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ORIGINAL RESEARCH

Increased QT Dispersion Is Linked to Worse Outcomes in Patients Hospitalized for Out-of-Hospital Cardiac Arrest

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BACKGROUND: The incidence and mortality of out-of-hospital cardiac arrest (OHCA) remains high, but predicting outcomes is challenging. Being able to better assess prognosis of hospitalized patients after return of spontaneous circulation would enable improved management of survival expectations. In this study, we assessed the predictive value of ECG indexes in hospitalized patients with OHCA.

METHODS AND RESULTS: PR interval and QT interval corrected by the Bazett formula (QTc) for all leads were calculated from standard 12-lead ECGs 24 hours after return of spontaneous circulation in 93 patients who were hospitalized following OHCA. PR interval and QT and QTc duration did not differentiate OHCA survivors and nonsurvivors. However, QT and QTc dispersion was significantly increased in patients who died during hospitalization compared with survivors discharged from the hospital ($P<0.01$). Logistic regression indicated a strong association between increased QT dispersion and in-hospital mortality ($P<0.0001$; area under the curve, 0.8918 for QT dispersion and 0.8673 for QTc dispersion). Multinomial logistic regression indicated that the increase of QTc dispersion correlated with worse Cerebral Performance Category scores at discharge ($P<0.001$; likelihood ratio, 51.42). There was also significant correlation between dispersion measures and serum potassium at the time of measurement and between dispersion measures and cumulative epinephrine administration. No difference existed regarding the number of measurable leads.

CONCLUSIONS: Lesser QT and QTc dispersion at 24 hours after return of spontaneous circulation was significantly associated with survival and neurologic status at discharge. Routine evaluation of QT and QTc dispersion during hospitalization following return of spontaneous circulation might improve outcome prognostication for patients hospitalized for OHCA.

Key Words: cardiac arrest ■ cardiopulmonary resuscitation ■ ECG ■ ECMO ■ QT interval electrocardiography

The 2018 American Heart Association Heart and Stroke Statistics indicate that >300 000 people in the United States had out-of-hospital cardiac arrest (OHCA), with 250 000 reported deaths.[1] Over the past decade, venoarterial extracorporeal cardiopulmonary membrane oxygenation (VA-ECMO) has emerged for the management of patients with OHCA.[2] Nonetheless, despite improvements in outcomes, mortality remains high, exceeding 85%.

Patients with OHCA exhibit multiorgan dysfunction secondary to the global ischemia associated with cardiac arrest.[3] This severe organ dysfunction adversely affects the conventional prognosticating tools that have been developed for assessment of intensive care patients.[4] Serum markers, such as neuron-specific enolase (NSE), have also been used, but their widespread use is limited by uncertainty regarding the optimal time of measurement, the optimal cutoff points, and the cost.[5] Despite acute multiorgan dysfunction, the majority of deaths are ultimately attributed to cardiovascular morbidity or brain death.[6] Therefore, a successful prognosticating tool should respond to both cardiac and cerebral insults.

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CLINICAL PERSPECTIVE

What Is New?

- The 12-lead ECG is an inexpensive and readily available tool with unexplored utility for management of patients with cardiac arrest.

What Are the Clinical Implications?

- QT dispersion calculated in the 24-hour 12-lead ECG following resuscitation can significantly improve the neuroprognostication of patients with cardiac arrest treated with extracorporeal cardiopulmonary membrane oxygenation.

Nonstandard Abbreviations and Acronyms

CPC	Cerebral Performance Category
CT	computed tomography
NSE	neuron-specific enolase
OHCA	out-of-hospital cardiac arrest
ROSC	return of spontaneous circulation
VA-ECMO	venoarterial extracorporeal membrane oxygenation

Recently, Endoh et al reported that heart rate variability following return of spontaneous circulation (ROSC) differed between survivors and deceased patients with OHCA and strongly correlated to neurologic outcome, indicating that electrical activity of the heart could contribute to survival prognostication after cardiac arrest.[7] The 12-lead ECG is an inexpensive and widely available tool that provides not only information regarding the status of intrinsic cardiac electrical function but also the input of extracardiac systems, particularly the central nervous system, to the electrical activity of the heart. Among other measurements derived from ECG recordings, the dispersion of the QT interval provides a readily accessible marker of repolarization abnormalities that is affected by alterations of both heart and brain activity. Consequently, we decided to assess whether QT and corrected QT (QTc) dispersion measures obtained at approximately 24 hours following hospital admission would be useful for prognostication of hospital survival in patients with OHCA.

MATERIALS AND METHODS

This study was approved by University of Minnesota institutional review board (STUDY00004017). The study population included patients who achieved ROSC after out-of-hospital refractory ventricular fibrillation and who were admitted for further care between December 2015 and August 2019. Given the retrospective nature of the study and in accordance with Health Insurance Portability and Accountability Act (HIPAA) regulations, consent for participation was waived. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to Marinos Kosmopoulos at marinos.kosmopoulos@gmail.com. This population has been described in detail[8] and consists of patients between 18 and 75 years old who were transferred from the scene of the arrest to the cardiac catheterization laboratory in <30 minutes. These patients underwent coronary angiography with primary percutaneous coronary intervention if either significant obstructive coronary artery disease or an acute coronary syndrome was identified.

If the patient had not achieved ROSC by the time of arrival at the cardiac catheterization laboratory, the treating interventional cardiologist would institute percutaneous VA-ECMO support. At 12 to 36 hours after cannulation, patients underwent ECG assessment with standard 12-lead ECG. Patients received therapeutic hypothermia under standard protocol with rapid intra-arrest infusion of ice-cold saline with a target temperature of 34°C, which could be allowed to reach 35°C if bleeding complications occurred. Patients were maintained at this temperature for approximately 24 hours.[8,9] Moreover, acute physiologic derangements after the arrest were also assessed through collection of plasma and arterial blood gas, and patients underwent computed tomography (CT) of the head at admission to assess for the presence of early brain injury. Patients' last available ECG before death or hospital discharge was also assessed. Patients who died in <72 hours after cannulation were excluded from the secondary ECG assessment.

Standard ECG was assessed for the number of leads with a measurable QT interval. If U waves were present, they were not included in the measured interval. The end of the QT interval was determined by intersection of the tangent with the T-wave downslope and isoelectric line. QT was corrected using the Bazett formula. Each trace was measured by the same individuals (M.K., T.G.) to minimize error. In case of interobserver variability >25 mm, a third observer (D.Y.) determined QT duration. To confirm that the observed trends did not result from the overestimation and underestimation of maximum and minimum QT, respectively, we also calculated the relative QT dispersion, which utilizes QT intervals from all leads and thus corrects for outlying measurements. If the presenting rhythm was atrial fibrillation, QT correction was done using the Fridericia formula, which is widely accepted to exhibit the best accuracy and reproducibility for these cases among

Table 1. Patient Baseline Characteristics

Patient Population	n	Age, Mean±SD	Male, n (%)
Survivors	41	54.93±1.91	25 (61.0)
Neurologically intact	30	55.45±2.38	20 (66.7)
Residual neurologic instability	11	53.58±3.18	5 (44.4)
Deceased	52	57.79±1.79	47 (90.4)
Total	93	57.38±2.99	72 (77.4)

the available methods. In contrast to the Bazett formula, in which corrected QT is calculated as the ratio of absolute QT to the square root of RR interval in seconds, the Fridericia formula uses the third root of RR. Although the Bazett formula is the most widely used, the Fridericia formula is considered to be the most accurate, so we decided to use both for our calculations.[10]

Calculation of absolute and relative dispersion measures was done as recommended by Priori et al.[11] In brief, absolute dispersion was calculated as the difference between the longest and shortest QT intervals, and relative QT dispersion was calculated as the ratio of the standard deviation of the QT interval in the 12 ECG leads to the average QT duration. The primary end points for this study were survival at discharge and neurologic status. Neurologic status at discharge was evaluated by Cerebral Performance Category (CPC) score, a widely used system for interpretation of neurocognitive outcomes in patients with cardiac arrest.[12,13] A score of 1 or 2 was treated as neurologically intact survival, scores 3 and 4 identified survivors with disabling neurologic impairment, and patients who did not survive were assigned a score of 5.

Statistical Analysis

Data analysis was done with STATA software (v15; StataCorp). The Student *t* test was used to assess for differences in ECG indexes between survivors and deceased patients. ANOVA was used to compare the ECG indexes among the various neurologic status measures at discharge. Binomial regression was used to assess predictions regarding survival, and multinomial regression was chosen to assess predictions regarding neurologic status at discharge. Ordinal logistic regression was done to assess the correlation between dispersion measures and neurologic outcome.

RESULTS

ECG Findings

Between January 2015 and August 2019, 192 patients with out-of-hospital ventricular tachycardia/ventricular fibrillation were admitted. None of the patients that received VA-ECMO support had achieved ROSC before the institution of percutaneous VA-ECMO support. All 93 patients in this investigation obtained ROSC within the first 24 hours of admission. ECG recordings at 12 to 36 hours after ROSC (mean time, 20 hours and 45 minutes; 95% CI, 19 hours and 18 minutes to 22 hours and 10 minutes) were available for 93 patients. Baseline characteristics and outcomes are shown in Table 1. Of the 93 patients, 68 had angiographically confirmed coronary artery disease and 25 had no evidence of coronary artery disease. In addition, 27 patients presented with acute thrombotic lesions, 34 had ischemic cardiomyopathy, and 18 had underlying nonischemic cardiomyopathy. One patient had arrest secondary to opiate overdose; for the remaining 13, the underlying cause was unidentified. Nine patients had ventricular rhythm, 12 patients had junctional rhythm, and 1 developed atrial fibrillation. Overall, 71 patients had sinus rhythm on their ECG recordings.

ECG indexes at 24 hours are summarized in Table 2. The interquartile ranges of ECG indexes at 24 hours are presented in Table 3, and those of discharge are summarized in Table 4. Deceased patients and survivors did not differ with regard to PR-interval duration. There was a trend of increased QT interval (P=0.07) in deceased patients compared

Table 2. Summary of Measured ECG Variables in Patients With Cardiac Arrest 24 Hours After ROSC

Marker	Total Population	Survivors	Neurologically Intact Survivors	Residual Neurologic Disability	Deceased
QT, ms	553.47±107.55	536.96±112.79	532.32±35.43	549.61±111.59	568.83±94.08
QTc, ms	557.54±91.49	545.20±91.78	534.14±97.08	574.38±71.92	569.71±90.11
PR, ms	175.85±38.75	171.01±36.99	175.63±38.30	153.32±27.08	179.98±40.28
QRS, ms	105.44±34.42	100.33±29.06	104.12±30.65	90.34±22.64	108.86±38.05
QT dispersion, ms	135.01±57.83	95.93±34.24	93.31±35.44	103.09±31.18	166.31±54.29
Bazett QTc dispersion, ms	139.18±57.74	104.62±40.33	103.37±43.33	108.04±32.31	167.53±54.75
Fridericia QTc dispersion, ms	135.33±55.61	98.31±33.13	95.09±33.66	106.8±31.59	165.26±52.74
Relative QT dispersion, ms	7.86±3.54	5.91±2.11	5.71±1.84	6.51±2.74	9.11±3.04

Data are shown as mean±SD. Neurologically intact: CPC 1–2 at discharge. Residual neurologic disability: CPC 3–4 at discharge. CPC indicates Cerebral Performance Category; QTc, corrected QT interval; and ROSC, return of spontaneous circulation.

Table 3. Interquartile Range of ECG Indexes 24 Hours After ROSC

Patient Population	Quartile, %	QT, ms	QTc, ms	PR, ms	QRS, ms	QTd, ms	Bazett QTcd, ms	Fridericia QTcd, ms	Relative QTd, ms	Temperature, °C, Mean±SD
Total population	25	476	509	142	83	94	100	101	5.03	34.35±1.2
	50	568	561	170	95	125	126	125	6.81	
	75	704	613	204	114	164	159	157	9.57	
	99	816	816	262	254	301	335	331	20.83	
Survivors	25	466	503	137	81	74	76	77	4.32	34.6±1.1
	50	513	543	164	91	88	94	100	5.25	
	75	616	608	201	111	107	111	112	6.59	
	99	772	692	244	200	206	197	185	13.32	
Neurologically intact	25	476	503	140	78	72	62	76	4.17	34.75±1.2
	50	518	538	164	87	77	85	87	5.13	
	75	600	583	206	106	107	99	112	6.33	
	99	772	692	244	136	172	158	159	10.52	
Residual neurologic disability	25	406	490	128	85	82	93	94	5.03	34.27±0.6
	50	498	570	140	97	91	105	102	6.11	
	75	647	631	166	111	112	115	120	7.66	
	99	703	666	195	200	206	197	186	13.32	
Deceased	25	520	538	155	85	126	126	126	6.35	34.1±1.3
	50	588	593	181	96	150	150	148	8.45	
	75	644	639	204	125	209	210	202	11.74	
	99	816	816	262	254	321	335	331	20.83	

Neurologically intact: CPC 1–2 at discharge. Residual neurologic disability: CPC 3–4 at discharge. CPC indicates Cerebral Performance Category; QTc, corrected QT interval; QTcd, corrected QT dispersion; QTd, QT dispersion; and ROSC, return of spontaneous circulation.

with survivors, whereas no difference was present regarding QTc.

Regarding dispersion measures, there was no significant difference when assessed for PR-interval dispersion (P=0.1383). When assessing for QT dispersion indexes, deceased patients had markedly increased QT dispersion, QTc dispersion, and relative QT and QTc dispersion at 24-hour ECG (P<0.01).

Predictive Value

Logistic regression was done to assess the predictive value of QT dispersion indexes with respect to survival (Table 5). Among the tested QT dispersion indexes, corrected dispersion yielded the highest accuracy, followed by absolute QT dispersion and relative QT dispersion. Among the 2 different methods for the calculation of QTc, the measurement derived by the Fridericia formula appeared to outperform the one derived from the Bazett formula, with better receiver operating characteristic area under the curve (0.89 compared with 0.86). Regarding specificity and sensitivity, 118 ms for QT dispersion, 120.7 ms for Bazett QTc dispersion, and 114.7 for Fridericia QT dispersion were identified as the most favorable indexes, with 85.19% sensitivity and 81.4% specificity for absolute QT dispersion and 89.8% sensitivity and 80% specificity for Fridericia QT dispersion. The detailed results of the sensitivity analysis can be found in Table S1. The receiver operating characteristic curve for the association between QT dispersion of the 24-hour 12-lead ECG and probability of survival of patients with OHCA is depicted in Figure 1.

NSE levels at admission were not significantly different between survivors and nonsurvivors.

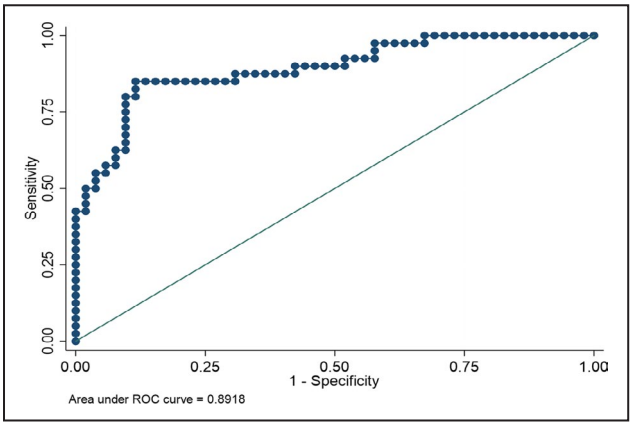

Figure 1. Receiver operating characteristic (ROC) curve for the association between QT dispersion of the 24-hour 12-lead ECG and survival of patients with out-of-hospital cardiac arrest.

However, at 24 hours, survivors' levels were markedly lower than those of deceased patients. NSE levels at 24 hours could reliably predict survival, with an area under the curve of 0.89. Both NSE and QT dispersion were independently associated with discharge outcomes in a multivariate model. Patients without a sinus rhythm had a higher nonsurvival probability trend. However, the difference in survival was not significant (P=0.15). Adjusting for sinus rhythm presence and the time elapsed from ROSC did not affect the association between QT dispersion and survival.

When patients were assessed according to neurologic status at discharge, ANOVA indicated no statistically significant differences among patients with different neurologic discharge status for QT, QTc, and PR intervals. However, when dispersion measures were assessed, significant differences were evident among QT dispersion indexes for patients with different outcomes, most importantly, QT dispersion, QTc dispersion, and relative QT dispersion, which are summarized in Table 5. Specifically, patients who were neurologically intact at discharge had significantly lower QT dispersion measurements compared with patients who had residual neurologic disability. Both groups had significantly lower QT dispersion than deceased patients.

Multinomial logistic regression indicated that QT and QTc dispersion could reliably predict neurologic status at discharge (Table 5 and Figure 2). The tested ECG values were independent of sex and age of the patients with cardiac arrest. Association between neurologic outcomes at discharge and QT dispersion and NSE measured at 24 hours remained significant for both variables when they were assessed together. ECGs at discharge were also analyzed.

In contrast to admission ECG, no association was found between QT dispersion indexes and survival on the discharge ECG. No difference was identified in average QRS intervals for both admission and discharge (Table 5). Moreover, we assessed the association between QT dispersion and findings on admission head CT. Patients with abnormal CT, defined as presence of brain herniation, loss of gray-white matter differentiation, or cerebral edema, had increased QT dispersion compared with patients without identified intracranial pathology (P=0.04). Nevertheless, regression analysis did not confirm this finding, although a nonsignificant trend was observed (P=0.09).

Sensitivity Analyses

To identify potential confounders for the relationship between QT dispersion and status at discharge, we

Table 4. Interquartile Range of ECG Indexes at Discharge

Patient Population	Quartile, %	QT, ms	QTc, ms	PR, ms	QRS, ms	QTd, ms	Bazett QTcd, ms	Fridericia QTcd, ms	Relative QTd, ms
Total population	25	346	514	142	99	75	108	89	6.13
	50	389	578	167	109	105	138	110	7.87
	75	446	625	187	126	130	186	145	10.6
	99	771	813	288	231	226	254	236	18.28
Survivors	25	350	503	137	96	75	104	78	6.13
	50	382	550	147	107	88	123	95	7.98
	75	438	612	171	112	122	177	137	9.66
	99	501	685	208	186	191	226	202	18.28
Neurologically intact	25	359	503	136	99	74	105	76	5.84
	50	384	543	145	109	85	117	94	7.46
	75	439	596	175	114	122	172	137	9.00
	99	499	692	208	183	191	226	202	14.52
Residual neurologic disability	25	340	530	139	82	91	121	83	7.75
	50	363	595	154	89	107	164	129	10.14
	75	444	508	166	99	134	191	154	14.68
	99	502	666	195	107	159	196	154	18.28
Deceased	25	342	542	153	103	126	76	94	6.05
	50	417	586	180	116	150	109	128	7.87
	75	492	634	219	131	209	134	145	10.61
	99	771	816	288	231	321	226	237	14.47

Neurologically intact: CPC 1–2 at discharge. Residual neurologic disability: CPC 3–4 at discharge. CPC indicates Cerebral Performance Category; QTc, corrected QT interval; QTcd, corrected QT dispersion; and QTd, QT dispersion.

assessed the relationship of QT dispersion with electrolytes at the time of measurement and with the administration of inotropes and catecholamines. Linear regression analysis indicated a significant negative correlation between QT dispersion and serum potassium at the time of the ECG being obtained (P=0.03) and a positive correlation between QT dispersion and epinephrine (P=0.001) and total dose of catecholamines, calculated as the sum of the dose of epinephrine, norepinephrine, and dopamine (P=0.04). QT dispersion's association with survival and neurologic status at discharge remained significant after adjustment for potassium and catecholamines No correlation was found between QT dispersion and dose of amiodarone, pH at the time of measurement, or temperature.

DISCUSSION

In our study, the associations of QT dispersion with neurologic status at discharge and with survival at discharge were assessed. Both QTc dispersion and uncorrected QT dispersion at 24 hours after ROSC was significantly associated with survival and with CPC at discharge in patients with OHCA. NSE provided a similar outcome, supporting our ECG observations, but at much higher cost.

OHCA is a highly morbid condition with an annual burden of >300 000 hospitalizations and 250 000 deaths.[1] Despite the improvement of outcomes with VA-ECMO hemodynamic support[3] and application of therapeutic hypothermia,[14] mortality is still high, and there is a need for development of novel prognostication techniques that will guide supportive care and permit establishment of reasonable treatment expectations. Furthermore, because most patients with OHCA die from either brain death or heart failure,[15] the prognostic indexes should focus on assessment of cerebral and cardiac injury in the first hours after the insult. In contrast, patients who have OHCA and are able to regain consciousness before hospital admission have a more positive neurologic prognosis than patients who are unable to regain consciousness in the field.[16] The highly specialized refractory ventricular tachycardia/ventricular fibrillation OHCA population in this investigation represents a difficult clinical scenario[8] in which novel prognostic markers of neurologic function may be of use. This is because obtaining ROSC in these patients suggests the possibility of a positive cardiac prognosis,[6] but the neurologic prognosis is often still difficult to address by the time ROSC has been obtained. Consequently, we think that QTc dispersion is a metric that might aid neurologic prognosis. Specifically, a QT dispersion cutoff value of 118 to 122 ms seems the most suitable for determining survival. However, like all the markers, QT dispersion is imperfect and should never be used without evaluation of other clinical and biochemical information.

QT Dispersion

Cardiac Injury

QT dispersion for assessment of brain injury has been performed previously in cases of stroke and

Table 5. Predictive Value of QT Dispersion Indexes 24 Hours After Arrest Regarding Survival After Refractory Ventricular Tachycardia/Ventricular Fibrillation

ECG Index	*P* Value	Likelihood Ratio	Area Under the Curve	Predicted Outcome
QTd	<0.00001	52.54	0.8918	Survival
QTc dispersion	<0.00001	36.74	0.8673	Survival
Relative QTd	0.0022	32.46	0.82	Survival
Absolute QT	0.05	3.7	0.6128	Survival
QTc	0.1883	1.73	0.5714	Survival
Fridericia QTcd	<0.00001	47.66	0.8913	Survival
Admission NSE	0.0768	3.13	0.65	Survival
24-h NSE	<0.00001	22.56	0.8942	Survival
QTd	<0.00001	55.4		Status at discharge
QTcd	<0.00001	36.36		Status at discharge
Relative QTd	<0.00001	35.47		Status at discharge
Absolute QT	0.1358	3.99		Status at discharge
QTc	0.4155	1.76		Status at discharge
Fridericia QTcd	<0.0001	47.4		Status at discharge
Admission NSE	0.04	6.14		Status at discharge
24-h NSE	<0.00001	22.65		Status at discharge

Status at discharge: neurologic outcome as assessed by CPC score. CPC indicates Cerebral Performance Category; NSE, neuron-specific enolase; QTc, corrected QT interval; QTcd, corrected QT dispersion; and QTd, QT dispersion.

subarachnoid hemorrhage.[17] Correct interpretation requires consideration of the timing of ECG recording and knowledge of other parameters that might interfere with repolarization such as electrolytes and temperature.[18,19] To address this issue, we included only ECGs performed 12 to 36 hours after ROSC and correlated the findings to electrolytes, temperature, and pH at the time at which the ECG was obtained and to the administered medications. We also used NSE as a separate measure to assess the validity of ECG findings.

QT dispersion was significantly affected by serum potassium and cumulative dose of epinephrine. However, the relationship between QT dispersion and survival remained significant in the multivariate analysis. No association was drawn between QT dispersion and body temperature; however, a temperature effect is something that should be expected. In our study, all patients were treated with therapeutic hypothermia, and thus there were minimal deviations in temperature at the time of measurement.

The connection between QT dispersion measures and heart and brain injury probably lies in the sympathetic innervation of the left ventricle. Sympathetic afferent fibers are distributed across the inferoposterior and anterior wall of the left ventricle.[20] Following myocardial ischemia, which occurs globally during cardiac arrest, sympathetic afferent fibers have been demonstrated to be activated[21] and consequently result in activation of the cardiac sympathetic efferent fibers.[22] QT dispersion is documented to be elevated in states of sympathetic activation such as hyperthyroidism[23] and alcoholism.[24] Even more important, acute physiologic activation of the sympathetic nervous system was shown to increase QT dispersion in a head-up tilt test of healthy individuals without any underlying disease.[25] In our study, we identified that the dose of epinephrine and the total dose of the composite of epinephrine, dobutamine, and norepinephrine were positively correlated to QT dispersion.

In accordance with previous reports, QT dispersion has been documented increasing in cases of myocardial ischemia, and successful reperfusion of ischemic areas is able to reverse that increase.[26] Compared with patients with unstable angina, patients presenting with ST-segment–elevation myocardial infarction had increased QT dispersion at the time of presentation.[27] Moreover, the increase of QT

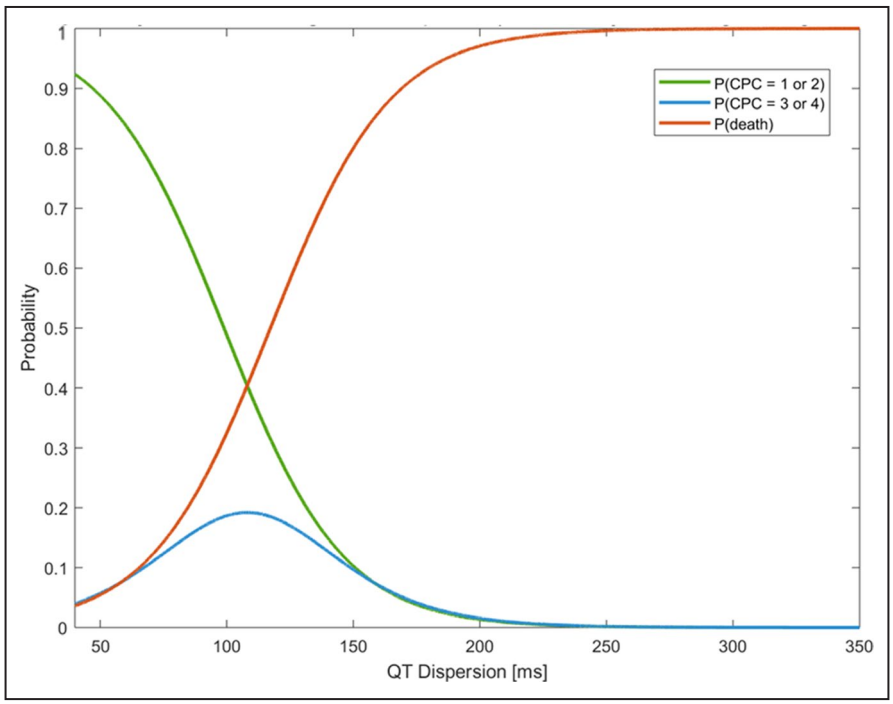

Figure 2. Probability of neurologic outcomes according to QT dispersion derived from 12-lead ECG 24 hours after return of spontaneous circulation in patients with out-of-hospital cardiac arrest (calculated by ordinal logistic regression).

Figure 2. The yellow line indicates the probability of discharge with a Cerebral Performance Category (CPC) score between 1 and 2. The red line indicates the probability of discharge with a CPC score between 3 and 4. The blue line indicates the probability of death. This figure shows that as QT dispersion increases, the probability of neurologically intact survival decreases while the probability of death increases. Survival with neurologic disability follows a distinct sigmoid curve.

dispersion correlates with tissue perfusion as assessed by Myocardial Blush Grade.[28] Studies have also correlated QT dispersion with the magnitude of viable left ventricle.[29] Counterintuitively, QT dispersion at 72 hours after the onset of ST-segment–elevation myocardial infarction was not associated with survival.[30] However, this analysis was done before the development of coronary angioplasty, and deep Q waves were equally present in both survivors and nonsurvivors. This result indicated that necrosis had already occurred in both groups, and therefore repolarization abnormalities should be universally expected.

Brain Injury

A second mechanism that might explain the strong association between neurologically intact survival and QT dispersion of the 24-hour ECG is its correlation with brain injury. QT dispersion has been noted to increase in cases of stroke when calculated at the first day after the event. Involvement of the insular cortex might be a crucial determinant for the observed increase in QT dispersion.[31,32] In particular, involvement of the insula is associated with alteration of sympathovagal balance, which results from a concomitant increase in circulating norepinephrine levels.[33] The autonomic instability that results from brain injury potentiates regional repolarization differences,[34] which might be represented by QT dispersion in patients with cardiac arrest treated with ECMO.[35,36] The hippocampus is another brain region that regulates the autonomic nervous system.[37] Temporal lobe seizures arising from the hippocampus have been reported to alter cardiac repolarization without affecting the heart rate[38,39] Whether these effects are carried through autonomic regulation or another pathway connecting the hippocampus and the left ventricle has yet to be elucidated. Finally, brainstem stimulation has been noted to alter cardiac repolarization.[40] Taken together, these findings point toward a potential brain injury effect on QT dispersion. In our study, there was a trend for association between abnormal findings on the head CT scan and increase in QT dispersion. However, the sensitivity of the CT scan of the head at admission of patients with cardiac arrest is uncertain[41]; therefore, the nonsignificant trend that was observed should be interpreted with caution.

Correlation of QT Dispersion and Clinical Outcomes

In our population, neurologically intact patients who survived did not have a decrease of QT dispersion in the discharge ECG. Bartos et al previously demonstrated that although the left ventricle recovers in the first 2 weeks following the arrest, neurologic recovery and rehabilitation is prolonged; the delayed recovery of the latter may account for the persistently elevated QT dispersion.[6] Moreover, despite their independence and intact consciousness, neurologically intact survivors still have significant deficits in memory and hippocampal atrophy.[42] The hippocampus is a potent regulator of the sympathetic nervous system, and thus lesions at that location may lead to autonomic instability[43] and potentially explain the increased QT dispersion seen in survivors. In deceased patients, QT dispersion significantly decreased in the discharge ECG. However, compared with the QT dispersion of the discharge ECG in OHCA survivors, it was still elevated (P=0.008). In patients with prolonged coma duration, normal electrical signals do not correlate with outcomes and do not seem to affect prognosis.[44] The absence of sinus rhythm was found more frequently in deceased patients; however, there was no statistical significance, and thus reassessment with a larger sample is necessary. The underlying heart disease also did not affect QT dispersion. The lack of association probably derives from the power of the effect of the global ischemic injury that results from cardiac arrest regardless of the underlying cause and affects both the heart and the brain.

Limitations

The findings in this report are subject to several important limitations. First, the study was retrospective and comprised a relatively small population of OHCA victims. Second, despite the established paradigms, QT interval utilization has important methodologic limitations. It has been argued that QT dispersion derives mostly from projection differences rather than true depolarization abnormalities. However, the data to support this criticism derive mostly from healthy individuals, and the projection effect has not been tested in patients with structural heart disease.[45] Moreover, the reproducibility of QT intervals in all leads is poor. Consequently, the absolute QT dispersion, which is derived from the difference between the minimum and the maximum QT interval, might be inaccurate and depends on the accuracy of the measurement.[46] To address these procedural limitations, we assessed the digitized ECGs twice with blinding to patient outcomes. Given the subjective nature of the measurements, each trace was measured by the same individuals to minimize error. To confirm that the observed trends did not result from the overestimation and underestimation of maximum and minimum QT, respectively, we also calculated the relative QT dispersion, which utilizes QT intervals from all leads and thus corrects for outlying measurements. Relative QT

dispersion also yielded strong associations with both survival and neurologic outcome. It is possible that patients with OHCA who are resuscitated in the field and are conscious on arrival may not have as marked, if any, QTc dispersion. This group of patients, by definition, exhibits a more positive neurologic prognosis than the patients with refractory ventricular tachycardia/ventricular fibrillation OHCA in this cohort because none of the refractory VT/VT patients with OHCA had regained spontaneous circulation or consciousness before institution of VA-ECMO support. We were unable to directly compare the QTc dispersion metric for the patients who had regained consciousness before arriving at the hospital and the patients with ventricular tachycardia/ventricular fibrillation OHCA in this cohort.

CONCLUSIONS

Cardiac arrest is a complex and highly morbid condition. Development of tools that can aid in the rapid assessment of neurologic injury is necessary. QT dispersion in the 24-hour ECG is a relatively simple and low-cost technique. If desired, it can be used in conjunction with other markers, significantly aiding in the prognostication of survival at discharge. Prospective validation in other cardiac arrest cohorts and application of techniques for automated calculation will determine its potential for wider clinical use.

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Disclosures

None.

Supplementary Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Sensitivity analysis for the QT dispersion cutpoint and survival at discharge.

Cutpoint (ms)	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 52.58..)	100.00%	0.00%	54.95%	1.0000	0.0000
(>= 54.75..)	100.00%	2.44%	56.04%	1.0250	0.0000
(>= 56.42..)	100.00%	4.88%	57.14%	1.0513	0.0000
(>= 57.01..)	100.00%	7.32%	58.24%	1.0789	0.0000
(>= 59.30..)	100.00%	9.76%	59.34%	1.1081	0.0000
(>= 62.01..)	100.00%	12.20%	60.44%	1.1389	0.0000
(>= 69.69..)	100.00%	14.63%	61.54%	1.1714	0.0000
(>= 76.44..)	100.00%	17.07%	62.64%	1.2059	0.0000
(>= 77.8378)	100.00%	19.51%	63.74%	1.2424	0.0000
(>= 77.98..)	100.00%	21.95%	64.84%	1.2813	0.0000
(>= 82.94..)	100.00%	24.39%	65.93%	1.3226	0.0000
(>= 83.41..)	100.00%	26.83%	67.03%	1.3667	0.0000
(>= 83.85..)	100.00%	29.27%	68.13%	1.4138	0.0000
(>= 85.8671)	100.00%	31.71%	69.23%	1.4643	0.0000
(>= 85.88..)	100.00%	34.15%	70.33%	1.5185	0.0000
(>= 87.81..)	100.00%	36.59%	71.43%	1.5769	0.0000
(>= 89.416)	100.00%	39.02%	72.53%	1.6400	0.0000
(>= 95.89..)	100.00%	41.46%	73.63%	1.7083	0.0000
(>= 96.25..)	98.00%	41.46%	72.53%	1.6742	0.0482
(>= 101)	98.00%	43.90%	73.63%	1.7470	0.0456
(>= 101.236)	98.00%	46.34%	74.73%	1.8264	0.0432
(>= 102.2..)	98.00%	48.78%	75.82%	1.9133	0.0410
(>= 104.3..)	96.00%	48.78%	74.73%	1.8743	0.0820
(>= 104.7..)	96.00%	51.22%	75.82%	1.9680	0.0781
(>= 105.0..)	96.00%	53.66%	76.92%	2.0716	0.0745

(>= 106.132)	94.00%	53.66%	75.82%	2.0284	0.1118
(>= 106.1..)	94.00%	56.10%	76.92%	2.1411	0.1070
(>= 106.6..)	92.00%	56.10%	75.82%	2.0956	0.1426
(>= 107.3..)	92.00%	58.54%	76.92%	2.2188	0.1367
(>= 107.9..)	92.00%	60.98%	78.02%	2.3575	0.1312
(>= 109.1..)	90.00%	60.98%	76.92%	2.3063	0.1640
(>= 109.8..)	90.00%	63.41%	78.02%	2.4600	0.1577
(>= 111.345)	90.00%	65.85%	79.12%	2.6357	0.1519
(>= 111.3..)	90.00%	68.29%	80.22%	2.8385	0.1464
(>= 112.2..)	90.00%	70.73%	81.32%	3.0750	0.1414
(>= 112.4..)	90.00%	73.17%	82.42%	3.3545	0.1367
(>= 113.8..)	90.00%	75.61%	83.52%	3.6900	0.1323
(>= 114.5..)	90.00%	78.05%	84.62%	4.1000	0.1281
(>= 117.2..)	88.00%	78.05%	83.52%	4.0089	0.1538
(>= 117.8..)	88.00%	80.49%	84.62%	4.5100	0.1491
(>= 121.1..)	88.00%	82.93%	85.71%	5.1543	0.1447
(>= 121.8..)	86.00%	82.93%	84.62%	5.0371	0.1688
(>= 123.508)	84.00%	82.93%	83.52%	4.9200	0.1929
(>= 124.8..)	82.00%	82.93%	82.42%	4.8029	0.2171
(>= 125.6..)	80.00%	82.93%	81.32%	4.6857	0.2412
(>= 125.8..)	78.00%	82.93%	80.22%	4.5686	0.2653
(>= 126.8..)	76.00%	82.93%	79.12%	4.4514	0.2894
(>= 128.0..)	74.00%	82.93%	78.02%	4.3343	0.3135
(>= 128.6..)	72.00%	82.93%	76.92%	4.2171	0.3376
(>= 130.0..)	70.00%	82.93%	75.82%	4.1000	0.3618
(>= 133.334)	68.00%	82.93%	74.73%	3.9829	0.3859
(>= 134.9..)	68.00%	85.37%	75.82%	4.6467	0.3749
(>= 135.5..)	66.00%	85.37%	74.73%	4.5100	0.3983
(>= 136.3..)	64.00%	85.37%	73.63%	4.3733	0.4217

(>= 136.9..)	62.00%	85.37%	72.53%	4.2367	0.4451
(>= 141.4..)	60.00%	85.37%	71.43%	4.1000	0.4686
(>= 143.8..)	58.00%	85.37%	70.33%	3.9633	0.4920
(>= 144.2..)	56.00%	85.37%	69.23%	3.8267	0.5154
(>= 144.4..)	56.00%	87.80%	70.33%	4.5920	0.5011
(>= 147.6..)	54.00%	87.80%	69.23%	4.4280	0.5239
(>= 150.832)	52.00%	87.80%	68.13%	4.2640	0.5467
(>= 150.9..)	50.00%	87.80%	67.03%	4.1000	0.5694
(>= 151.336)	48.00%	87.80%	65.93%	3.9360	0.5922
(>= 151.6..)	46.00%	87.80%	64.84%	3.7720	0.6150
(>= 152.8..)	46.00%	90.24%	65.93%	4.7150	0.5984
(>= 153.393)	44.00%	90.24%	64.84%	4.5100	0.6205
(>= 156.4..)	42.00%	90.24%	63.74%	4.3050	0.6427
(>= 157.3..)	40.00%	90.24%	62.64%	4.1000	0.6649
(>= 158.5..)	40.00%	92.68%	63.74%	5.4667	0.6474
(>= 159.0..)	40.00%	95.12%	64.84%	8.2000	0.6308
(>= 161.5..)	38.00%	95.12%	63.74%	7.7900	0.6518
(>= 169.8..)	36.00%	95.12%	62.64%	7.3800	0.6728
(>= 181.9..)	34.00%	95.12%	61.54%	6.9700	0.6938
(>= 188.3..)	32.00%	95.12%	60.44%	6.5600	0.7149
(>= 197.691)	32.00%	97.56%	61.54%	13.1200	0.6970
(>= 203.0..)	30.00%	97.56%	60.44%	12.3000	0.7175
(>= 204.1..)	28.00%	97.56%	59.34%	11.4800	0.7380
(>= 208.933)	26.00%	97.56%	58.24%	10.6600	0.7585
(>= 210.667)	24.00%	97.56%	57.14%	9.8400	0.7790
(>= 215.0..)	22.00%	97.56%	56.04%	9.0200	0.7995
(>= 216.3..)	20.00%	97.56%	54.95%	8.2000	0.8200
(>= 217.4..)	18.00%	97.56%	53.85%	7.3800	0.8405
(>= 219.1..)	16.00%	97.56%	52.75%	6.5600	0.8610

(>= 232.4..)	14.00%	97.56%	51.65%	5.7400	0.8815
(>= 234.9..)	12.00%	97.56%	50.55%	4.9200	0.9020
(>= 261.591)	10.00%	97.56%	49.45%	4.1000	0.9225
(>= 265)	8.00%	97.56%	48.35%	3.2800	0.9430
(>= 266.7..)	6.00%	97.56%	47.25%	2.4600	0.9635
(>= 269.8..)	4.00%	97.56%	46.15%	1.6400	0.9840
(>= 290.1..)	4.00%	100.00%	47.25%	0.9600	
(>= 335.3..)	2.00%	100.00%	46.15%	0.9800	
(> 335.3..)	0.00%	100.00%	45.05%	1.0000	