INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

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

(Intern Med 55: 2927-2932, 2016)
(DOI: 10.2169/internalmedicine.55.6702)

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).

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Received for publication October 16, 2015; Accepted for publication March 1, 2016
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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	0.793
DM	3	10	0.059
$CHADS_2$ 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

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.

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 with stroke were diagnosed based on the findings from neurological observations and magnetic resonance imaging (MRI) and or computed tomography (CT). Intracranial artery luminal stenosis of >50% was considered significant as determined by magnetic resonance angiography. Carotid artery luminal stenosis of >50% was defined as significant stenosis as assessed by ultrasound. Patients underwent continuous in-hospital ECG monitoring for at least 3 days following the stroke episode. Patients who had documented episodes of paroxysmal AF (duration >30 sec) were defined as cardioembolic stroke patients. Patients without any known AF who had significant stenosis of the carotid artery and/or intracranial artery were defined as atherosclerotic stroke patients. Ischemic stroke patients without significant stenosis of both the carotid artery and intracranial artery were defined as cardioembolic stroke cases even if they had no known episodes of paroxysmal AF.

Holter ECGs were recorded for 24 hours within two weeks after an acute stroke episode and CM5 (the modified chest lead V5) lead was used for automatic QT measurements because of the morphological stability of T wave. No subject was being treated with any drugs affecting the QT interval. A digital ECG recording device (FM-180, Fukuda Denshi, Tokyo, Japan) with a sampling rate of 128/sec was used with an automatic measurement system (SCM-8000, Fukuda Denshi). The QT interval was plotted against the RR interval from averaged ECG waves obtained by the summation of consecutive QRS-T complexes during each 15 seconds period over 24 hours without any episodes of paroxysmal AF (8). Therefore, a maximum total of 5,760 data points could be obtained for each subject. The analyzing system determined the top and the end of the T wave according to the following algorithm. The top of the T wave was determined as the point where the first derivative of the T wave changed from positive to negative or negative to positive. The end of the T wave was determined by the crossing point between the baseline and the slope fitting the descending part of the T wave using the regression tangent. In each subject, the detection level of the T wave first derivative was set as the average level of the ST segment. The dependence of the QT interval on the RR interval was analyzed for each patient using linear regression ([QT] = A[RR] + B; where A is the slope and B is the intercept). In each subject visual checks verified the automatic QT interval measurements.

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

Intern Med 55: 2927-2932, 2016 DOI: 10.2169/internalmedicine.55.6702

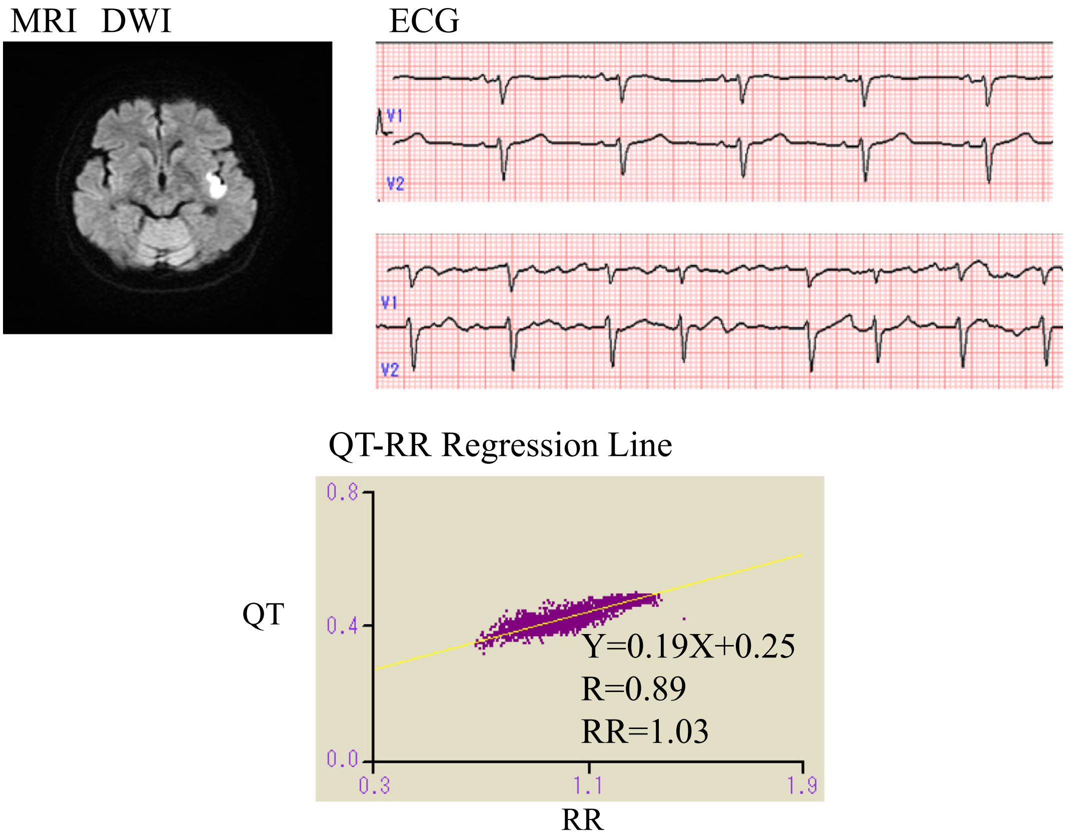

Figure 1. **Representative QT-RR relationship in a 65-year-old woman with cardioembolic stroke. MRI: magnetic resonance imaging, DWI: diffusion weighted imaging**

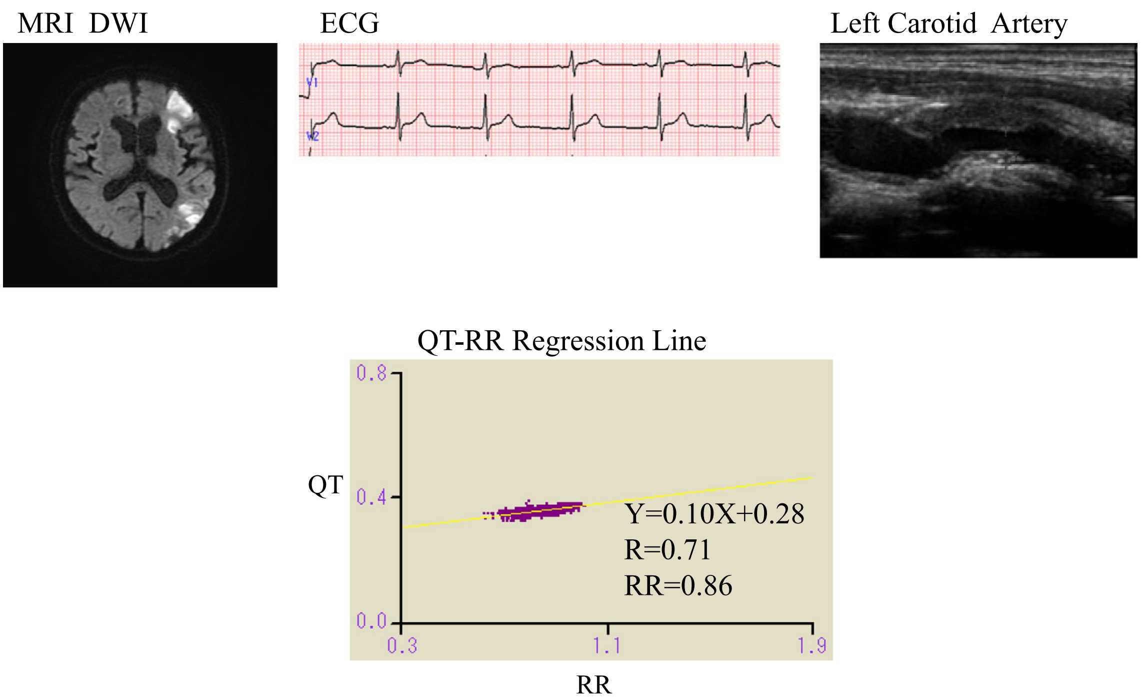

Figure 2. **Representative QT-RR relationship in a 73-year-old man with atherosclerotic stroke. MRI: magnetic resonance imaging, DWI: diffusion weighted imaging**

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=

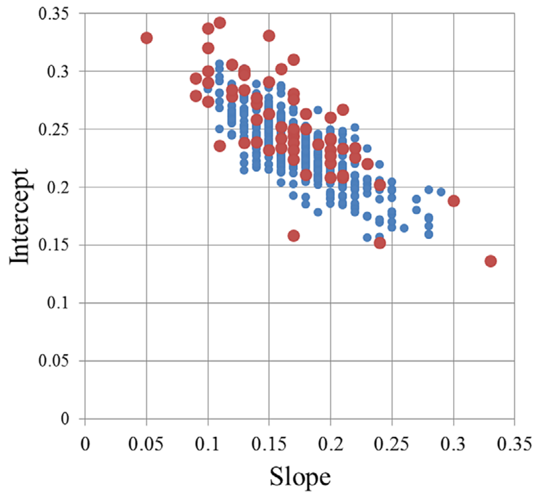

Figure 3. Scatter plots of the QT-RR regression line slope and intercept in healthy subjects (466) and ischemic stroke patients (62).

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	12	19	
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
$CHADS_2$ 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±0.049	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

-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).

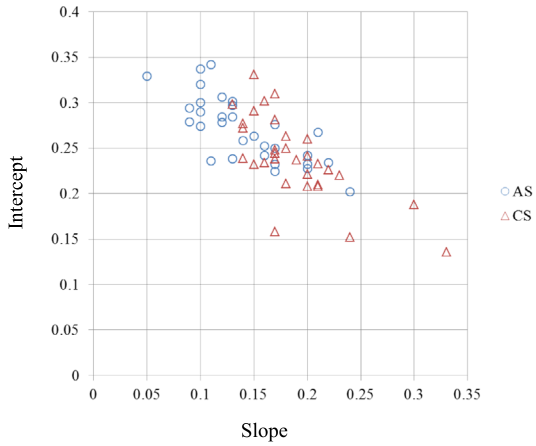

Figure 4. Scatter plots of the QT-RR regression line slope and intercept in cardioembolic stroke (CS, brown triangle) and atherosclerotic stroke (AS, blue circle).

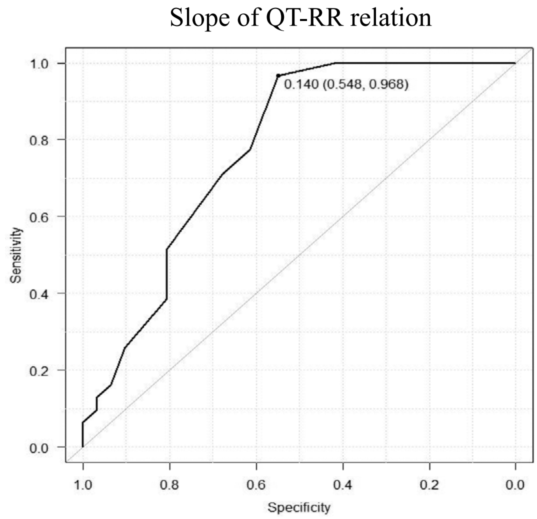

Figure 5. A receiver operating characteristic (ROC) curve analysis for predicting cardioembolic stroke using the slope of QT-RR regression line.

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).

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 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). Cygaukievicz et al. demonstrated that a QT-RR slope of >0.22 was associated with increased total mortality in patients with chronic heart failure (13). Shimono 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.

Slope and intercept relationship of the QT-RR regression line in patients with ischemic stroke

In the present study, the mean slope of QT-RR regression was significantly greater in cardioembolic stroke than in atherosclerotic stroke, but the mean RR, the mean QT, or the mean QTc did not show any significant difference between them. The QT-RR relationship has considerable intersubject variability, and it is very difficult to obtain the optimal heart rate correction formula that could permit an accurate comparison of the corrected QT intervals (8). Compared with the conventional QT evaluation using the heart rate correction formula, the slope of the QT-RR relation during 24-hour Holter ECG may be less affected by the sampling heart rate. The steeper slope of the QT-RR relation suggested not only a longer QT at lower heart rates, but also a shorter QT at higher heart rates. These findings are compatible with the J-shaped association between QTc and the risk of AF (5).

Although the mechanism for these associations remains unclear, both the presence of AF in itself and the remodeled left atrium having possibility of paroxysmal AF may be associated with an increased risk of cardioembolic stroke. A steeper slope of QT-RR regression has been reported as a surrogate indicator of subclinical atherosclerosis and autonomic nerve dysfunction and subsequently could be a predictor of cardiovascular mortality (12, 13). Most of cardioembolic risk factors, such as diabetes mellitus, hypertension, aging, female gender, and congestive heart failure, showed a steeper slope of QT-RR regression. Hence, in association with an increased risk of paroxysmal AF, patients with steeper slope of QT-RR regression may have an increased risk of cardioembolic stroke.

The present study was retrospective and was limited by the small number of patients investigated. Therefore, further prospective studies with larger numbers of patients are needed to clarify the role of the QT-RR regression slope and intercept relationship as a marker of cardioembolic episodes in patients with acute ischemic stroke. No AF episodes could be detected in about two-thirds patients classified as cardioembolic stroke in the present study. Further ECG monitoring to detect such episodes of AF should be done for these patients.

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).

Acknowledgement

We gratefully acknowledge the valuable technical assistance of Ms. Kumiko Kobayashi.

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