measured the QT interval. The QT interval was measured from the onset of the QRS complex to the end of the T-wave. In the presence of the U-wave, the end of the T-wave was determined using the tangent method on the descending limb of the T-wave to determine at which point it intersected the baseline.[8] QTd was calculated as the difference between the maximum and minimum QT intervals, and was corrected for heart rate using Bazett's formula.[9] Inter-rater and intra-rater variability were assessed using 40 randomly chosen ECGs. Both readers were blinded to all previous measurements.

To avoid including confounding cardiac conditions, we excluded any ECG that had (1) less than 11 readable leads, (2) evidence of atrial fibrillation, (3) evidence of right or left bundle branch block, (4) evidence of pacemaker rhythm, and/or (5) evidence of ST elevation myocardial infarction.

Outcome Measures

We used 3 standardized measures to determine short-term patient clinical outcome at discharge: (1) NIHSS score, (2) mRS score, and (3) discharge disposition. Favorable clinical outcomes were defined as mRS score of 0-1, discharge NIHSS score less than 2, or discharge to home.

Determination of Insular Cortical Involvement

A neuroradiologist determined insular cortex involvement using patients' neuroimaging using standardized anatomic brain imaging atlases.

Statistical Methods

Spearman's correlations (r_s) were calculated for QTd and NIHSS score at discharge. NIHSS and mRS scores are reported with corresponding Loess plots where appropriate.[10] Logistic regression was used to predict (in separate models) mRS score (dichotomized as 0 or 1 versus >1), disposition to other than home, and NIHSS score greater than 1 at discharge. Predictors were QTd, race (black versus other), gender, age, NIHSS score at admission, history of stroke, and history of CVD.

Hosmer-Lemeshow tests of fit of models to the data were applied[11]; polynomials in score predictors were added as necessary to achieve fit. Odds ratios (ORs) with 95% Wald-based confidence intervals (CIs) and P values based on likelihood ratio tests are reported. In a secondary analysis, logistic regression was used to predict insular infarct from QTd alone. Intraclass correlations (ICCs) are reported as measures of inter- and intra-rater reliability of QTd, based on 2-way random effects models using an absolute agreement criterion.

Results

From a total of 412 subjects admitted to the hospital with acute cerebrovascular disease, 267 were excluded from the final analysis for the following reasons: TIA (n = 86), less than 11 readable ECG leads (n = 83), hemorrhagic stroke (n = 44), unable to confirm ischemic stroke diagnosis (i.e., stroke mimics; n = 18), evidence of right or left bundle branch block (n = 16), evidence of atrial fibrillation (n = 13), evidence of pacemaker rhythm (n = 5), evidence of ST elevation MI (n = 1), and premature ventricular contraction (n = 1).

Of 145 subjects included in the final analysis, the median QTd at admission was 78 milliseconds (IQR 59-98, range 8-241) and median admission NIHSS score was 4 (IQR 2-6, range 0-29). Twenty-eight percent had a history of CVD and 24% had a prior stroke. The median age

was 65 years (IQR 56-75, range 28-94); there were a total of 90 (62%) female patients and 98 (68%) black patients.

Inter-rater and intra-rater reliability were ICC = .96 and ICC = .98, respectively.

Sixty-two (43%) patients had a discharge mRS score 0-1 [mean QTd = 79.79 ± 34.19 standard deviation (SD) milliseconds], 59 (41%) patients had a discharge NIHSS score less than 2 [mean QTd = 83.44 ± 35.79 (SD) milliseconds], and 78 (54%) had a home disposition [mean QTd = 79.42 ± 32.17 (SD) milliseconds].

QTd did not predict clinical outcome for mRS score (OR = 1.001, 95% CI .99-1.01 $P = .85$; Fig 1), NIHSS score at discharge (OR = .994, 95%CI .98-1.01, $P = .30$; Fig 2), or discharge disposition (OR = 1.001, 95% CI .99-1.01, $P = .81$). Admission NIHSS score was an independent predictor of outcome for all 3 outcome measures ($P < .001$). History of stroke was an independent predictor for mRS score ($P = .016$). In addition, black subjects had a significantly worse discharge disposition ($P = .002$). In the secondary analysis, insular cortex involvement did not correlate with QTd magnitude (OR = 1.009, 95% CI .99-1.02, $P = .45$). The area under ROC curve for the model was .58, and the test of model fit was $P = .450$.

Discussion

We attempted to clarify if admission QTd in AIS patients is useful in predicting short-term clinical outcome by the NIHSS score, mRS, and discharge disposition. Additionally, we evaluated the effect of stroke location in the insular cortex region on admission QTd. We found that admission QTd did not predict short-term clinical outcome for NIHSS score, mRS, or discharge disposition. In addition, strokes in the insular cortical region did not correlate with QTd magnitude.

Most studies that have previously evaluated the prognostic value of QTd in acute stroke have focused on hemorrhagic stroke patients.[12-15] We focused on AIS with a confirmed diagnosis and excluded records, which confirmed a hemorrhagic stroke or TIA. We also excluded records where ECGs were concerning for technical or physiologic confounders.

In order to systematically evaluate the quality and consistency of the QTd measurement, 2 independent reviewers blinded to the clinical data performed the assessment, which yielded very high agreement supporting consistency and validity of our QTd data. In other studies, it was unclear if readers were blinded to clinical data and most studies did not report intra-rater or inter-rater variability of QTd measurement. Our sample size was also relatively large compared to other published studies. We cannot exclude the possibility, however, of a type II error.

In 1 previous study, a positive trend was found between baseline QTd (in both AIS and hemorrhagic stroke patients), and discharge NIHSS score and mRS.[16] A more recent observational case control study had similar findings that showed the mean QTd was correlated with admission NIHSS and discharge mRS scores, and QTd was significantly higher in nonsurviving as

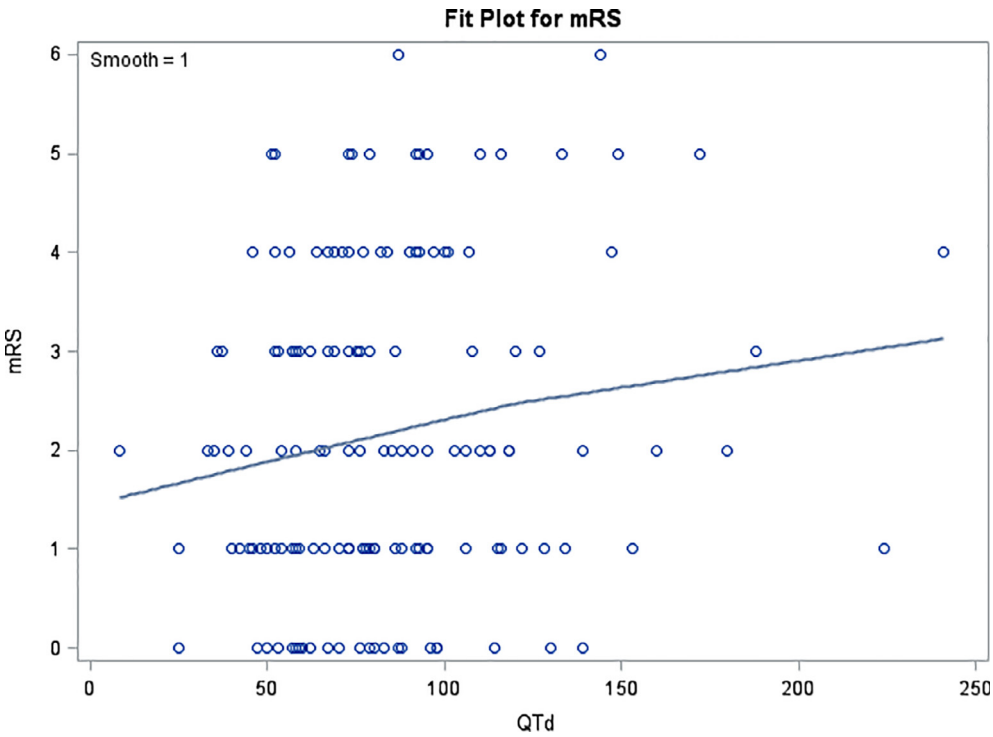

Figure 1. *Loess plot: Magnitude of QT dispersion and mRS. Bivariate analysis:* $r_S = +.14$, $N = 145$, $P = .082$. *Abbreviation: mRS, modified Rankin Scale.*

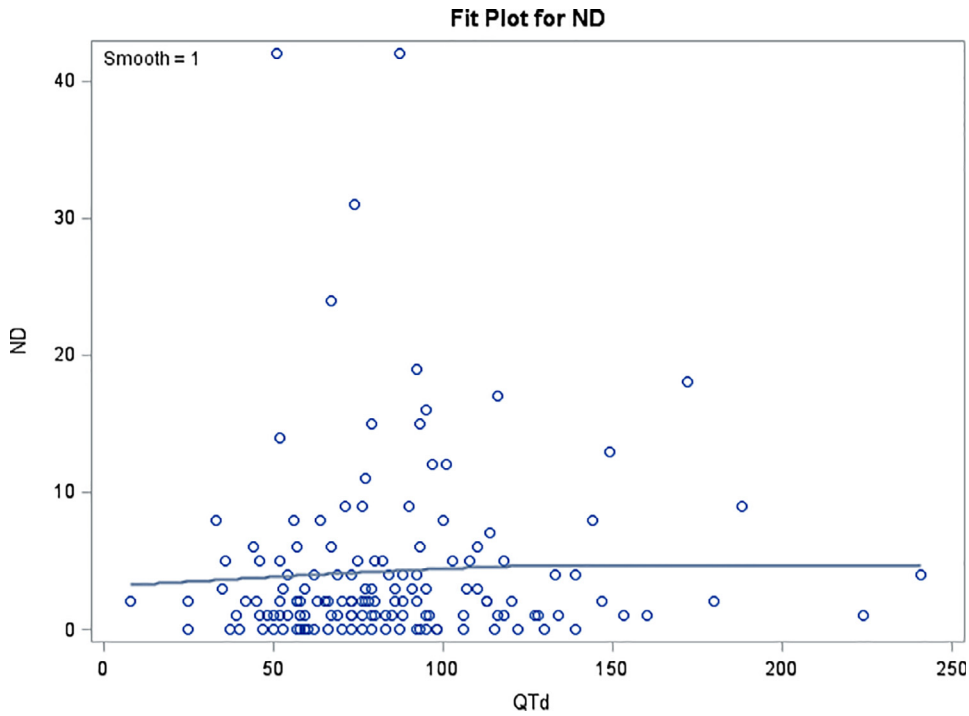

Figure 2. *Loess plot: Magnitude of QT dispersion and NIHSS at discharge. Bivariate analysis:* $r_S = +.10$, $N = 145$, $P = .229$. *Abbreviation: NIHSS, National Institutes of Health Stroke Scale.*

compared to surviving stroke patients.[17] However, in our study, we were unable to confirm these findings.

Five published studies evaluated baseline predictive value of QTd in acute stroke.[12-14,16,17] Four studies evaluated only hemorrhagic stroke patients.[12-15] These studies compared baseline QTd of stroke survivors to stroke nonsurvivors. In 3 of the 5 studies, nonsurviving stroke patients were reported to have significantly higher QTd values as compared to stroke nonsurvivors.[13,16,18] This suggests that QTd may have some prognostic value in predicting stroke fatalities, and that QTd may be more valuable in certain settings of acute stroke (i.e., hemorrhagic versus ischemic). However, QTd values were found to be broad and overlapping, making it difficult to make any firm conclusions about QTd's predictive value. As a majority of our subjects had a minor stroke (NIHSS scores 0-5) on admission, predictive power was limited.

In our study, we did not report if patients developed ventricular arrhythmias or other cardiac consequences as a result of their AIS. However, 1 study reported significantly higher QTd values in subarachnoid hemorrhage patients who developed ventricular arrhythmias than in patients who did not develop ventricular arrhythmias.[15] In another study, patients suffering from severe subarachnoid hemorrhage with elevated admission QTd measurements were more likely to develop cardiorespiratory compromise as compared to patients with lower QTd values.[19] In terms of the association between acute stroke and cardiac abnormalities, 2 studies reported that catecholamine concentrations positively correlated with QTd in hemorrhagic stroke.[20,21] These findings support the idea that an increased QTd is secondary to sympathetic hyperactivity and may mediate the occurrence of cardiac abnormalities.

Based on literature suggesting a role of insular cortical lesions in acute ECG abnormalities, we explored this relationship in our cohort. AIS patients with and without insular cortex involvement did not differ in QTd values on admission ECG. Two previously published studies demonstrated that strokes involving the insular cortex had significantly greater QTd values than strokes without insular cortex involvement.[22,23] However, we were unable to confirm these findings.

The results of the present study differ from some prior studies. As the method of QTd determination has remained constant across the studies, 1 possible explanation is the patient population that we studied. More than half of our patients had either CVD or a prior stroke, and the presence of chronic conditions that prolong QTd could be diluting out the acute effects of the stroke. Also, approximately two-thirds of our patients were female and most were African American. Since both female gender and black race are associated with left ventricular hypertrophy and left ventricular hypertrophy is associated with higher QTd, then perhaps these factors could potentially explain the differences between studies. QTd values in this study are higher than previously reported in prior studies.

Our study had several limitations. It was a retrospective design, so it is only hypothesis generating. We were unable to collect prestroke ECGs or serial ECGs, which

would have provided a more accurate assessment of the relationship between AIS and QTd. We also did not control for serum electrolytes or medications that may alter the QT interval.

In summary, we were unable to demonstrate a short-term prognostic predictive value of admission QTd in the setting of AIS using NIHSS score, mRS, and discharge disposition. Additionally, we did not find any significant differences in QTd between AIS in the insular cortex versus other stroke locations. Additionally, it will be important to clarify if stroke type and location (e.g., brainstem) may affect QTd differently.

References

1. Zaputović L, Mavrić Z, Zaninović-Jurjević T, et al. Relationship between QT dispersion and the incidence of early ventricular arrhythmias in patients with acute myocardial infarction. Int J Cardiol 1997;62:211-216.
2. Voigt L, Haq SA, Mitre CA, et al. Effect of obstructive sleep apnea on QT dispersion: a potential mechanism of sudden cardiac death. Cardiology 2011;118:68-73.
3. Barr CS, Naas A, Freeman M, et al. QT dispersion and sudden unexpected death in chronic heart failure. Lancet 1994;343:327-329.
4. Glancy JM, Garratt CJ, Woods KL, et al. QT dispersion and mortality after myocardial infarction. Lancet 1995;345:945-948.
5. Nagai M, Hoshide S, Kario K. The insular cortex and cardiovascular system: a new insight into the brain-heart axis. J Am Soc Hypertens 2010;4:174-182.
6. Brott T, Adams Jr HP, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864-870.
7. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-607.
8. Lepeschkin E, Surawicz B. The measurement of the Q-T interval of the electrocardiogram. Circulation 1952;6:378-388.
9. Bazett HC. An analysis of the time relations of the electrocardiograms. Heart 1920;7:353-370.
10. Cleveland WS, Grosse E, Shyu WM. Local regression models. In: Chambers JM, Hastie TJ, eds. Statistical models in S, Wadsworth & Brooks/Cole; 1992.
11. Hosmer DW, Lemeshow S. A goodness-of-fit test for the multiple logistic regression model. Commun Stat 1980;9:1043-1069.
12. Chao CC, Wang TL, Chong CF, et al. Prognostic value of QT parameters in patients with acute hemorrhagic stroke: a prospective evaluation with respect to mortality and post-hospitalization bed confinement. J Chin Med Assoc 2009;72:124-132.
13. Huang CH, Chen WJ, Chang WT, et al. QTc dispersion as a prognostic factor in intracerebral hemorrhage. Am J Emerg Med 2004;22:141-144.
14. Golbasi Z, Selcoki Y, Eraslan T, et al. QT dispersion. Is it an independent risk factor for in-hospital mortality in patients with intracerebral hemorrhage? Jpn Heart J 1999;40:405-411.
15. Sato K, Kato M, Yoshimoto T. QT intervals and QT dispersion in patients with subarachnoid hemorrhage. J Anesth 2001;15:74-77.
16. Lazar J, Manzella S, Moonjelly J, et al. The prognostic value of QT dispersion in patients presenting with acute neurological events. J Invasive Cardiol 2003;15:31-35.
17. Rahar KK, Pahadiya HR, Barupal KG, et al. The QT dispersion and QTc dispersion in patients presenting with acute neurological events and its impact on early prognosis. J Neurosci Rural Pract 2016;7:61-66.
18. Bicakci S, Donmez Y, Ozeren A, et al. QT dispersion on ECG in acute ischemic stroke and its impact on early prognosis. Neurosciences (Riyadh) 2008;13:366-369.
19. Macmillan CS, Andrews PJ, Struthers AD. QTc dispersion as a marker for medical complications after severe subarachnoid haemorrhage. Eur J Anaesthesiol 2003;20:537-542.
20. Randell T, Tanskanen P, Scheinin M, et al. QT dispersion after subarachnoid hemorrhage. J Neurosurg Anesthesiol 1999;11:163-166.
21. Hanci V, GuI S, Dogan SM. Evaluation of P wave and corrected QT dispersion in subarachnoid haemorrhage. Anaesth Intensive Care 2010;38:128-132.
22. Alabd AA, Fouad A, Abdel-Nasser R, et al. QT interval dispersion pattern in patients with acute ischemic stroke: does the site of infarction matter. Int J Angiol 2009;18:177-181.
23. Eckardt M, Gerlach L, Welter FL. Prolongation of the frequency-corrected QT dispersion following cerebral strokes with involvement of the insula of Reil. Eur Neurol 1999;42:190-193.