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Effect of essential hypertension on QTc dispersion in patients with intracerebral haemorrhage

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Aim: To investigate the effects of essential hypertension on QTc dispersion (QTcd) in patients with intracerebral haematoma (ICH).

Materials and methods: This prospective study included adult patients presenting with acute ICH within the first 24 h of ictus to the Emergency Department (ED). On admission, following the first clinical assessment of patients, a complete 12-lead ECG and non-contrast computed tomography (CT) were obtained from each patient. Then, the patients were divided into 2 subgroups according to the presence of hypertension history. The patient groups were compared to each other as well as the control group for QTcd.

Results: The study groups consisted of 47 hypertensive (group 1) without evidence of left ventricular hypertrophy and 30 non-hypertensive patients (group 2). Forthy two subjects served as control. While in the hypertensive patient group mean QTcd was 49.36 ± 20 ms, in the non-hypertensive group, it was 48.00 ± 19 ms (P > 0.05).

Conclusion: In the present study, although QTcd was higher in the group 1 compared to group 2, this difference was not statistically significant. Thus, systemic hypertension does not seem to have a great effect on post-stroke QTcd in ICH patients.

Key words: Hypertension, intracerebral hemorrhage, QTc dispersion

Beyin içi kanamalı hastalarda QTc dispersiyon üzerine esansiyel hipertansiyonun etkisi

Amaç: Bu çalışmanın amacı beyin içi kanamalı (BİK) hastalarda QTc dispersion (QTcd) üzerine esansiyel hipertansiyonun etkilerini araştırmak idi.

Yöntem ve gereç: Bu ileriye dönük çalışma acil servise ilk 24 saat içinde BİK ile başvuran hastalardan oluşturuldu. Başvuruda, her bir hastadan EKG ve kontrastsız beyin tomografisi (BT) elde edildi. Daha sonra hastalar hipertansiyon öyküsünün varlığına gore 2 gruba ayrıldı. Hasta grupları QTc dispersiyon (QTcd) için kontroller ve herbiri diğeri ile karşılaştırıldı.

Bulgular: Çalışma grupları sol ventrikül hipertrofisi olmayan 47 hipertansif hasta (grup 1), 30 hipertansif olmayan hasta (grup 2) ve 42 kontrol kişilerden oluşturuldu. Hipertansif hasta grubunda ortalama QTcd 49,36 ± 20 ms iken hipertansiyonu olmayan grupta 48,00 ± 19 ms idi (P > 0,05).

Sonuç: Bu çalışmada, hernekadar QTcd değeri grup 2 ile karşılaştırıldığında grup 1'de daha yüksekti ise de bu fark anlamlı değildi (P > 0,05). Böylece sistemik hipertansiyonun BİK'lı hastalarda inme sonrası QTcd üzerine büyük bir etkiye sahip olmadığı gözükmektedir.

Anahtar sözcükler: Hipertansiyon, beyin içi kanama, QTc dispersiyon

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Introduction

The QTc dispersion (QTcd) is a marker of cardiac repolarisation abnormality and is defined as the difference between the longest QTc and the shortest QTc interval in the surface electrocardiogram (ECG) (1,2). It has been reported that repolarisation abnormalities are risk factors for cardiac arrhythmias and sudden death in some cardiac and noncardiac diseases, and QTcd has been shown to be well-correlated with the risk of arrhythmia and mortality (1,3,4). In cerebrovascular diseases, autonomic nerve system dysfunction influences cardiac repolarisation (1,5). It has been reported that autonomic tone has an important role in the regulation of the QT interval (6). It has also been reported that autonomic nervous system dysfunction changes the QTcd (7,8). Responsible mechanisms for post-stroke autonomic nervous system dysfunction have included increased catecholamine activity, impaired baroreflex sensitivity (BRS), and involvement of autonomic cardiac control centres, including the insular cortex in the brain (1,6,9–19). Increased QTcd due to insular cortex damage has been demonstrated in both experimental and clinical studies (1,13,20).

Some studies have suggested that, in hypertensive patients, an increased frequency of electrocardiographic abnormalities is related to end organ damage (21-23). Perkiomaki et al. reported that very few hypertensive patients without left ventricular hypertrophy (LVH) versus one third of hypertensive patients with LVH had an abnormal QT apex dispersion (24). It has been suggested that there are changes in autonomic cardiac control in hypertensive patients compared with those who are normotensive (23). Baroreflex impairment has commonly been described in hypertensive subjects (25). Chronic hypertension, and hence atherosclerosis in the carotid sinus and aortic arch, which are specialised vascular segments where baroreceptors are located, are associated with impaired baroreceptor functions (e.g., decreased sensitivity) (26,27). Thus, our hypothesis is that QTcd during the acute phase of intracerebral haemorrhage (ICH) may be higher in hypertensive patients with ICH compared to those without hypertension. In the literature, the studies reporting QTc changes in patients with isolated ICH are few (1,28-30). Two of these studies are case reports (28,29). Huang et al. (1) retrospectively studied the QTcd on the initial ECGs of survival and non-survival patients with ICH in the emergency department (ED). They reported that an increased QTcd in the initial ED ECG is an important prognostic factor for ICH (1). To the best of our knowledge, this is the first prospective study comparing isolated ICH patient groups with and without hypertension for QTcd on the admission of ECG. Therefore, the aim of the present study was to investigate the effects of essential hypertension on QTcd in ICH patients.

Materials and methods

This prospective study was approved by the local ethics committee of our university. Patients older than 18 years presenting consecutively with acute ICH within the first 24 h of ictus to the ED of University Hospital during 1 year were included in this study.

The control group was composed of patients with non-neurologic diseases that do not affect ECGs and without any cardiac problems and health workers employed at the university hospital. The control group was similar to the patient group in terms of age and sex distribution. The control subjects with non-neurologic diseases were hospitalised for idiopathic thrombocytopenic purpura, minor trauma, mild gastrointestinal bleeding, hypertensive attack without encephalopathy, and viral gastroenteritis. The ICH patients and controls were included in the study after their informed consent or that of their families (for unconscious patients) was obtained. Both patients and controls were divided into hypertensive and non-hypertensive subgroups according to the presence of a history of hypertension. Group 1 included hypertensive patients with ICH and group 2 included non-hypertensive patients with ICH.

The inclusion criteria were: (1) age 18 years or older; (2) presenting within the first 24 h of symptom onset; and (3) evidence of ICH on head CT scan.

Exclusion criteria were as follows: (1) past medical history or evidence of any cardiac disease, such as ventricular tachyarrhythmia, atrial fibrillation, ischemic heart disease, with cardiac wall motion abnormality detected by echocardiography, and/or elevated levels of biochemical markers of myocardial injury, diabetes mellitus, renal dysfunction (creatinine

>2mg/dL), dermatomyositis, or other conditions associated with autonomic dysfunction, such as electrolyte imbalance, anaemia, malnutrition, and acute infection; (2) a history of taking any drugs known to affect cardiovascular or autonomic functions, such as tricyclic antidepressants, antihypertensives, or antiarrhythmics; (3) the presence of subarachnoid haemorrhage in the fissures and/or sulcuses; (4) the presence of LVH documented electrocardiographically or echocardiographically; and (5) the presence of findings consistent with an acute ischemic infarct in a vascular territory.

Hypertensive patients were determined according to (1) the presence of a history of hypertension; (2) the presence of systolic blood pressure greater than 140 mmHg and/or diastolic blood pressure greater than 90 mmHg on previous medical records (31); and (3) taking any antihypertensive medications. However, increased blood pressure on arrival was not accepted as a diagnostic criterion.

In our study, all stroke patients were examined by a neurologist (DA) following a detailed history obtained from the patients or family members. On admission, systolic and diastolic blood pressure values were obtained simultaneously using both automatic and manual methods.

The stroke patients had a complete 12-lead ECG examination (Nihon Kohden; Cardiofax GEM ECG-9020K, Japan) and non-contrast computed tomography (CT) of the head following the first assessment and management of acute stroke in the ED. Similarly, a complete 12-lead ECG was performed on each control subject. All ECGs were recorded at a paper speed of 25 mm/s with a gain of 10mm/mV and a filter setting of 35 Hz during a resting state.

The diagnosis of ICH was based on evidence of haematoma on non-contrast CT scans in all stroke patients. The CT examinations were performed using a helical CT scanner (X press/ GX model TSX- 002 a, Toshiba). Standard axial 5 mm and 10 mm cuts were obtained through the posterior fossa and supratentorial regions, respectively.

Data analysis:

The non-contrast CTs were reviewed by an experienced neuroradiologist (SN), blinded to all clinical data apart from the expected lesion side. The size and location of haematomas were evaluated based on the brain CT studies. The size of haematoma was calculated using the formula $0.5 \times a \times b \times c$, where a and b are the largest perpendicular diameters of the haematoma measured on the CT scan, and c is the number of slices multiplied by the slice thickness (32). Lesion localisations were categorised as right and left according to the hemisphere involved, and as basal ganglionar, thalamic, lobar (lateral to the external capsule), and mixed (combined) according to the region involved within each hemisphere.

The ECGs were reviewed by a cardiologist (OY) blinded to all information except the number of patients. Heart rate was determined by dividing 300 by the number of large squares in the consecutive R-R interval (33). The QT intervals were measured from the onset of the QRS to the end of the T wave using a tangential method. The QTc interval was calculated using Bazett's formula: $QTc = QT / \sqrt{RR}$ (33). Prolongation of the QTc was defined as greater than 0.44 s, and non-prolongation was defined as less than 0.44 s (33). The QTcd (maximum QTc-minimum QTc) was obtained from the difference between the longest and shortest QTc interval following measuring of the QTc interval complexes in each lead of a standard 12-lead ECG (34).

At the end of the study period, the patient groups were compared to each other and the control groups for QTcd. Additionally, lesion localisations were compared to each other for QTcd and the relationship between the size of haematoma and QTcd and between QTcd and systolic, and diastolic blood pressure values on admission were investigated.

Statistical methods:

The results were analysed using the computer software (SPSS version 15.0). A $P < 0.05$ was considered statistically significant in all tests. Because the data in our study were non-normally distributed, the statistical analyses were performed using non-parametric tests.

The Mann-Whitney test was used to compare the patient and control groups for QTcd. Similarly, groups 1 and 2 were compared using the Mann-Whitney test for QTcd. In the patient groups, the comparison of the right and left hemispheres for QTcd was performed using the Mann-Whitney test. A Kruskal-Wallis

analysis was used to determine the difference among lesion localisations in the hemispheres for QTcd in the patients. The Spearman Rho correlation test was used to investigate the relationship between the size of haematoma and QTcd and between QTcd and systolic and diastolic blood pressure values on admission.

Results

During the study period, about 400 patients presented to our hospital with acute stroke. Of these patients, 120 had ICH; however, only 103 patients met all inclusion criteria. Twenty-six patients (11 with cerebellar haemorrhage, 5 with brainstem haemorrhage, 3 with multifocal haemorrhage, and 7 with intraventricular haemorrhage) were excluded from the study. The study group consisted of the remaining 77 patients (47 hypertensive without evidence of LVH and 30 non-hypertensive). The control group consisted of 42 subjects (22 hypertensive without LVH and 20 non-hypertensive). The mean age was 63.16 ± 13 years in the patient group and 61.95 ± 18 years in the control group (P > 0.05).

The mean QTcd was 48.83 ± 19 ms for the patient group and 39.52 ± 20 ms for the control group. The difference between the patient and control groups for QTcd was statistically significant (P = 0.018, Figure). The subgroup analysis of QTcd received higher value in the hypertensive patients compared with the non-hypertensive patients, although this difference was not significant (49.36 ± 20 versus 48.00 ± 19, P > 0.05, Figure). When compared with each subgroup of the control subjects, mean QTcd values in both patient subgroups were significantly higher (P < 0.05, Figure). The mean size of haematoma was 105.0 ± 103 mm^3. There was a significant, but weak, positive correlation between the size of haematoma and QTcd in the ICH group (P = 0.392, r = 0.099). However, there was no significant correlation between QTcd and age.

The mean admission systolic and diastolic blood pressure values of all patients were 177.46 ± 39 and 98.10 ± 17 mmHg, respectively. Systolic and diastolic blood pressure values were 181.7 ± 41 and 98.7 ± 15 mmHg in the hypertensive patients, respectively, and 170.8 ± 36 and 97.1 ± 19 mmHg in the non-hypertensive patients, respectively (P = 0.242 and 0.251, respectively).

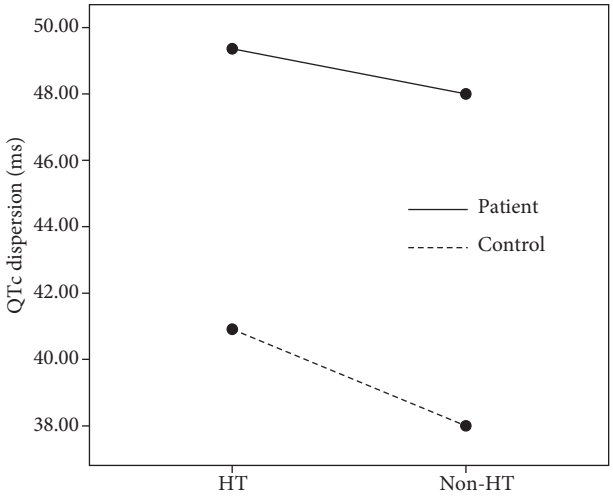

Figure. QTc dispersion in the patient and control groups with and without hypertension. In both patients and control subjects, those hypertensive patients had insignificantly higher QTc dispersion than those non-hypertensive ones (P > 0.05).

*P = 0.018, QTc dispersion in all patients vs control group.
HT: Hypertensive; Non-HT: Non-hypertensive

In the present study, there was no significant correlation between the initial systolic blood pressures and QTc-dispersion (P = 0.602, r = 0.06) or between the initial diastolic blood pressures and QTc-dispersion (P = 0.910, r = 0.013).

Of the lesions shown on the CT scans, 54.5% (n = 42) were in the right hemisphere, and 45.5% (n = 35) were in the left hemisphere. There was no significant difference between right and left hemispheric involvement for QTcd in the ICH patients (P > 0.05, Table).

Table. QTc-dispersion values according to the localisations and lateralisations of lesions in cranial computed tomographies of the patients.

		QTc-dispersion (ms)
Localisation*	Basal Ganglion (n = 33)	47.57 ± 20
	Thalamic (n = 13)	53.84 ± 21
	Lober (n = 31)	47.0 ± 16
Lateralisation*	Right Hemisphere (n = 42)	48.80 ± 20
	Left Hemisphere (n = 35)	48.85 ± 18

*P > 0.05 compared with each other of the localisations and lateralisations of lesions for QTc dispersion in the patients.

Of the patients, 42.8% (n = 33) had a basal ganglion haemorrhage, 16.9% (n = 13) had a thalamic haemorrhage, and 40.3% (n = 31) had a lobar haemorrhage (Table). However, there was not a statistically significant difference among 3 lesion localisations for QTcd in the ICH patients (P > 0.05, Table).

The QTcd values related to the localisations and lateralisations of lesions in the patients are presented in the Table.

Discussion

Electrocardiographic abnormalities in acute stroke are well documented (1,9,10,12,15,19,28,33-35). It has been suggested that increased QTcd and other ECG abnormalities are associated with increased catecholamine activity, impaired BRS, and involvement of autonomic cardiovascular control centres, such as the insular cortex, amygdale, and lateral hypothalamus in the brain (1,9-17). Insular damage may cause the increased activation of the sympathico–adrenal system because of decreased inhibitory insular activity (36). Tatschl et al. reported a prolongated QT interval in 31% of 122 acute stroke patients with insular involvement (37). Eckardt et al. observed a significantly longer QTcd in patients with insular involvement compared to those without insular involvement by ischemic stroke (13). However, a reduction in BRS and an elevation in plasma catecholamine levels (as a result of the activation of the sympathico–adrenal system) have been documented in patients with acute stroke (ischemic and hemorrhagic); impaired baroreflex is also commonly seen in hypertensive patients without stroke (16,24,25,27,36,38). It is known that atheroma often affects the carotid sinus and aortic arch, which are specialised vascular segments where baroreceptors are located. Hirschl et al. showed that in humans, carotid atheroma decreases BRS, and endarterectomy may improve baroreceptor reflex function (27). Autonomic cardiac control has been shown to be altered in hypertensive patients compared with their normotensive counterparts (23). While an impaired BRS results in impaired vagal reflexes, which may cause arrhythmias, reduction in BRS results in increased sympathetic activity (15). It has been suggested that reductions in BRS are associated with QTc prolongation, ventricular tachyarrhythmias, and sudden cardiac death (17). Unlike previous studies investigating abnormal QTc intervals (increased QTcd or QTc interval prolongation) in stroke patients, we compared hypertensive and non-hypertensive patients with ICH for QTcd in our study. However, in the present study, QTcd values were higher in both the hypertensive patient group and the hypertensive control group than in the non-hypertensive patient and control groups. These differences were not statistically significant. These results may show that hypertension has little effect on QTcd in ICH patients. On the other hand, we found that QTcds were significantly higher in ICH patients compared with control patients. This result supports the data of studies focused on QT-interval changes due to stroke. Additionally, in our study, there were no correlations between QTcd and the initial blood pressure values or between QTcd and age. These results show that ICH can cause a change in QTcd independent of age, essential hypertension, and blood pressure values.

We also found a significant, but weak, correlation between the size of haematoma and QTcd in the ICH group. However, there was no correlation between QTcd and the localisation of haematoma in our study. Afsar et al. reported that QTcd was greater in patients with larger lesions than in those with smaller lesions in the first 24 h (35). However, they did not find significant differences between QTcd and lesion localisation (35). Thus, our results are consistent with data from this study.

Most studies investigating hemispheric laterality have suggested that involvement of the right hemisphere by stroke produces a more significant increase in sympathetic cardiovascular effects compared with the left hemisphere (9-13,18,34,36,37,39-41). Sander and Klingelhofer (18) showed that right hemisphere infarction caused higher serum noradrenaline levels and resulted in increased blood pressure and longer QTc prolongation compared to left hemisphere infarcts. An animal stroke (by electrical lesion) model study has also indicated that the right insula regulates cardiovascular sympathetic tone and the left insular cortex regulates cardiac parasympathetic and

baroreceptor function (42). In contrast to most studies, Hilz et al. showed that inactivation of the left hemisphere resulted in increased sympathetic nervous system activity and impaired BRS in their epilepsy study (43). Korpelainen et al. suggested that autonomic cardiovascular disturbances may be seen in both right and left hemisphere infarcts (44). We found no significant difference between the right and left hemispheres for QTcd values in the ICH patients. Therefore, we think that both right and left hemisphere involvement by ICH may have a similar influence on QTcd.

The major limitation of the present study was the small sample size of the subgroups divided according to history of hypertension for the statistical analysis.

Conclusion

In the present study, although QTcd was higher in the hypertensive patients compared with non-hypertensive patients, these differences were not statistically significant. Thus, systemic hypertension does not seem to have a great effect on post-stroke QTcd in ICH patients. However, further large prospective studies investigating the effect of hypertension on QTcd in ICH patients are needed to support the present findings.

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