Acute Stroke Increases QT Dispersion in Patients Without Known Cardiac Diseases

Nazire Afsar, MD; Ali S. Fak, MD; Jacques T. Metzger, MD; Guy Van Melle, PhD; Lukas Kappenberger, MD; Julien Bogousslavsky, MD

Background: Electrocardiographic changes are well known to appear with acute cerebrovascular events.

Objective: To investigate if QT dispersion (QTd) is increased in patients who have an acute stroke and if this increase could be related to lesion extent and/or localization.

Design: The study group consisted of 36 patients who had an acute stroke and no history or signs of cardiovascular disease. An age-matched control group (n=19) free of cardiovascular disease was also included. Simultaneous 12-lead electrocardiograms (ECGs) were recorded within the first 24 hours (24h-ECG) and after 72 hours (72h-ECG) from stroke onset. QT dispersion was assessed both manually and automatically with assessors blinded to the clinical data.

Results: QT dispersion, corrected QTd, and automated QTd were significantly increased in the 24h-ECG compared with the 72h-ECG (60 [range, 20-80] milliseconds vs 40 [range, 0-80] milliseconds, P<.005; mean [SD], 56 [19] vs 36 [21] milliseconds, P<.001; and 50 [range, 14-94] vs 34 [range, 0-84] milliseconds, P<.005, respectively). However, QTd in the 72h-ECG was similar to QTd in the control group. While in the 24h-ECG corrected QTd was significantly greater in patients with large infarcts and large hemorrhages (mean [SD], 70 [20] vs 51 [20] milliseconds, P<.05), in the 72h-ECG corrected QTd was greater in patients with right- vs left-sided lesions (mean [SD], 39 [18] vs 24 [18] milliseconds, P<.05).

Conclusions: QT dispersion is increased in the first 24 hours in patients with acute stroke and no cardiovascular disease compared with the control group. Although this finding seems to be related to the size of the lesion rather than to the localization or type of stroke, after 72 hours specific lesion localization could also influence the QTd.

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INCREASED QT dispersion (QTd) on the surface electrocardiogram (ECG) is considered a measure of repolarization inhomogeneity of the myocardium that could represent an electrophysiologic substrate for ventricular arrhythmias.1-3 It has been defined in a variety of cardiac and noncardiac disease states and is also reported to be a noninvasive risk marker for arrhythmias and mortality in a number of diseases.4-9 There is evidence for an interaction between the central nervous system and the cardiovascular system during acute cerebrovascular events.10,11 Although ST-segment and T-wave changes in the ECG are well-known consequences of stroke,12 arrhythmias13 and cardiac autonomic changes14 have also been reported. All these abnormalities seem to be associated with lesions of autonomic cardiac control centers10,14,15 However, the issue of increased QTd in acute stroke has not been thoroughly evaluated. This study was designed to assess whether QTd is increased in patients with acute cerebrovascular events, and whether this increase is related to lesion size and/or localization.

METHODS

This was a prospective, comparative, blind, controlled study.

PARTICIPANTS

Patient Group

Patients older than 18 years hospitalized for acute cerebrovascular events within the first 24 hours of symptom onset were candidates for the study. Those without any history or sign of cardiac disease and who had ischemic or hemorrhagic right-sided or left-sided cerebrovascular events localized in either the carotid or vertebral territory were included in the study provided that a 12-lead ECG was re-
corded for this study within the 24 hours following symptom onset.

Control Group

The control subjects were chosen among patients hospitalized for diseases other than those of a cardiac or neurologic origin. Participants were matched for age by group.

EXCLUSION CRITERIA

Patients presenting with lacunar strokes or transient ischemic attacks were excluded. All patients who had a history or clinical or laboratory evidence of ischemic or valvular heart disease, heart failure, cardiac arrhythmia, any kind of cardiomyopathy, or diabetes mellitus were also excluded. Patients with systemic hypertension were included unless they had either electrocardiographically or echocardiographically documented left ventricular hypertrophy. Patients taking any medication known to affect repolarization parameters on the ECG (last dose taken within 5 serum half-lives for the drug in question) were excluded; these medications were digoxin, any antiarrhythmic drug, phenothiazines, tricyclic antidepressant drugs, lithium carbonate, erythromycin stearate, theophylline, and levodopa. Patients and controls whose ECGs revealed a bundle-branch block pattern or who had abnormal serum potassium and/or calcium concentrations were also excluded.

ECG ASSESSMENT

Simultaneous 12-lead ECGs were recorded within the first 24 hours (24h-ECG) and again between 72 and 120 hours (72h-ECG) after stroke onset following neurologic stabilization of the patients. Electrocardiograms for all study subjects were recorded using the same ECG recorder (Schiller Cardiovit, Baar, Switzerland) operated by the same investigator (A.S.F.), using a speed of 25 mm/s, a gain of 10 mm/mV, and a filter setting of 30 to 400 Hz. All ECGs were assessed blindly at the end of the study by an independent cardiologist (A.S.F.). At least 3 consecutive cycles were measured for each lead. The QT interval was measured from the onset of the QRS deflection to the end of the T wave, as the intersection of the isoelectric baseline and the tangent of the maximal T-wave slope. Precordial leads with a peak T-wave amplitude of 0.02 mV were excluded, and the analysis was based on the measurements taken from the remaining leads. Only ECGs with 6 or more total leads and 3 or more precordial leads with measurable QT intervals were considered. The QT intervals were corrected using the formula of Bazett and the corrected QTd (QTcd) was derived. As the QT interval on the surface ECG represents the repolarization period of the cardiac myocytes and differs according to the underlying heart rate, several formulas have been proposed to compare the QT intervals in different heart rates and in different individuals. The formula of Bazett is perhaps the most widely accepted one; that is, the QT duration over the square root of RR interval (a derivative of heart rate) both in seconds. The QTd and QTcd were defined as the difference between the maximal and minimal values for the QT interval or QTcd, respectively, in any of the available 12 leads. Automated QT interval and automated QT dispersion (aQTd) were measured from median complexes on the digital ECGs using interactive software (model CS-200; Schiller Cardiovit) that detects QRS onset and T-wave offset, and were blindly validated by one of us (A.S.F.).

NEUROLOGIC ASSESSMENT

A complete neurologic examination was performed by the same physician (N.A.) on enrollment in the study and after 72 hours. All patients who had a stroke underwent cranial computed tomography on enrollment. Reassessment with computed tomographic or magnetic resonance imaging was performed whenever necessary. Patients with ischemic stroke were classified according to the classifications reported by Bamford et al., that is, total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), and posterior circulation infarct (PACI). Patients with hemorrhagic stroke were classified as having either a large hemorrhage (>33 mm in diameter, with or without ventricular extension) or a small hemorrhage (<33 mm). Results from patients with TACI and large hemorrhage were compared with those from patients with PACI and small hemorrhage to determine the effect of lesion size. Results from patients with right-sided lesions (all subtypes together) were compared with those for patients with left-sided lesions to assess the laterality effect. Insular involvement in patients with TACI and PACI was assessed on the basis of brain imaging with computed tomography and/or magnetic resonance imaging; patients with hemorrhages were excluded from this analysis.

STATISTICAL ANALYSIS

Statistical analysis (GraphPad InStat–1990-1993, version 2.02) was made using the t test for normally distributed continuous random variables, and the Mann-Whitney test for nonnormally distributed continuous random variables. While mean (SD) values were used for the t test, median and range values were used for the Mann-Whitney test. A paired-nonparametric test (Wilcoxon signed rank test) was used to analyze 2 consecutive ECG parameters in the same patient. P < .05 was considered statistically significant for all analyses.

RESULTS

CLINICAL AND ECG DATA

During a 7-month period, 200 patients with acute cerebrovascular events were admitted to the hospital. Of these, 33 who presented later than 24 hours after symptom onset were excluded from the study. Fifty-eight patients presenting with either lacunar strokes or transient ischemic attacks were also excluded. One patient with an acute basilar artery thrombosis died shortly after arrival in the emergency department. Sixty patients were excluded because of concomitant cardiac disease and/or use of the medications cited in the “Methods” section as follows: coronary heart disease (40 patients); heart failure (2); valvular heart disease (2); cardiac transplantation (1); history of atrial fibrillation–flutter (30); pacemaker implantation (2); sick sinus syndrome (2); history of ventricular arrhythmia (1); and medication (5) (some patients had >1 exclusion criterion). Three patients with either ECG or echocardiographic criteria for left ventricular hypertrophy were excluded. A further 9 patients were excluded because ECG abnormalities were detected (bundle branch block in 6 and atrioventricular conduction disturbances in 3). The study group consisted of the remaining 36 patients (22 men and 14 women) and the control group consisted of 19 patients (9 men and 10 women). The mean (SD) ages for the study and control groups were 68 (12) and 62 (12) years, respectively (P = .08). Of the patients who had a stroke, 19 had right-sided and 15 had left-sided lesions. There were 30 ischemic and 6 hemorrhagic strokes. The stroke type was TACI in 8, PACI in 13, posterior circulation infarct in 8, and parenchymal hemorrhage in 6 (5 patients with hem-
size, being significantly greater in patients with large lesions.

In the present study, the QTd of the patients who had an acute stroke was significantly higher than controls in lesions compared with patients with small lesions (Table 2). The QTd and aQTd values did not show a significant difference. In the 72h-ECG, there were no significant differences in QTd values between large and small lesions.

Table 2. QT Dispersion According to Stroke Type and Lesion Localizations in 24h-ECG and 72h-ECG

<table>
<thead>
<tr>
<th>Variable</th>
<th>QTd, ms</th>
<th>Mean (SD), ms</th>
<th>aQTd, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h-ECG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>60 (20-120)†</td>
<td>70 (20)†</td>
<td>60 (26-90)</td>
</tr>
<tr>
<td>Small</td>
<td>45 (20-80)†</td>
<td>51 (20)</td>
<td>48 (14-94)</td>
</tr>
<tr>
<td>Right</td>
<td>60 (20-80)†</td>
<td>58 (21)</td>
<td>51 (0-94)</td>
</tr>
<tr>
<td>Left</td>
<td>60 (20-120)†</td>
<td>60 (20)</td>
<td>52 (26-90)</td>
</tr>
<tr>
<td>Insular involvement</td>
<td>Yes</td>
<td>60 (40-80)</td>
<td>59 (17)</td>
</tr>
<tr>
<td>No</td>
<td>60 (20-80)†</td>
<td>53 (25)</td>
<td>44 (26-90)</td>
</tr>
<tr>
<td>Stroke type</td>
<td>Hemorrhagic</td>
<td>80 (20-120)</td>
<td>74 (25)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>60 (20-80)†</td>
<td>58 (19)</td>
<td>50 (0-94)</td>
</tr>
<tr>
<td>72h-ECG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>40 (20-80)†</td>
<td>33 (13)</td>
<td>36 (10-84)</td>
</tr>
<tr>
<td>Small</td>
<td>25 (1-60)†</td>
<td>28 (16)</td>
<td>34 (0-52)</td>
</tr>
<tr>
<td>Right</td>
<td>40 (20-80)†</td>
<td>39 (18)†</td>
<td>32 (10-52)</td>
</tr>
<tr>
<td>Left</td>
<td>20 (1-80)†</td>
<td>24 (18)</td>
<td>37 (0-84)</td>
</tr>
<tr>
<td>Insular involvement</td>
<td>Yes</td>
<td>20 (0-80)</td>
<td>27 (26)</td>
</tr>
<tr>
<td>No</td>
<td>30 (20-80)†</td>
<td>36 (14)</td>
<td>32 (26-52)</td>
</tr>
<tr>
<td>Stroke type</td>
<td>Hemorrhagic</td>
<td>40 (39-40)</td>
<td>42 (7)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>20 (1-80)†</td>
<td>35 (22)</td>
<td>33 (0-84)</td>
</tr>
</tbody>
</table>

Table 2. QT Dispersion in Patients With Stroke and Control Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>QTd, ms</th>
<th>Mean (SD), ms</th>
<th>aQTd, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h-ECG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTd median (range), ms</td>
<td>60 (20-80)†</td>
<td>40 (0-80)</td>
<td>20 (0-40)</td>
</tr>
<tr>
<td>QTcd, ms</td>
<td>56 (19)†</td>
<td>36 (21)</td>
<td>30 (14)</td>
</tr>
<tr>
<td>aQTd, median (range), ms</td>
<td>50 (14-94)‡</td>
<td>34 (0-84)</td>
<td>28 (10-42)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>75 (14)</td>
<td>70 (12)</td>
<td>78 (17)</td>
</tr>
</tbody>
</table>

Abbreviations: aQTd, automated QT dispersion; QTcd, corrected QT dispersion; QTd, QT dispersion; 24h-ECG, 24-hour electrocardiogram recorded in the first 24 hours after stroke onset; 72h-ECG, 72-hour electrocardiogram recorded after the index event between 72 and 120 hours.

*Data are given as median (range) unless otherwise indicated. †P<.005. ‡P<.001 compared with 72h-ECG.

QTD ACCORDING TO LESION SIZE

In the 24h-ECG, QTcd was found to correlate with lesion size, being significantly greater in patients with large lesions compared with patients with small lesions (Table 2). The QTd and aQTd values did not show a significant difference. In the 72h-ECG, there were no significant differences in QTd values between large and small lesions.

QTD ACCORDING TO LESION LOCALIZATION

In the 24h-ECG, there was no significant difference between increased QTd, QTcd, aQTd, and stroke localization. However, in the 72h-ECG, patients with right-sided lesions were found to have significantly greater QTcd values; QTd and aQTd values seemed also greater in those who had right-sided lesions, although the difference was not statistically significant (Table 2).

Four patients did not survive the acute hospitalization period. Three died within 72 hours, so 72h-ECGs were unavailable. QT dispersion increased in the 72h-ECG compared with the 24h-ECG in the fourth patient, who died secondary to temporal herniation, and in a patient whose condition deteriorated owing to rebleeding.

COMMENT

In the present study, the QTd of the patients who had an acute stroke was significantly higher than controls in
the first 24 hours following stroke, then tended to decrease to normal levels after 72 hours after stroke onset. In patients with large infarcts and large cerebral hemorrhages, QTd was significantly greater than in patients with more restricted lesions. In the first 24 hours following stroke, there was not a significant difference between QTd and infarct localization or stroke type. However, in the 72h-ECG, patients with right-sided lesions had a greater tendency to have increased QTd than those with left-sided lesions.

As the heart has an important and pronounced autonomic innervation, it is to be expected that acute disturbances of the central nervous system might result in a wide spectrum of cardiac functional disorders. Indeed, acute cerebrovascular events have long been known to cause ST-segment changes and T-wave abnormalities. Recently, Randell et al reported that patients with subarachnoid hemorrhage have increased QTd compared with controls; they also observed episodes of cardiac arrhythmias in these patients. Similarly, Eckardt et al reported increased QTd in patients who had a stroke that involved the insular cortex. In 40 patients with unilateral ischemic stroke, patients with insular cortex involvement were found to have increased QTd compared with patients without such involvement. However, it is likely these studies included patients who already had cardiac disease. Considering the rate of concomitant cardiac disease in patients with acute cerebrovascular events, this raises the possibility of the effect of preexisting heart disease on QTd. In our study, patients were prospectively selected to be free of any history or signs of cardiac disease and, therefore, the increased QTd seen in our patients most probably resulted from the acute cerebrovascular event itself, clearly indicating that stroke increases QTd in the acute phase.

The increased QTd seen during acute cerebrovascular events could be related either specifically to lesion localization or to humoral effects of the acute insult. Stroke patients are known to have increased sympathetic activity. Myers et al found significantly higher levels of plasma catecholamines, especially norepinephrine, in patients with stroke, and suggested that this increased sympathetic activity could produce the cardiac abnormalities seen in cerebral infarction. The lack of correlation between QTd and plasma norepinephrine levels seen in the study of Eckardt et al might be related to differences in study design and patient population. Their study group consisted of patients with unilateral stroke, including those with concomitant cardiac diseases, and only 1 ECG was recorded in the first 72 hours. Our findings seem to be consistent with the suggestion that the humoral effects of acute insult play a more important role in the early periods of stroke. However, we have no data on plasma catecholamine levels.

However, experimental and clinical data suggest that specific areas in the brain could be responsible for autonomic cardiac control. Oppenheimer et al observed that prolonged stimulation of the rat insular cortex produces cardiac repolarization changes and atrioventricular block leading to death in asystole. Moreover, Eckardt et al reported that QTd in patients with insular cortex involvement is greater than in those without insular involvement. Tokgozoglu et al also observed that heart rate variability was significantly decreased in stroke patients with insular involvement. These data suggest that lesions in specific areas could lead to cardiac autonomic dysfunction and, thus, could increase QTd. However, in the study of Tokgozoglu et al, the time of assessment of heart rate variability relative to stroke onset was not recorded. In contrast, in our study the increased QTd in the 24h-ECG was not significantly different between right- and left-sided lesions. However, the mean (SD) time from onset of symptoms to the 24h-ECG was relatively short (14.8 [6.8] hours). Nevertheless, when QTd in the 72h-ECGs for both groups was compared, patients with right-sided lesions tended to have higher values. The lack of any significant difference in QTd between patients with right- and left-sided lesions in the 24h-ECG and the greater QTd in right-sided lesions in the 72h-ECG suggest that in the very early period of acute cerebrovascular events, lesion localization might play a minor role compared with the systemic effects of the acute insult itself, whereas, at a later stage, the effect of specific lesion localization could be more prominent.

In the present study, QTd was assessed both manually and automatically. Although the mean QTd, QTcd, and aQTd values differed somewhat, a high level of statistical significance was reached when the 24h-ECG and 72h-ECG data were compared, regardless of the method used. When Savelieva et al compared the data derived from manual and automated assessment of QTd in both controls and patients with hypertrophic cardiomyopathy, despite a poor level of agreement between the 2 methods, both were found to be independently useful in identifying controls and patients with cardiomyopathy on the basis of the degree of QTd. Thus, both automated and manual measurements of QTd seem to be relevant. However, whether QTd assessments should be based on corrected QT intervals is a matter of controversy, and, for the time being, it seems reasonable to assess both absolute and QTcd.

Plasma catecholamine levels were not measured in our study and, therefore, the suggestion that the increased QTd seen in the very early period of acute stroke might be due to humoral effects of the acute insult is somewhat speculative. In addition, the size of the patient population did not allow detailed subgroup analysis, and effects of lesion localization on QTd might have been better demonstrated by more frequent ECG recordings in the first few days of the acute cerebrovascular event.

Despite these limitations, we found that acute stroke increases QTd in patients without any known cardiac diseases. The increase in QTd seems to be more prominent in the early periods of stroke and to be related to humoral effects of the acute insult. However, within 72 hours, lesion localization might also play a part. As increased QTd could represent a substrate for arrhythmias, close ECG monitoring of stroke patients during the acute phase could be advantageous.

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