QT interval dispersion pattern in patients with acute ischemic stroke: Does the site of infarction matter?

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BACKGROUND: QT interval dispersion (QTD) is an independent predictor of outcome following acute neurological events.

OBJECTIVES: To explore QTD patterns and their relation to the affected cerebral region in patients with acute ischemic stroke.

METHODS: Thirty patients with first acute ischemic stroke (the first stroke the patients had ever experienced) (study group) and 30 healthy controls (control group) were enrolled. Patients underwent magnetic resonance imaging to confirm and localize cerebral damage. Patients in the study group were further subdivided according to the site of infarction into four subgroups – namely, cortical, subcortical, brain stem and cerebellar infarctions, as well as according to insular involvement. All included subjects underwent 12-lead electrocardiography to measure QTD and corrected QT dispersion (QTcD).

RESULTS: In the study group, both QTD and QTcD on the first hospitalization day were significantly higher than in the control group ($P < 0.05$ for both). Similarly, in the study group, both QTD and QTcD values on the first hospitalization day were significantly higher than the respective values on the third day ($P < 0.001$ for both). No significant differences were found among the four territorial subgroups, or between right- and left-sided subgroups, regarding QT interval measurements, whether on the first or third day ($P > 0.05$ for all). However, 'first-day' QTD and QTcD of patients with insular involvement were significantly higher than in those without such involvement ($P < 0.001$ for both).

CONCLUSIONS: Both QTD and QTcD increased significantly in patients with acute ischemic stroke during the first hospitalization day. This increase of 'first-day' QTD and QTcD was significantly higher in patients with insular involvement than in those without such involvement.

Key Words: QT dispersion; QT interval; Stroke

There is considerable evidence that the QT interval is closely related to ventricular action potential, and is a good noninvasive measure of the repolarization process. Several reports indicate that regional differences in static QT interval measurement (QT dispersion [QTD]) from a surface 12-lead electrocardiogram (ECG) may provide an indirect measure of the underlying nonhomogeneity of ventricular repolarization (1).

QTD is defined as the difference between the longest and shortest QT intervals on a surface ECG (2). An increase in QTD is reported to predict the occurrence of life-threatening ventricular tachyarrhythmias and sudden cardiac death in patients with ischemic heart disease (3). Furthermore, QTD was found to increase during episodes of myocardial ischemia or infarction (4).

In addition, QTD was demonstrated as an independent predictor of functional outcome and mortality following acute neurological events (5). In another study, the change in QTD (calculated as the absolute difference between QTD measured on admission and on the last available ECG) was significantly higher in patients who died than in survivors, and was associated with changes in neurological function in patients treated with thrombolytic therapy for acute ischemic stroke (6). Nevertheless, one report (7) attributed the increased QTD to associated myocardial injury in patients with acute neurological events, and another report (8) related these changes to pre-existing heart disease rather than stroke.

Central nervous system-mediated cardiac injury is a field of mounting interest pertaining to brain-heart interactions. In a cross-sectional study design, we explored QTD patterns and their relation to the affected cerebral region in a series of

patients with first acute ischemic stroke (the first stroke the patients had ever experienced).

METHODS

Patient selection

Thirty patients, who were admitted to the critical care unit with acute ischemic stroke, during the period from August 2008 to March 2009 (study group), as well as 30 healthy subjects (control group) were enrolled. Patients were considered to be eligible for enrollment if they had an episode of first territorial infarction presenting within the first 24 h of symptom onset. The diagnosis of acute ischemic stroke was based on the standard clinical criteria on presentation and was confirmed by magnetic resonance imaging (MRI) as discussed later. Patients with lacunar brain infarction, previous myocardial infarction within the previous four weeks, previously diagnosed congenital long QT syndrome, atrial fibrillation, paced rhythm or bundle branch block, known organic heart disease (valvular, ischemic or cardiomyopathy) as well as those receiving medications known to prolong the QT interval (eg, quinidine, amiodarone, etc) were excluded. Before inclusion, informed written consent was obtained from each patient after a full explanation of the study protocol, and the study protocol was reviewed and approved by the local institutional human research committee as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2002.

Definition of risk factors

The presence of hypertension was defined as a systolic blood pressure of 140 mmHg or greater, and/or a diastolic blood pressure of 90 mmHg or greater, previously recorded by repeated

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TABLE 1
Baseline characteristics of the two individual study groups

Characteristic	Study group (n=30)	Control group (n=30)	P
Age, years	62±10.7	62±11.7	>0.05
Male sex	17 (56)	14 (46)	>0.05
Diabetes mellitus	12 (40)	8 (26)	>0.05
Hypertension	24 (80)	21 (70)	>0.05
Family history of IHD	13 (43)	14 (46)	>0.05
Statin therapy	13 (43)	0 (0)	>0.05

Continuous variables are presented as mean ± SD, while categorical variables are presented as n (%). IHD Ischemic heart disease

noninvasive office measurements, which led to lifestyle modification or antihypertensive drug therapy. The presence of diabetes mellitus was defined as a fasting plasma glucose of 7 mmol/L or greater, and/or a 2 h postload glucose level of 11 mmol/L or greater, or receiving specific antidiabetic drug therapy.

Methods

All 30 patients underwent brain MRI shortly after admission to confirm the diagnosis of acute ischemic stroke and localize the site of cerebral damage. The diagnosis of acute ischemic stroke was based on visualization of a hypodense area surrounded by an area of brain edema.

Patients eligible for reperfusion therapy (presenting within 4 h after symptom onset) received pharmacological reperfusion therapy in the form of streptokinase 1,500,000 U administered by intravenous infusion over 30 min to 60 min.

All enrolled subjects (30 patients and 30 controls) underwent a resting high-quality 12-lead ECG recording, which was subsequently evaluated by an expert electrophysiologist blinded to both clinical and MRI data. QT interval was measured, using the manual technique, as the time in milliseconds (ms) between the first deflection of the QRS complex and the point of return of the T wave to the isoelectric line. Measurements were obtained in three consecutive complexes in each lead and the mean value was used. The leads in which the end of the T wave could not be clearly identified were excluded from analysis (9). In leads with a U wave, the nadir between the T and U waves was considered to be the end of the T wave. The maximal and minimal QT intervals were recorded, and the QTD was calculated as the difference between the two intervals, being individually recorded for each patient (10). The corrected QT (QTc) interval was then calculated using Bazett's formula: QTc interval = QT interval/square root of RR (11). Finally, the QTc dispersion (QTcD) was calculated as the difference between the maximal and minimal QTc intervals. These measurements were estimated once for the control group; for the study group, they were estimated on the first and third day of hospitalization. The mean values of the QT and QTc intervals, as well as the QTD and QTcD, were calculated for each group separately, and among the study group, on the first and third hospitalization day separately.

Patient subgroups

Patients in the study group were further subdivided according to the site of lesion (as shown on MRI) into subgroups with cortical, subcortical, brainstem and cerebellar infarctions. Furthermore, they were categorized according to the side of

TABLE 2
QT interval measurements in the two individual groups during the first hospitalization day

Measurement	Study group (n=30)	Control group (n=30)	P
QT maximal	399±35	376±25	>0.05
QT minimal	342±32	333±22	>0.05
QTD	56±19	43±5	0.001
QTc maximal	438±31	432±20	>0.05
QTc minimal	387±35	384±20	>0.05
QTcD	62±21	48±5	0.001

All variables are presented as mean ± SD in ms. QTc Corrected QT interval; QTcD Corrected QT dispersion; QTD QT dispersion

lesion into subgroups of right- and left-sided infarctions. Similarly, study group patients were classified according to 'insular' involvement into two subgroups – namely, those with and those without insular involvement. The mean values of the above measurements were calculated for each subgroup separately, on the first and third hospitalization day.

Statistical analysis

All continuous variables were presented as mean ± SD, if they were normally distributed. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Categorical variables were described with absolute and relative (percentage) frequencies. Pearson χ^2 and unpaired *t* tests were used to compare the distribution of categorical and continuous variables, respectively, between the study and the control groups. A paired *t* test was used to compare QT intervals and QTD values within the study group between the first and third hospitalization days. ANOVA was used to compare QT intervals and QTD values among the subgroups with cortical, subcortical, brainstem and cerebellar infarctions. Finally, an unpaired *t* test was used to compare QT intervals and QTD values between the two subgroups with right-sided and left-sided infarctions, as well as between patients with and without insular involvement. All tests were two sided and a probability value of $P < 0.05$ was considered to be statistically significant. Analyses were performed with the SPSS statistical package, version 12.0 (SPSS Inc, USA).

RESULTS

A total of 60 patients were enrolled in the current study, which comprised 30 patients with acute ischemic stroke (study group) and 30 healthy subjects (control group). Table 1 shows the baseline clinical characteristics of the two individual groups. The mean age of the study group was 62±10.7 years, 17 (56.7%) being men. The two individual groups were statistically matched regarding age, sex, diabetes mellitus, hypertension, family history of ischemic heart disease and statin therapy. Among the study group, there were nine patients with cortical, 12 with subcortical, eight with brain stem and one with cerebellar infarction. Similarly, 13 patients in the study group had right-sided and 17 had left-sided infarction, and nine had insular involvement while 21 did not have such involvement.

In the study group, both QTD and QTcD on the first day of admission were significantly higher than the corresponding values in the control group (56.3±19.7 ms versus 43±5.4 ms, and 62.6±21.5 ms versus 48.8±5.2 ms, respectively, $P < 0.05$ for both) (Table 2).

TABLE 3
QT interval measurements in the study group (n=30) on the first and third hospitalization days

Measurement	First day	Third day	P
QT maximal	399±35	386±39	>0.05
QT minimal	342±32	342±33	>0.05
QTD	56±19	43±10	<0.001
QTc maximal	438±31	441±43	>0.05
QTc minimal	387±35	398±34	>0.05
QTcD	62±21	50±13	<0.001

All variables are presented as mean ± SD in ms. QTc Corrected QT interval; QTcD Corrected QT dispersion; QTD QT dispersion

TABLE 4
QT interval measurements in the various territorial subgroups during the first and third hospitalization days

Measurement	Cortical (n=9)	Subcortical (n=12)	Brain stem (n=8)	Cerebellar (n=1)	P
First day					
QT maximal	397±33	393±33	408±45	400	>0.05
QT minimal	337±36	338±32	352±32	360	>0.05
QTD	60±17	55±22	56±20	40	>0.05
QTc maximal	304±31	427±33	445±29	455	>0.05
QTc minimal	399±45	381±34	379±22	407	>0.05
QTcD	66±20	58±24	66±20	48	>0.05
Third day					
QT maximal	367±48	393±37	400±28	360	>0.05
QT minimal	322±38	351±33	355±17	320	>0.05
QTD	45±13	41±5	45±14	40	>0.05
QTc maximal	443±20	434±30	444±74	480	>0.05
QTc minimal	392±19	396±33	402±51	432	>0.05
QTcD	52±11	45±5	54±21	52	>0.05

All variables are presented as mean ± SD in ms. QTc Corrected QT interval; QTcD Corrected QT dispersion; QTD QT dispersion

Similarly, in the study group, both QTD and QTcD on the first day of hospitalization were significantly higher than the corresponding values on the third day of hospitalization in the same group (56.3±19.7 ms versus 43.7±10.7 ms, and 62.6±21.5 ms versus 50.4±13.3 ms, respectively, $P<0.001$ for both) (Table 3).

When the study group patients were divided into four subgroups according to the site of lesion (as shown on MRI), no significant differences were found between these subgroups regarding the different values of QT interval measurement, whether on the first day or the third day ($P>0.05$ for all) (Table 4).

Similarly, when the study group patients were divided into two subgroups according to the side of lesion (right or left sided), no significant differences were found between these two subgroups regarding the different values of QT interval measurement, whether on the first day or the third day ($P>0.05$ for all) (Table 5).

Nevertheless, when the study group patients were divided into two subgroups according to insular involvement, it was found that 'first-day' QTD and QTcD of patients with insular involvement were significantly higher than in those without such involvement ($P<0.001$ for both). Yet, there were no significant differences between the two subgroups regarding the other QT interval measurements on the first day and all QT interval measurements on the third day of hospitalization ($P>0.05$ for all) (Table 6).

TABLE 5
QT interval measurements in the right- and left-sided subgroups during the first and third hospitalization days

Measurement	Right-sided (n=13)	Left-sided (n=17)	P
First day			
QT maximal	397±34	400±38	>0.05
QT minimal	337±32	347±33	>0.05
QTD	60±20	53±18	>0.05
QTc maximal	430±39	444±22	>0.05
QTc minimal	384±39	389±32	>0.05
QTcD	65±24	59±18	>0.05
Third day			
QT maximal	388±49	384±30	>0.05
QT minimal	342±40	342±27	>0.05
QTD	45±12	41±9	>0.05
QTc maximal	438±28	443±53	>0.05
QTc minimal	388±25	407±40	>0.05
QTcD	50±13	50±13	>0.05

All variables are presented as mean ± SD in ms. QTc Corrected QT interval; QTcD Corrected QT dispersion; QTD QT dispersion

TABLE 6
QT interval measurements in the subgroups of insular involvement and no insular involvement during the first and third hospitalization days

Measurement	Insular involvement (n=9)	No insular involvement (n=21)	P
First day			
QT maximal	393±36	401±36	>0.05
QT minimal	322±35	351±27	>0.05
QTD	71±17	50±17	<0.001
QTc maximal	443±25	435±34	>0.05
QTc minimal	387±48	387±29	>0.05
QTcD	79±21	55±17	<0.001
Third day			
QT maximal	372±45	392±36	>0.05
QT minimal	326±34	349±31	>0.05
QTD	45±13	42±9	>0.05
QTc maximal	430±25	445±49	>0.05
QTc minimal	380±22	405±37	>0.05
QTcD	51±11	49±14	>0.05

All variables are presented as mean ± SD in ms. QTc Corrected QT interval; QTcD Corrected QT dispersion; QTD QT dispersion

Moreover, there was no significant difference in the QTD or QTcD between the subgroups of hypertensive versus normotensive patients, diabetic versus nondiabetic patients, or those on statin therapy versus those not on statin therapy ($P>0.05$ for all) (data not shown).

DISCUSSION

There is a good body of evidence suggesting that autonomic regulation of the cardiovascular system is altered by acute brain injury. QT prolongation, T wave changes, and supraventricular and ventricular tachyarrhythmias are common ECG manifestations of stroke, regardless of the presence of pre-existing heart disease. Additionally, greater variability of systolic blood pressure was noted in patients with acute stroke compared with controls (12).

Course of QT dispersion during acute stroke

Similar to a few previous reports (5,13), the current study demonstrated a significant increase in both QTD and QTcD

among patients in the acute phase of ischemic stroke compared with the healthy control subjects. Previously, some reports (5,8) ascribed these changes to pre-existing heart disease; however, in the current study, we excluded cardiac conditions that would potentially increase QTD to exclusively elucidate the effect of cardiovascular autonomic dysregulation associated with ischemic stroke. On the other hand, several explanations have been put forward to account for ventricular repolarization changes associated with stroke. Centrally mediated sympathetic hyperactivity (5,14,15), reduced cardiac parasympathetic innervation (16,17) and abnormal baroreceptor function (12) might explain these findings.

Recent work has suggested that oxidative stress might play a role in the development of ventricular repolarization abnormalities. The infusion of a nitric oxide synthase inhibitor was associated with a significant increase of both QTD and QTcD in healthy rabbits (18). Reactive oxygen species are abundantly generated during acute ischemic stroke and there is a robust body of evidence indicating that oxidative stress is an important mediator of tissue injury in acute ischemic stroke (19).

Both QTD and QTcD among the study group decreased significantly on the third day compared with the first day of hospitalization. It is noteworthy that both QTD and QTcD on the third day of hospitalization were statistically similar to the corresponding values in the control group ($P>0.05$ for both, data not shown).

QT dispersion in different sites of stroke

The study by Afsar et al (13) reported no significant differences in QTD and QTcD among different territories of stroke categorized according to the supplying artery (anterior, middle and posterior cerebral artery). However, they demonstrated that QTcD correlates with lesion size, being significantly greater in patients with large lesions than those with small lesions on 'first-day' ECG recordings. Yet, these differences were no longer significant in 'third-day' recordings (13). To the best of the authors' knowledge, the current study was the first to compare QTD and QTcD among the various anatomical-functional territories (cortical, subcortical, brain stem and cerebellar) of the brain and, similarly, it found no significant differences in QTD and QTcD measurements among these territories, whether on the first or third day of hospitalization. Global 'functional' involvement of the cardiovascular autonomic control centres in the acute phase of stroke, regardless of the site of damage, might explain, at least in part, the universal increase of QTD and QTcD on the first day of hospitalization, as well as its return to 'control' values on the third hospitalization day.

In contrast with our results, two previous peer-reviewed articles (20,21) described the 'lateralization' of cardiovascular autonomic control centres between the two cerebral hemispheres, with sympathetic activation linked to the right hemisphere and parasympathetic activation linked to the left hemisphere. Nevertheless, the current study showed no significant differences in QTD and QTcD measurements between right- and left-sided brain lesions whether on the first or the third day of hospitalization. It would seem that the increase of QTD and QTcD on the first day of hospitalization is the outcome of a complex interplay of various factors that implicate

'cardiovascular autonomic control centres' from the two hemispheres of the brain.

Importantly, the current study demonstrated that patients with insular involvement had significantly greater 'first-day' QTD and QTcD than those without such involvement. Oppenheimer et al (22) used a rat model to assess the effects of electrical stimulation to the insular cortex on the ECG. The study group was compared with two control groups – one that received similar stimulation to an area of cortex outside the insula and another that had an electrode inserted into the insular cortex but did not receive electrical stimulation. None of the control animals developed significant ECG changes, while study animals developed changes consisting of alterations in P wave morphology, prolonged PR interval, widening of the QRS complex and ST segment depression. Moreover, study animals developed premature ventricular complexes, complete heart block, worsening bradycardia and, eventually, asystole.

The animals in the aforementioned study also had increased plasma noradrenaline concentrations, while control animals had no such change. The authors concluded that stimulation of the insular cortex produced increased cardiac sympathetic activity (as shown by elevated noradrenaline levels) that resulted in the observed ECG changes. Additionally, 58% of the experimental animals showed diffuse cardiac myocytolysis – a change characteristic of catecholamine excess – that did not occur in any of the control animals. The authors speculated that this structural damage might have been the substrate for the observed ECG changes. Eventually, they attributed the observed dysrhythmias to excess sympathetic activity, but explained the bradycardia and asystole by noting that parasympathetic areas of the insula may have been stimulated as well (22).

Clinical implications

Because increased QTD is known to predict the occurrence of life-threatening ventricular arrhythmias and sudden cardiac death (3), its occurrence in the early phase of acute ischemic stroke implies a high-risk paradigm of this fairly common clinical scenario. Moreover, the higher QTD in patients with insular involvement would possibly categorize these patients in a further 'higher risk' category, and might also foresee a worse prognosis (5). Yet, the return of QTD values to 'near control' levels on the third hospitalization day might provide reasonable reassurance regarding the ventricular repolarization state at this phase of stroke.

CONCLUSION

Both QTD and QTcD increased significantly in patients with acute ischemic stroke during the first day of admission, and returned to 'control values' on the third day. This increase of QTD and QTcD in acute ischemic stroke is universal regardless of the site and side of damage. However, the increase of 'first-day' QTD and QTcD was significantly higher in patients with insular involvement than in those without such involvement.

Limitations of the study

Our findings are based on a single-centre study with a relatively small sample size – a fact that makes it difficult to make reliable conclusions. Multicentre studies using the same protocol and

examining a larger number of patients are needed. As well, measurement of the QT interval would be better performed automatically, by means of computer software. Another limitation of the study is the possibility of selection bias because we studied a cohort of patients with first acute ischemic stroke, thus it is not known whether our findings can be safely extrapolated to all patients with stroke. Finally, the cross-sectional

nature of the design, which does not infer any causal or temporal relationship, necessitates careful interpretation of the results.

DISCLOSURE: None of the authors have conflicts of interest to declare.

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