QT interval prolongation in patients with acute ischemic stroke: a report in northwest China

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Abstract
Aims: QT interval prolongation is common in patients with stroke and increases the risk of malignant arrhythmia and sudden death. Our aim was to analyze differences in the QT interval and electrocardiogram abnormalities between acute ischemic stroke patients and controls.

Methods: We retrospectively collected data from 273 patients with acute ischemic stroke from the neurological intensive care unit and 495 controls from other departments. A standard 12-lead electrocardiogram was recorded within 24 hours of hospitalization. Clinical information, the QT interval corrected for heart rate (QTc), and the incidence of electrocardiogram abnormalities were compared between groups.

Results: There was no difference in age, sex, or the prevalence of hypertension or diabetes mellitus between the acute ischemic stroke group and controls. Acute ischemic stroke patients showed a significantly longer QTc and a higher incidence of both sinus bradycardia and ST-T changes compared with controls. We also showed that the changes in electrocardiogram results observed in acute ischemic stroke might be transient.

Conclusion: Acute ischemic stroke patients may have a longer QT interval and a higher incidence of electrocardiogram abnormalities. In clinical practice, careful attention should be paid to acute ischemic stroke patients to prevent malignant arrhythmia.
Keywords
Acute ischemic stroke, QT interval, electrocardiogram abnormalities, malignant arrhythmia, prevention, sinus bradycardia, ST-T changes, transient changes

Introduction
Ischemic stroke specifically refers to a central nervous system infarction that is accompanied by overt symptoms. Ischemic stroke is the most common type of stroke. Electrocardiographic (ECG) changes are frequently observed in ischemic stroke, and they are noticed gradually by clinicians. ECG changes often occur 12 to 48 hours after illness onset, and are transient, lasting for no more than 1 week. Nearly every type of ECG change, including cardiac arrhythmias, such as ventricular premature beats (VPB) or supraventricular ectopic beats, ventricular tachycardia (VT) and atrial flutter (AFL)/fibrillation (AF), and repolarization abnormalities (ST-segment changes, QT interval prolongation and increased QT interval dispersion) have been described in stroke patients. A prolonged QT interval corrected for heart rate (QTc) was reported in 23% to 45% of patients during acute stroke and it was associated with cardiac arrhythmias and sudden death. In this study, the QTc and ECG abnormalities were compared between acute ischemic stroke patients and controls.

Materials and methods

Patient selection
This was a retrospective study. Data from patients with acute ischemic stroke (stroke patients) who were admitted to the neurological intensive care unit were collected for the period from January 2016 to June 2018 at the First Affiliated Hospital of Xi’an Jiaotong University, and patients in other departments were enrolled as controls. Patients were enrolled if they had an episode of first acute ischemic stroke and presented within the first 24 hours of symptom onset. The diagnosis of ischemic stroke was confirmed by computed tomography (CT) scanning or magnetic resonance imaging (MRI). The exclusion criteria included hemorrhagic stroke, subarachnoid hemorrhage (SAH), previous myocardial infarction, congenital long QT syndrome, paced rhythm, known organic heart disease (valvular or ischemic cardiomyopathy), and use of drugs that prolong QT intervals (antiarrhythmic, antimalarials and psychotropic drugs). Patients in the control group had no previous brain lesions or heart diseases. Patients in the control group had lower back pain, leg pain, hypertension, or diabetes mellitus and they did not take drugs that prolong QT intervals. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xi’an Jiaotong University (No.XJTU1AF2017LSKL-191). Written informed consent was obtained from all patients.

All patients had a standard ECG recorded within 24 hours of admission. ECGs were analyzed by a physician who was blinded to the diagnosis and patient groupings. The QT interval was measured manually. QTc was calculated using the Bazett formula, as follows: $\text{QTc}_{\text{Baz}} = \frac{\text{QT}}{\sqrt{RR}}$. ST-T changes included ST segment
(elevation and depression) and T-wave changes (e.g., inversion and flat). ST segment depression referred to ST segments that were depressed >0.05 mV at 0.06 s after the J-point. The T wave was normally in the same direction as the terminal QRS forces; otherwise, it was inverted. Sinus bradycardia was defined as a heart rate that was lower than 60 beats/minute. Severe sinus arrest referred to pauses longer than 3 seconds. Malignant arrhythmia included ventricular tachycardia, ventricular fibrillation, or very severe sinus arrest and third degree atrioventricular block. A detailed clinical history was taken from the patients or their accompanying relatives. Clinical data were collected from all patients and included age, sex, history of hypertension, and diabetes mellitus (DM).

**Statistical analysis**

Statistical analysis was performed using the SPSS 18.0 data editor (SPSS Inc., Chicago, IL, USA). Continuous data are reported as the mean ± standard deviation, and frequencies are expressed as percentages. Continuous variables were compared using the Student’s t-test between the two groups. Comparisons among groups were made using a two-way ANOVA, and frequencies were compared using the Chi-squared test. The level of significance was set at *P* < 0.05.

**Results**

**Clinical characteristics**

Table 1 shows the clinical characteristics of the stroke patients and controls. There were 273 patients with acute ischemic stroke who were included in our study (male, 180; mean age, 61.59 ± 13.23 years old) and were similar to the 495 controls (male, 292; mean age, 61.13 ± 13.38 years old). There was no significant difference between the two groups in the sex ratio or the proportion of individuals with hypertension or DM. These results suggest that the baseline data were consistent.

**ECG characteristics between the two groups**

The ECG characteristics of both groups are shown in Table 2. The QTc interval in the stroke patients was 415.35 ± 31.40 ms and was significantly longer than that found in the control group (407.58 ± 23.25 ms, *P* < 0.05). In stroke patients, 27.11% of the patients manifested ST-T changes. Arrhythmia occurred in some patients, including 14 (5.12%) with VPB and 39 (14.29%) with sinus bradycardia. There were significant differences in the ECG abnormalities of the two groups (*P* < 0.05). Among the 273 stroke patients, 181 underwent MRI diffusion-weighted imaging (MRI-DWI) examinations, and the rest were evaluated by CT. Based on MRI-DWI images, the infarction locations were divided into five groups: the basal ganglia and thalamus, the periventricular area, multiple lacunar infarctions, lobar lesions, and the cerebellum and brainstem. Table 3 shows that there were no differences in QTc, ST-T changes, sinus bradycardia, or VPB among the subgroups.

**ECG changes may be transient in patients with acute ischemic stroke**

ECG changes might be dynamic and transient over time in patients with acute ischemic stroke. As shown in Figure 1, in one patient, VPB was detected at admission (Figure 1a), and AF occurred 2 days later (Figure 1b). However, ECG was completely normal after 10 days (Figure 1c) in the same patient. Figure 2 shows that in another patient, ECG showed changes in ST-T (T wave flat and inversion) in leads V4 to V6 at admission (Figure 2a), but T-wave
morpology was normal after several days
(Figure 2b).

In this study, hyperhomocysteinemia
(11.36%) and hyperlipidemia (10.62%)
were frequent among acute ischemic
stroke patients. Twenty (7.33%) patients
died during hospitalization. No malignant
arrhythmias were detected on ECG in our
study. We compared the data between
patients who died in the hospital and
patients without death events. The QTc
was 422.53 ± 48.67 ms in the patients who
died, and this was longer than that found in
the patients without death events (414.82
± 29.81 ms), but the difference was not
significant.

**Discussion**

Stroke is a common cause of death in
China\(^5\) and a major cause of disability
in adolescents,\(^6\) with approximately half of
Figure 1. Heart rhythm changes in a patient. (a) Ventricular premature beats were recorded at admission, (b) Atrial fibrillation occurred 2 days after admission and (c) Sinus rhythm in ECG in the same patient 10 days later.
the patients experiencing neurological damage, failing to regain self-care ability, and needing long-term care. The incidence and prevalence of stroke increases with age. The most common type of stroke is ischemic stroke. According to the Trial of Org 10172 in the Acute Stroke Treatment (TOAST) classification, ischemic stroke can be divided into five groups: large artery atherosclerosis (LAA), small vessel disease, cardioembolic disease (CE), other determined etiology, and undermined etiology. CE is the most common ischemic subtype in patients over 80 years of age and it has a high mortality rate. This may be associated with the large infarction size that is associated with cardiogenic brain embolism. The major risk factors for cardioembolic

![Figure 2. ST-T changes in a patient. (a) ST segment changes and a low and flat T wave in the V4, V5, and V6 leads at admission and (b) ST segment, and T wave morphology were normal several days later.](image-url)
stroke are AF, recent myocardial infarction, mechanical prosthetic valve, dilated myocardiopathy, and mitral rheumatic stenosis. It has been reported that most ischemic stroke patients have multiple risk factors, including hypertension, heart disease, AF, dyslipidemia, DM, and lack of exercise. In our study, risk factors, such as the occurrence of hypertension, DM, hyperhomocysteinemia, and dyslipidemia, were common in patients with acute ischemic stroke.

The main findings of this study are that QTc was significantly longer in patients with acute ischemic stroke compared with controls and that the occurrence of ECG abnormalities was prevalent. However, when we divided the locations of cerebral infarction into five parts, there was no significant difference observed in the QTc among them. The QTc interval observed on ECG is considered to be closely associated with ventricular action potentials, which is also a good noninvasive measure of the repolarization process. A prolonged QT interval forms a substrate for malignant ventricular arrhythmias. Previous studies have shown that prolonged QT intervals are predictors of early mortality in acute ischemic stroke patients. Intracranial pathology is frequently associated with ECG changes, including ST-segment depression, QT interval prolongation, ventricular arrhythmias, and heart rate variability. The incidence of new-onset cardiac arrhythmias following stroke in patients varies widely depending on the type of stroke. Lavy et al. found that the incidence of these abnormalities was 39%, whereas Goldstein found that the incidence was 25% in stroke patients and 3% in controls. The occurrence of cardiac arrhythmias was most frequently evaluated among patients with SAH. Daniele et al. performed a study focused on cardiac arrhythmias after stroke and they found that cardiac arrhythmias were observed in 21.9% of patients with ischemic strokes, including 26.8% of patients with right hemispheric lesions and 14.3% of patients with left hemispheric lesions. The mechanisms responsible for the changes observed on ECG in patients with acute ischemic stroke have not been fully clarified. There may be several possible reasons for this. First, some evidence suggests that the central autonomic network is responsible for central generation and the integration of cardiac autonomic control. Studies have suggested that the brain controls the function of the cardiovascular autonomic nervous system (ANS). The right hemisphere is believed to predominate in sympathetic responses, whereas the left hemisphere predominantly elicits parasympathetic responses. Previous studies have shown that the insular cortex plays a central role in autonomous nervous regulation, with the right side associated with sympathetic autonomic and the left related to parasympathetic autonomic tone. Ischemic stroke attacks, ischemia, anoxia, and increased intracranial pressure may lead to dysfunction of the ANS and increased circulating catecholamines, thus affecting repolarization and causing changes in ECG or even myocardial lesions. Second, stroke often causes electrolyte disorders, such as hypokalemia, hyponatremia, and hypochloremia, which result from neurmodulation, vomiting, dehydration, and fasting. Third, patients with ischemic stroke often have concurrent LAA. Atherosclerosis is a systemic artery disease that usually involves multiple arteries, including coronary and cerebral arteries. Recently, peripheral arterial atherosclerosis has been classified as an equal risk factor for coronary heart disease. Therefore, ischemic stroke patients also have a high risk of coronary heart disease, which may affect QTc and the occurrence of cardiac arrhythmias. Finally, the occurrence of hyperhomocysteinemia was common in ischemic stroke patients in our study. However, we did not routinely detect
plasma homocysteine concentrations in the control group. Previous studies found that plasma homocysteine levels were associated with QTc in the general population.\(^{27}\) Therefore, we speculated that hyperhomocysteinemia might have an effect on QT prolongation. In our study, when the subgroup analysis was performed, the QTc did not differ. One reason is that there may be some deviations in our grouping. Another reason may be that ECG changes might not be specific to a particular location, and widely distributed neurons and pathways in the central nervous system could participate in the regulation of the cardiac ANS.\(^{28}\)

There is still some controversy regarding whether prolongation of QT can predict the prognosis in patients with acute ischemic stroke. Hromádka et al. found that prolonged QTc after 48 hours of acute ischemic stroke was closely related to neurological outcome and 1-year mortality.\(^{29}\) A study also revealed that QT dispersion could predict the functional outcome and mortality after acute neurological events.\(^{30}\) However, Chao et al.\(^{31}\) and Golbasi et al.\(^{32}\) showed that QTc had no significant predictive value for prognosis. In our study, we did not observe a significant difference in QTc between patients who died and those who survived. Many factors can affect patient prognosis, such as the location and size of the infarction, infection, and complications.\(^{33,34}\) In our study, the main cause of death was massive cerebral infarction. Additional larger, prospective, and well-designed studies are needed to explore the relationship between QTc and prognosis in patients with acute ischemic stroke.

Here, we also observed the occurrence of paroxysmal AF and VPB in a patient. Previous studies found that the ANS plays a major role in atrial arrhythmias and can result in ECG changes marking atrial dysfunction.\(^{35}\) Moreover, atrial dysfunction is a potential pathogenic factor in cryptogenic stroke. Additionally, the ANS is closely related to the occurrence of ventricular arrhythmia.\(^{36}\) ECG markers of atrial dysfunction include P wave dispersion, P wave duration, PR interval, P wave area, P wave terminal force in lead V1, P wave axis, and premature atrial contractions. We checked the case again and discovered atrial expansion with a left atrial diameter of 35 mm in this 83-year-old patient. Therefore, we inferred that in this patient, AF and prolonged PR might reflect atrial dysfunction, increasing the chance of ischemic stroke. Thus, when stroke occurred, ventricular arrhythmia appeared.

There are some limitations to our study. First, we could not absolutely exclude patients with coronary artery disease who shared similar risk factors because we did not conduct echocardiography or coronary angiography, and this may have affected the QTc interval. Second, we did not obtain the previous ECG before ischemic stroke and did not repeat ECG examination in every patient, so we could not observe dynamic changes in ECG. Additionally, we did not follow up the patients, so the relationship between prolonged QTc and long-term prognoses could not be explored.

**Conclusion**

Arrhythmias and ischemic-like and repolarization changes are common in ischemic stroke patients. Therefore, appropriate management and optimal care are needed for these patients.

**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

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