Differences in the Slope of the QT-RR Relation Based on 24-Hour Holter ECG Recordings between Cardioembolic and Atherosclerotic Stroke

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Abstract

Objective Detecting paroxysmal atrial fibrillation in patients with ischemic stroke presenting in sinus rhythm is difficult because such episodes are often short, and they are also frequently asymptomatic. It is possible that the ventricular repolarization dynamics may reflect atrial vulnerability and cardioembolic stroke. Hence, we compared the QT-RR relation between cardioembolic stroke and atherosclerotic stroke during sinus rhythm.

Methods The subjects comprised 62 consecutive ischemic stroke patients including 31 with cardioembolic strokes (71.8±12.7 years, 17 men) and 31 with atherosclerotic strokes (74.8±10.8 years, 23 men). The QT and RR intervals were measured from ECG waves based on a 15-sec averaged ECG during 24-hour Holter recording using an automatic QT analyzing system. The QT interval dependence on the RR interval was analyzed using a linear regression line for each subject ([QT]=A[RR]+B; where A is the slope and B is the y-intercept).

Results The mean slope of the QT-RR relation was significantly greater in cardioembolic stroke than in atherosclerotic stroke (0.187±0.044 vs. 0.142±0.045, p<0.001). The mean QT, RR, or QTc during 24-hour Holter recordings did not differ between them. An increased slope (>0.14) of the QT-RR regression line could predict cardioembolic stroke with 97% sensitivity, 55% specificity and a positive predictive value of 64%.

Conclusion The increased slope of the QT-RR linear regression line based on 24-hour Holter ECG in patients with ischemic stroke presenting in sinus rhythm may therefore be a simple and useful marker for cardioembolic stroke.

Key words: atherosclerotic stroke, cardioembolic stroke, paroxysmal atrial fibrillation, QT-RR relation

Introduction

In patients with acute ischemic stroke presenting in sinus rhythm, it is sometimes difficult to detect the association of paroxysmal atrial fibrillation (AF) because such episodes of paroxysmal AF are often short, and they are also frequently asymptomatic (1). The ventricular repolarization dynamics are considered to be a marker of ventricular vulnerability (2). The same channel as the determinants of ventricular repolarization could affect part of atrial repolarization (3). Hence, the ventricular repolarization dynamics may also reflect atrial vulnerability. Several previous studies have reported that QTc prolongation is associated with an increased risk of AF and stroke independent of the traditional stroke risk factors (4, 5). It is proposed that a prolonged QT existed before and after cardioembolic stroke episodes and the presence of a prolonged QT may be used as a marker for cardioembolic stroke. However, heart rate correction using the Bazett formula has serious limitations for evaluating the QT interval at lower and higher heart rates (6, 7). We have previously demonstrated the usefulness of the QT-RR slope and intercept assessment in ventricular repolarization dynamics using 24-hour Holter ECG recordings (8).
**Materials and Methods**

This retrospective study consisted of 62 consecutive patients who had acute ischemic stroke including 31 patients (17 men, 14 women, average age 71.8±12.7 years) with cardioembolic stroke and 31 patients (23 men, 8 women, average age 74.8±10.8 years) with atherosclerotic stroke. Any patients with persistent or permanent AF were excluded. All patients who had acute ischemic stroke including 31 patients (17 men, 14 women, average age 71.8±12.7 years) with atherosclerotic stroke.

We hypothesized that the assessment of the QT-RR relation can be used as a marker of cardioembolic stroke. In this study, we retrospectively evaluated the QT-RR relation based on a 15-sec averaged ECG during 24-hour Holter ECG recordings in patients who had acute ischemic stroke and compared the QT-RR regression line between cardioembolic and atherosclerotic stroke.

**Table 1. Clinical Characteristics and the QT-RR Regression Line Slope and Intercept in Cardioembolic and Atherosclerotic Stroke.**

|                      | Cardioembolic Stroke | Atherosclerotic Stroke | p value |
|----------------------|----------------------|------------------------|---------|
| n                    | 31                   | 31                     |         |
| Age (years)          | 71.8±12.7            | 74.8±10.8              | 0.344   |
| male/female          | 17/14                | 23/8                   | 0.184   |
| HT                   | 20                   | 23                     | 0.582   |
| DL                   | 12                   | 11                     | 0.783   |
| DM                   | 3                    | 10                     | 0.059   |
| CHADS2 score         | 3.29±0.82            | 3.65±0.71              | 0.074   |
| LVEF (%)             | 65.3±6.6             | 64.4±6.0               | 0.580   |
| LAD (mm)             | 32.8±8.3             | 34.4±4.5               | 0.370   |
| Mean RR (sec)        | 0.897±0.149          | 0.911±0.149            | 0.735   |
| Mean QT (sec)        | 0.407±0.048          | 0.397±0.032            | 0.358   |
| Mean QTc             | 0.431±0.032          | 0.417±0.033            | 0.105   |
| Slope of QT-RR       | 0.187±0.044          | 0.142±0.045            | <0.001  |
| Intercept of QT-RR   | 0.241±0.045          | 0.270±0.036            | <0.05   |

Data presented as mean±SD.

HT: hypertension, DL: dyslipidemia, DM: diabetes mellitus, LVEF: left ventricular ejection fraction, LAD: left atrial dimension

The results are presented as the mean ± standard deviation (SD). Unpaired data were analyzed using the Student’s t-test for continuous variables and the chi-square analysis for categorical variables. A receiver operating characteristic (ROC) curve analysis for predicting cardioembolic stroke was performed to calculate the optimal cutoff value for the slope of the QT-RR regression line. Statistical significance was set at p<0.05. Data were analyzed using the SPSS software program for Windows.

**Results**

Patients with cardioembolic stroke consisted of 12 patients having episodes of paroxysmal AF and 19 patients without significant stenosis of both the carotid artery and intracranial artery. The number of patients with frequent episodes of premature atrial contraction (>1,000/24 hours) did not differ between the cardioembolic and atherosclerotic stroke groups (5 vs. 3). There was no significant difference in terms of the patient clinical characteristics between cardioembolic stroke and atherosclerotic stroke (Table 1). A representative QT-RR relationship in a 65-year-old woman with cardioembolic stroke is shown in Fig. 1. She had right hemiplegia and aphasia on admission and showed no episodes of paroxysmal AF. Continuous ECG monitoring revealed an episode of paroxysmal AF. The slope and intercept of the QT-RR regression was 0.19 and 0.25. Fig. 2 shows a 73-year-old man with atherosclerotic stroke. On admission he had aphasia. ECG monitoring revealed no episode of paroxysmal AF, but ultrasound showed 92% stenosis of left carotid artery. The slope and intercept of the QT-RR
regression was 0.10 and 0.28. A scatter diagram of the QT-RR linear regression line slope and intercept in acute ischemic stroke patients showed similar negative linear correlations to the control subjects (7) (ischemic stroke: B=
Figure 3. Scatter plots of the QT-RR regression line slope and intercept in healthy subjects (466) and ischemic stroke patients (62).

Figure 4. Scatter plots of the QT-RR regression line slope and intercept in cardioembolic stroke (CS, brown triangle) and atherosclerotic stroke (AS, blue circle).

Table 2. Clinical Characteristics and the QT-RR Regression Line Slope and Intercept in Cardioembolic Stroke Patients with and without Episodes of Paroxysmal Atrial Fibrillation (AF).

| Episodes of AF | No episode of AF | p value |
|---------------|-----------------|---------|
| n             |                 |         |
| Age (years)   | 75.5±9.4        | 70.3±13.8 | ns   |
| male/female   | 7/5             | 10/9    | ns   |
| HT            | 7               | 13      | ns   |
| DL            | 4               | 8       | ns   |
| DM            | 2               | 1       | ns   |
| CHADS2 score  | 3.33±1.07       | 3.26±0.65 | ns   |
| LVEF (%)      | 67.5±8.3        | 64.2±5.4 | ns   |
| LAD (mm)      | 33.5±5.2        | 32.4±9.7 | ns   |
| Mean RR (sec) | 0.894±0.122     | 0.884±0.163 | ns   |
| Mean QT (sec) | 0.405±0.052     | 0.404±0.044 | ns   |
| Mean QTc      | 0.429±0.043     | 0.432±0.023 | ns   |
| Slope of QT-RR| 0.195±0.048     | 0.183±0.042 | ns   |
| Intercept of QT-RR | 0.231±0.040     | 0.244±0.043 | ns   |

Data presented as mean ± SD.

HT: hypertension, DL: dyslipidemia, DM: diabetes mellitus, LVEF: left ventricular ejection fraction, LAD: left atrial dimension, ns: no significant

Discussion

The major findings of the present study were as follows: (1) the mean slope of the QT-RR relation was significantly greater in cardioembolic stroke than in atherosclerotic stroke; (2) the mean RR, the mean QT, or the mean QTc during 24-hour Holter ECG recordings did not differ between cardioembolic and atherosclerotic stroke; (3) an in-

-0.67A+0.36, r=-0.77; control subjects: B=-0.62A+0.34, r=-0.79 (Fig. 3). The distribution of the scatter diagram in cardioembolic stroke shifted to the right lower area compared to that in atherosclerotic stroke (Fig. 4). The mean slope of the QT-RR regression line was significantly greater in cardioembolic stroke than in atherosclerotic stroke (0.187±0.044 vs. 0.142±0.045, p<0.001) and the mean intercept was significantly smaller in cardioembolic stroke than in atherosclerotic stroke (0.241±0.045 vs. 0.270±0.036, p<0.05, Table 1). The mean QT, the mean RR, or the mean QTc using Bazett formula during 24-hour Holter ECG recording did not differ between cardioembolic and atherosclerotic stroke. In cardioembolic stroke there were no differences in the clinical characteristics and the QT-RR relations between the patients with and those without documented episodes of

paroxysmal AF (Table 2).

An ROC curve analysis for predicting cardioembolic stroke was performed to calculate the optimal cutoff value for the slope of QT-RR regression line. The area under the curve of the slope of QT-RR regression line was 0.775 and the optimal cutoff value to predict cardioembolic stroke was 1.40 yielding 97% sensitivity, 55% specificity, a positive predictive value of 64%, and a negative predictive value of 93% (Fig. 5).
increased slope (≥0.14) of the QT-RR regression line could predict cardioembolic stroke with 97% sensitivity, 55% specificity, and a 63% positive predictive value. We speculate that the QT-RR regression line slope during the 24-hour Holter ECG may therefore be a new useful marker for cardioembolic stroke.

**Slope and intercept relationship of the QT-RR regression line**

The QT-RR dynamics were affected both by the QT-RR slope and by the QT-RR intercept. We evaluated the relationship between the slope and the intercept using a scatter plot and we found a statistically significant negative correlation between the QT-RR slope and intercept among a large number of healthy subjects (8). This distribution may be related to the differences in background repolarization in each subject. A combination of the rapid component of the delayed rectifier potassium current (IKr) and the slow component of the delayed rectifier potassium current (IKs) may play an important role in the modulation of ventricular repolarization to heart rate (9). It is possible that the suppression of IKr mainly increases the QT-RR slope and decreases the intercept; on the other hand, the suppression of IKs is known to mainly decrease the QT-RR slope and increase the intercept (10).

An analysis of the QT-RR slope from the 24-hour Holter ECG is commonly used to evaluate the QT dynamics. An increased slope of the QT-RR regression line was observed in patients with post-myocardial infarction (11), long QT syndrome (10), dilated cardiomyopathy (2), congestive heart failure (12, 13), and diabetic patients with autonomic dysfunction (14). Watanabe et al. reported that the QT-RR slope >0.17 was associated with sudden death in patients with stable chronic heart failure (12). A QT-RR slope >0.19 was proposed to be an independent risk marker for sudden death in patients with dilated cardiomyopathy (2). Cygankiewicz et al. demonstrated that a QT-RR slope of >0.22 was associated with increased total mortality in patients with chronic heart failure (13). Shimon et al. showed an inverse relationship between the high frequency component of the heart rate variability and the slope of QT-RR regression in diabetic patients and suggested an association between a steeper slope of QT-RR regression and diabetic neuropathy (14).

**QT interval and cardioembolic stroke**

Several previous studies have reported that QTc prolongation is associated with an increased risk of incident AF independent of traditional AF risk factors (5, 15). An increased risk of AF in patients with long QT syndrome has also been reported (3). A prolonged QT interval may be related to enhanced activity of the late Na current which increases intracellular Ca and triggered automaticity in the atrium. QT prolongation is a well-known predictor of cardiovascular mortality and is also a marker of cardiac disease. Hence, it is possible that a prolonged QT is associated with cardiac disease in itself and is not associated with AF directly. On the other hand, Nielsen demonstrated not only a longer QT, but also a shorter QT to be a risk marker of lone AF having no underlying structural heart disease (J-shaped association) (5).

A prolonged QTc also has been reported to be a risk marker of ischemic stroke and the post-stroke prognosis (4). Hoshino et al. assessed the predictive value of a prolonged QTc in paroxysmal AF detection after acute ischemic stroke (16). They found the QTc to be significantly longer in patients with paroxysmal AF than in those without.

**Conclusion**

The slope of the QT-RR regression line during 24-hour...
Holter ECG may thus be a simple and useful marker for cardioembolic stroke.

The authors state that they have no Conflict of Interest (COI).

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