Temporal changes of QT dispersion in patients with acute ischemic stroke

Akut iskemik inmeli hastalarda QT dispersiyonun zamansal değişimi

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Abstract

Aim: Ischemic stroke is a significant cause of morbidity and mortality and can lead to fatal arrhythmias even in the absence of underlying cardiac pathology. The objective of this study was to investigate the impact of acute ischemic stroke on QT dispersion and its temporal changes over time.

Methods: A total of 124 patients with acute ischemic stroke who did not receive any reperfusion treatment were included in the study. Corrected QT dispersion (QTcd) values were obtained from 12-lead surface electrocardiograms taken within the first 12 hours and after 48 hours of stroke onset. These values were compared with those of 93 age and sex-matched control subjects. The effects of diabetes and lesion lateralization on QT dispersion were also analyzed. Stroke patients whose lesions were clearly localized to either the right or left hemisphere were divided into two subgroups. The change in QT dispersion overtime during the follow-up period was also determined.

Results: The study included 124 patients with acute ischemic stroke (54 females and 70 males) with a mean age of 67±11 years, as well as a control group of 93 subjects (49 females and 44 males) with a mean age of 69±8 years. The QTcd values of the stroke group were significantly longer than the control group in the first 12 hours of symptom onset. However, after 48 hours, the QTcd values of the stroke group decreased and the difference between the two groups was not statistically significant. The presence of diabetes mellitus caused a more significant increase in QT dispersion, and after 48 hours, the QTcd values of diabetic stroke patients were still significantly longer. The QTcd values of patients with left hemispheric lesions were significantly longer than those of patients with right hemispheric lesions, and this difference persisted after 48 hours.

Conclusion: This study found that QT dispersion increases during the first few hours of ischemic stroke and decreases during the treatment period. This increase is more obvious and lasts longer in stroke patients with diabetes and left hemispheric lesions. The results suggest that QT dispersion may be a useful prognostic indicator for patients with acute ischemic stroke.

Keywords: Electrocardiography; myocardium; stroke

Öz

Amaç: İskemik inme, önemli bir morbidite ve mortalite nedenidir ve temel kardiyak patoloji olmadan ölümcül aritmilere neden olabilir. Bu çalışmanın amacı, akut iskemik inmenin QT dispersiyonu üzerindeki etkisini ve zaman içindeki değişimlerini araştırmaktır.

Yöntemler: Çalışmaya, reperfüzyon tedavisi almayan 124 akut iskemik inme hastası dahil edildi. İlk 12 saat ve 48 saat sonra alınan 12 derivasyonlu yüzey elektrokardiyogramlarından düzeltilmiş QT dispersiyonu (QTcd) değerleri elde edildi. Bu değerler, 93 yaş ve cinsiyet açısından eşleştirilmiş kontrol grubu ile karşılaştırıldı. Diyabet ve lezyon lateralizasyonunun QT dispersiyonu üzerindeki etkileri de analiz edildi. Lezyonları net bir şekilde sağ veya sol hemisfere lokalize olan inme hastaları iki alt gruba ayrıldı. İzlem dönemi boyunca QT dispersiyonundaki değişim de belirlendi.

Bulgular: Çalışmaya, ortalama yaşları 67±11 yıl olan 124 akut iskemik inme hastası (54 kadın ve 70 erkek) ve ortalama yaşları 69±8 yıl olan 93 kontrol grubu (49 kadın ve 44 erkek) dahil edildi. İlk 12 saatte, inme grubunun QTcd değerleri kontrol grubuna göre önemli ölçüde daha uzundu. Ancak 48 saat sonra, inme grubunun QTcd değerleri azaldı ve iki grup arasındaki fark istatistiksel olarak anlamsız hale geldi. Diyabet varlığı QT dispersiyonunda daha belirgin bir artışa neden oldu ve 48 saat sonra, diyabetik inme hastalarının QTcd değerleri hala anlamlı ölçüde daha uzundu. Sol hemisferik lezyonları olan hastaların QTcd değerleri, sağ hemisferik lezyonları olan hastaların değerlerinden önemli ölçüde daha uzundu ve bu fark 48 saat sonra da devam etti.

Sonuç: Bu çalışma, iskemik inmenin ilk saatlerinde QT dispersiyonunun arttığını ve tedavi dönemi boyunca azaldığını buldu. Bu artış, diyabetik ve sol hemisferik lezyonları olan inme hastalarında daha belirgin ve daha uzun sürdü. Sonuçlar, QT dispersiyonunun akut iskemik inme hastaları için kullanışlı bir prognostik gösterge olabileceğini düşündürmektedir.

Anahtar Sözcükler: Elektrokardiyografi; miyokard; inme

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INTRODUCTION

Stroke is an important cause of mortality and morbidity. Among all stroke types ischemic stroke is the most common type and accounts for nearly 90% (1). Although cardiac arrhythmias can cause stroke, it is well-known that stroke can also cause arrhythmias and it has been shown that nearly 70% of stroke patients may have different types of arrhythmia (2). This two-way equation is most probably due to neuronal and vascular connections between the heart and brain. The heart gets its autonomic nervous innervation via both sympathetic and parasympathetic neurons and vagus nerve is responsible for the parasympathetic innervation of the heart, whose increased activity has been shown to cause arrhythmias (2). Moreover, it is known that sympathetic over-activity that comes from intermediolateral column of the thoracic spinal cord can be a reason for cardiac rhythm disturbances. An imbalance between sympathetic and parasympathetic systems might cause cardiac problems seen during an acute stroke. Nearly 90% of stroke patients have ECG changes most common of which are tall, spinous T waves and elongated QT intervals. Approximately 40% of ECGs from stroke patients may demonstrate repolarization abnormalities (2).

QT dispersion which is believed to be a reflection of ventricular repolarization abnormality can show regional heterogeneity in myocardial repolarization. Increased QT dispersion may be due to a problem in ventricular recovery time which may result in severe ventricular arrhythmias via reentrant mechanisms (3). There has been a debate about the usefulness of QT dispersion in recent years. Nonetheless, interest in the role of it predicting arrhythmias has continued in regard to determining the prognosis of different disease states. QT dispersion was shown to be increased in various cardiac pathologies such as myocardial infarction, heart failure, hypertrophic cardiomyopathy and left ventricular hypertrophy (4-6). It has also been shown that QT dispersion is prolonged during acute stroke and an independent predictor of mortality following acute neurological events (7,8). In this study we tried to evaluate the effects of time, location, and comorbidities such as diabetes on QT dispersion of stroke patients so that a close insight into the heart and brain relationship could be possible.

METHODS

Study population

124 acute ischemic stroke patients who were admitted to the emergency care unit of Abant Izzet Baysal University Hospital with their first ischemic stroke and subsequently hospitalized were included in the study. In addition, 93 age and sex-matched control subjects were recruited for comparison. Patients over the age of 18 who were admitted to the emergency room within 12 hours of symptom onset and had a 12-lead ECG at admission and between 48-96 hours of the acute event were included in the study. There were no statistical differences between the two groups in terms of age, sex, diabetes, hypertension, smoking history, LV hypertrophy, or hyperlipidemia.

The diagnosis of stroke was confirmed by at least one consultant emergency physician and a consultant neurologist using recurrent computed tomography or MRI scan images, in addition to a complete neurological examination. The patients were then followed up in the neurology ward. We focused on stroke patients whose lesions were localized to either the right or left hemisphere and divided them into two subgroups based on the lateralization of their lesions. Furthermore, we examined changes in QT dispersion overtime during the follow-up period. All included patients had moderate to severe disability, as determined by a Modified Rankin Scale score of 3, 4, or 5. They also underwent complete blood analysis, including lipid profile, thyroid, liver, and renal function tests, at least two ECGs, transthoracic echocardiography, and two CT scans. None of the patients received thrombolytic treatment or percutaneous intervention for reperfusion. Patients with known coronary artery disease, atrial fibrillation or any other non-sinus rhythm, heart failure, cardiomyopathy, bronchial asthma, chronic obstructive pulmonary disease, anemia, hypo/hyperthyroidism, LV systolic dysfunction (LVEF below 55%) or diastolic dysfunction (more than impaired relaxation), left ventricular wall motion abnormality, valvular disease, systolic pulmonary artery pressure over 35mmHg, dilatation of any heart chamber, or thrombus in a chamber were excluded. Cases with lacunar infarcts, intracranial hemorrhages, or transient ischemic attacks were also excluded, as well as those

with electrolyte disturbances or taking medication that can affect repolarization, such as antiarrhythmic, digitalis, theophyllines, levodopa, antipsychotic, or antidepressant drugs. Additionally, patients with P or U waves, bundle branch block, or if the initial part of the Q wave and last part of the T wave were not easily recognized from the isoelectric line were also excluded.

The study plan was in agreement with the ethical guidelines of the local ethical committee and the relevant standards of the revised Declaration of Helsinki. Ethics committee approval was obtained from Abant İzzet Baysal University İzzet Baysal Faculty of Medicine Health Sciences Non-interventional Clinical Research Ethics Committee for the study (date: 12.05.2009, decision no: 96).

12-Lead ECG Evaluation

Twelve-lead ECG recordings were taken from all subjects, first at the time of admission and second between 48-96 hours, using Nihon-Kohden ECG-9132K. A paper speed of 25 mm/s and a gain of 10 mm/mV were used for all recordings. Names on the ECGs were obscured when transferred to electronic format to ensure that the investigator evaluating the ECGs was blind to the owners of the ECGs. All QT calculations were performed by a cardiologist and repeated blindly to decrease intra-observer variability. ECGs were converted to digital format and magnified 400 times to precisely measure the time interval from the onset of the Q wave to the end of the T wave for each lead. The average of the QT interval in three consecutive cycles in each lead was recorded. The end of the T wave was established as the point of regaining the isoelectric line. The nadir between the two waves was recorded as the termination of the T wave when a T wave was invaded by a U wave. Bazett's formula (QTc=QT/√RR interval) was used to correct the effect of heart rate and calculate the corrected QT intervals. The difference between the longest and shortest corrected QT intervals was recorded as the QT dispersion.

Stroke Patients with Diabetes Mellitus

Since the presence of diabetes can affect QT dispersion, we divided the stroke group into diabetic and non-diabetic subgroups (9). Patients with poorly controlled diabetes, defined as having a glycated hemoglobin (HbA1C) level greater than 9.0%, were excluded from the study. The diabetic and non-diabetic stroke groups were similar in terms of age, sex, hypertension, hyperlipidemia, smoking, left ventricular hypertrophy, diastolic dysfunction, mitral regurgitation, and aortic regurgitation.

Statistical Analysis

The statistical analysis was performed using the Statistical Package for Social Sciences 15.0 for Windows. Descriptive statistics were calculated and all data were expressed as mean ± standard deviation and % ratio. Student's t-test was used to compare quantitative values between two groups, while Pearson's chi-squared test ($\chi 2$) was used to compare qualitative values. Paired t-test was used to analyze data from different time periods within the same group. A p-value below 0.05 was considered statistically significant. Reproducibility was assessed by reanalyzing 15 randomly selected patients. The results were reported as intra-observer reliability. Additionally, the reproducibility was calculated by a second independent observer and reported as inter-observer reproducibility.

RESULTS

124 acute ischemic stroke patients (54 female and 70 male, mean age 67±11 years) and a control group of 93 subjects (49 female, 44 male) with a mean age of 69±8 years were included in this study. The corrected QT dispersion (QTcd) from the first 12-hour ECGs of the stroke group (ms) was higher than that of the control group (55.5±14.6 and 41.9±17.6, respectively, p<0.001). However, when we compared the QTcd values of the stroke group from the ECGs taken after 48 hours of the acute event (44.2±15.2) with those of the control group, there was no longer any significant difference (P=0.312) (Table 1). The difference between the first 12-hour QTcd values of the diabetic stroke and the nondiabetic stroke groups was statistically significant (61.5±16.0 ms, 52.2 ms, respectively; P=0.001). The QTcd of the diabetic stroke group after 48 hours of the acute event (51.3±15.7) was significantly longer than that of the nondiabetic stroke group (P<0.001). Interestingly, although the first 12-hour QTcd values of both the diabetic and non-diabetic groups were higher than those of the control group, after 48 hours, this difference was not significant for the non-diabetic group (40.1±14.0

Table 1: Characteristic features of stroke and control groups and QTcd values from first 12 hours and after 48 hours of acute event.

	Stroke group (n = 124)	Control group (n = 93)	p values
Age (years)	67 ± 11	69±8	0.155
Gender (F/M)	54/70	49/44	0.182
Diabetes Mellitus	45(%36)	39(%41)	0.398
Hypertension	80(%64)	57(%61)	0.626
Hyperlipidemia	32(%25)	31(%33)	0.227
Smokers	20(%16)	18(%19)	0.488
LV hypertrophy	29(%23)	28(%30)	0.266
Diastolic dysfunction	62(%50)	58(%62)	0.070
Mild MR	37(%29)	24(%25)	0.513
Mild AR	13(%10)	7(%7)	0.456
QTcd12 (ms)	55.5± 14.6	41.9±17.6	**<0.001**
QTcd48^{+} (ms)	44.2±15.6	41.9±17.6	0.312

AR: Aortic regurgitation, F: Female, LV: Left ventricular, M: Male, MR: Mitral regurgitation, n: Number, QTc: Corrected QT.

Table 2. Decrease in QTcd values by time

	QTcd 12 (ms)	QTcd 48^{+}(ms)	p value
Stroke (n=124)	55.5±14.6	44.2±15.6	**<0.001**
DM(+) stroke (n=45)	61.5±16.0	51.3±15.7	**<0.001**
DM(-) stroke (n=79)	52.2±12.7	40.1±14	**<0.001**

DM: Diabetes Mellitus, n: Number, QTc: Corrected QT

Table 3. QTcd values in relation to hemispheric lateralization

	Right hemispheric stroke (n = 51)	Left hemispheric stroke (n = 44)	p value
QTcd12 (ms)	51.3±13.7	61.8±15.3	**0.001**
QTcd48^{+}(ms)	41.3±15.6	50.2±16.5	**0.008**

n: Number, QTc: Corrected QT

Table 4. QTcd values of right and left hemispheric lesions among diabetic stroke patients

	DM (+) Right hemispheric stroke (n = 18)	DM (+) Left hemispheric stroke (n = 17)	p value
QTcd12 (ms)	56.8±16.6	67±15.5	0.065
QTcd48^{+}(ms)	48.7±17.8	56±14.8	0.193

DM: Diabetes Mellitus, n: Number, QTc: Corrected QT

Table 5. QTcd values of right and left hemispheric lesions among non-diabetic stroke patients

	DM(-)Right hemispheric stroke (n = 33)	DM(-) Left hemispheric stroke (n = 27)	p value
QTcd12 (ms)	48.3±11	58.4±14.4	**0.003**
QTcd48^{+}(ms)	37.3±12.8	46.4±16.7	**0.021**

DM: Diabetes Mellitus, n: Number, QTc: Corrected QT

ms) with a P value of 0.477. However, there was still a significant difference between the diabetic stroke group (51.3±15.7ms) and the control group (41.9±17.6ms). We also observed a significant decrease in QTcd values between the first 12 hours and after 48 hours of the acute event, from 55.5±14.6 ms to 44.2±15.6 ms, which was statistically significant (P<0.001). This decrease was also significant for the diabetic and non-diabetic stroke subgroups, from 61.5±16.0 ms to 51.3±15.7 and 52.2±12.7 to 40.1±14.0 ms, respectively, with a P value<0.001 for both subgroups (Table 2).

Patients with stroke were classified into two subgroups based on the location of their brain lesion, either in the right or left hemisphere. The first 12-hour QTcd values for patients with right hemisphere lesions were 61.8±15.3ms, whereas those for patients with left hemisphere lesions were 51.3±13.7ms. The values for the period after 48 hours were 50.2±16.5ms for right hemisphere lesions and 41.3±15.6ms for left hemisphere lesions, respectively. Both differences were statistically significant with P values of 0.001 for QTcd12 and 0.008 for QTcd48+ (Table 3).

The diabetic stroke group was also divided into two subgroups based on the location of their lesion. The mean first 12-hour QTcd value for diabetic stroke patients with left hemisphere lesions was 67±15.5ms, which was not statistically different from the value for those with right hemisphere lesions at 56.8±16.6ms (P=0.065). This lack of significance was also observed for the QTcd48+ values, which were 56.0±14.8ms for left hemisphere lesions and 48.7±17.8ms for right hemisphere lesions, respectively, with a P value of 0.193 (Table 4). However, for both QTcd12 (48.3±11.0ms for right hemisphere lesions and 58.4±14.4ms for left hemisphere lesions) and QTcd48+ values (37.3±12.8ms for right hemisphere stroke and 46.4±16.7ms for left hemisphere stroke), the differences between right and left hemisphere lesions were significant, with higher values observed for left hemisphere lesions (P=0.003 and 0.021, respectively) (Table 5).

DISCUSSION AND CONCLUSION

The present study investigated the relationship between corrected QT dispersion (QTcd) values and acute ischemic stroke, as well as the effect of diabetic status and lesion location on QTcd. Our results indicate that QTcd values in the first 12 hours after stroke onset were significantly higher in the stroke group compared to the control group, but this difference disappeared after 48 hours. Moreover, the diabetic stroke group had higher QTcd values than the non-diabetic group, both in the first 12 hours and after 48 hours. Interestingly, we found that the decrease in QTcd values between the first 12 hours and 48 hours after stroke onset was significant, indicating that QTcd values may be more useful in the acute phase of stroke.

Although some doubt has emerged about the usefulness of QT dispersion in recent years hindering it to be used in daily practice, it is widely acknowledged that QT dispersion has the potential of giving information about ventricular repolarization abnormality and therefore predicting malign arrhythmias; moreover, there are some studies showing that QT dispersion has a potential to predict sudden death even in otherwise healthy individuals (10-12).

The relationship between stroke and the risk of sudden death has been a subject of interest for many years, and there exist several studies related to stroke and QT dispersion (2). ECG changes due to stroke itself, rather than an underlying cardiac pathology, can be divided into two major categories: arrhythmias and repolarization abnormalities (13). Therefore, our aim in planning this study was to investigate if there was any significant relationship between stroke, especially the ischemic type, and QT dispersion, which is believed to reflect repolarization abnormalities. However, we were aware of the existence of some studies on this issue. Thus, we planned to delve deeper and explore what happens to QT dispersion in acute stroke patients over time. Furthermore, we aimed to investigate the effect of additional factors to stroke, such as diabetes and lesion lateralization, on QT dispersion, which have not received enough attention so far. Myers et al. showed that stroke patients had higher levels of norepinephrine, epinephrine, and dopamine, indicating increased sympathetic activity. They concluded that this increase might be the reason for cardiac arrhythmias, ECG changes, and blood pressure changes (14).

Studies have shown that increased QT dispersion during hospital admission for acute neurologic events

is related to in-hospital mortality and functional status during discharge (15). Sato et al. concluded that patients with subarachnoid hemorrhage had significantly longer QT dispersion values during the early hours of the event (16). Additionally, Eckardt et al. showed that patients with unilateral cerebral ischemia had increased QT dispersion that was not related to increased catecholamine levels (17).

In our study, we aimed to evaluate the change in QT dispersion of acute ischemic stroke patients over time. We observed that the effect of stroke on QT dispersion was most pronounced in the first 12 hours after stroke onset and decreased significantly after 48 hours. Afsar et al. also evaluated the effect of stroke on QT dispersion during the early course of the disease. They compared the QT dispersion values of 36 stroke patients, including cases of intracranial bleeding, without any known cardiovascular disease or diabetes to the QT dispersion values of 19 control cases. They showed that in the stroke group, QT dispersion during the first 12 hours was significantly longer than in the control group. However, QT dispersion in the stroke group decreased over time, and the difference from the control group became insignificant after the first 72 hours (18). These results were similar to ours, and they suggest that the early hours of acute stroke are more dangerous in terms of severe arrhythmias. Furthermore, when we compared the stroke and control groups, we found that the diabetic stroke group had significantly higher QT dispersion values than the control group after 48 hours of the acute event. This finding highlights the importance of diabetes in potentiating the effects of stroke on QT dispersion.

Our study also yielded interesting results regarding the relationship between lesion lateralization and QTcd. We found that patients with left hemispheric lesions had significantly longer QTcd values than those with right hemispheric lesions during both the first 12 and 48-96 hour periods. Interestingly, this difference was more pronounced in the nondiabetic group, as lesion location had no significant effect on QT dispersion in the diabetic group. These findings contrast with those of Afsar et al, who found longer QTcd for right hemispheric lesions compared to left after 72 hours of stroke, but no difference in the first 24 hours. Lane et al reported that decreased parasympathetic activity due to right hemispheric lesions may cause supraventricular tachycardia due to imbalanced sympathetic overactivity, and, that supraventricular arrhythmias are more common with right hemispheric lesions because the parasympathetic activity is more dominant in the atria and sympathetic in the ventricles. They also suggested that left hemispheric lesions are more likely to cause ventricular arrhythmias, which is consistent with our results (19).

However, Tokgözoğlu et al have argued that lesions in both hemispheres could lead to cardiac pathologies and sudden death through autonomic mechanisms. They highlighted the relationship between right insular lesions and decreased heart rate variability (HRV), which can lead to sudden death (20). Oppenheimer et al also found similar results and emphasized the significance of the insular cortex in sudden death (21). However, the Northern Manhattan Study (NOMAS), has shown that infarcts involving the left parietal lobe are associated with increased cardiac event rates (22). This is consistent with our finding that lesion lateralization does not affect QTcd values in diabetic stroke patients. Our results suggest that in this patient population, the importance of lesion lateralization on QTcd values may be diminished.

Diabetes is a significant risk factor for stroke, and it is widely recognized that it can increase mortality during and after stroke (23). Therefore, in our study, we aimed to investigate the effect of the combination of diabetes and stroke on QT dispersion. Among the stroke group, 36% of patients and 41% of control cases were diabetics, and all of them had type II diabetes. We excluded patients with coronary artery disease and heart failure. Diabetic autonomic neuropathy can cause symptoms several years after the onset of diabetes, but subclinical autonomic dysfunction may be detectable 1-2 years after the first diagnosis (24). Therefore, the combination of stroke and diabetes may have a more significant impact on QT dispersion, possibly due to additional effects on autonomic dysfunction.

Our study found that diabetic stroke patients had significantly higher QTcd12 and QTcd48 values than non-diabetic stroke patients, and this prolongation was still significant after 48 hours when compared to the control group. This suggests that diabetes has a prolonged effect on QTcd in stroke patients, indicat-

ing the need for extra attention to this group in daily practice. Close monitoring of patients during the acute phase of stroke is well known to improve the quality of medical care and increase the possibility of better outcomes during hospital discharge, up to 2.5 times (25). Therefore, this close monitoring period may need to be extended for diabetic stroke patients to achieve better results in terms of mortality.

Our study has several limitations. First, it was a single-center study, which may limit the generalizability of our findings. Second, the sample size was relatively small, which may have limited our statistical power to detect some significant differences. Third, we did not collect follow-up data such as post-discharge death and re-hospitalization, which could have provided more insight into the long-term effects of stroke on QT dispersion.

Although there is still some debate about the usefulness of QT dispersion, our results suggest that it may be a useful parameter for evaluating the risk of cardiac complications in stroke patients. Given the important connections between the central nervous system and the heart, CNS disorders such as stroke have the potential to affect membrane repolarization of ventricular myocytes, leading to QT dispersion. The effect of stroke on QT dispersion diminishes over time, but some factors such as diabetes can prolong this effect. Furthermore, lesion lateralization is an important factor that can increase QT dispersion further. Future studies on QT dispersion should investigate whether this parameter can be used to identify stroke patients at higher risk of cardiac complications and help guide clinical management.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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