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TPE, TPE Dispersion and TPE/QT Ratio As Risk Indicators of Malign Ventricular Arrhythmia In Acute Cerebrovascular Event

Akut Serebrovasküler Olaylarda Malign Ventrüküler Aritminin Risk Göstergeleri Olarak TPE, TPE Dispersiyon ve TPE/QT Oranı

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Abstract

Introduction: Although there are limited data on the change of Tpeak-tend (Tpe), Tpe dispersion (Tpe-d) and Tpe/QT rate, which are new predictors of ventricular arrhythmias in acute ischemic stroke (AIS) and acute hemorrhagic stroke (AHS), these parameters have not been evaluated in the transient ischemic attack (TIA). The aim of this study is to evaluate the variation of these parameters by including the TIA and performing a more detailed electrocardiographic (ECG) analysis.

Materials and Methods: In this prospective study, patients were put into three groups as 30 with AIS (mean age, 61.17±14.14 years; 15 women), 20 with AHS (mean age, 65.05±9.50 years; 10 women), and 30 with TIA (mean age 58.10±13.32 years; 15 women). Thirty sex- and age-matched healthy controls were recruited. Tp-e, Tpe-d and Tp-e/QT rate were calculated from 12-lead ECG.

Results: In AIS and AHS both previous and new arrhythmia parameters were significantly more prolonged, compared to controls and patients with TIA. The prolonged parameter was specific to the derivations of V5 and V6. A positive correlation was present between the age, and Tpe, QTcmax and QTd (r= 0.21, p= 0.028; r= 0.19, p= 0.032; and, r= 0.22, p= 0.013, respectively).

Conclusion: Our study revealed that ventricular repolarization parameters such as Tpe, Tpe-d and Tpe/QT do not change in TIA, however, both AIS and AHS increase these indexes. This may explain the increased risk of ventricular arrhythmias in acute stroke patients. Moreover, in acute stroke patients, leads V5 and V6 on the ECG appear to be suitable for assessing ventricular repolarization.

Keywords: Acute cerebrovascular accident; Tpe interval; Tpe/QT ratio; transient ischemic attack.

Özet

Amaç: Akut iskemik inme (AİS) ve akut hemorajik inmede (AHS) yeni ventriküler aritmi öngördürücüleri olan Tpeak-Tend (Tpe), Tpe dispersiyon (Tpe-d) ve Tpe/QT oranı'ın değişimine dair sınırlı sayıda veri bulunmasına rağmen, geçici iskemik atakta (GİA) bu parametreler değerlendirilmemiştir. Bu çalışmanın amacı, GİA'yı da dahil ederek ve daha detaylı bir elektrokardiyografik (EKG) analiz yaparak bu parametrelerin değişimini değerlendirmektir.

Gereç ve Yöntem: Bu prospektif çalışmada hastalar, AİS'lu 30 (ort. yaş, 61.17±14.14 yıl; 15 kadın), AHS'lu 20 (ort. yaş, 65.05±9.50 yıl; 10 kadın) ve GİA'lı 30 hasta (ort. yaş 58.10 ± 13.32 yıl; 15 kadın) olmak üzere üç gruba ayrıldı. Yaş ve cinsiyet uyumlu 30 sağlıklı birey kontrol grubu olarak alındı. 12-lead EKG'den Tp-e, Tpe dispersiyon ve Tpe/QT oranı hesaplandı.

Bulgular: AİS ve AHS grubunda hem eski hem de yeni (Tpe, Tpe-d, Tpe/QT oranı) aritmi parametreleri GİA ve kontrol grubu ile karşılaştırıldığında anlamlı şekilde uzamıştı. Bu uzama V5 ve V6 derivasyonlarına özgündü. Yaş ile Tp-e, QTcmax ve QTd arasında pozitif korelasyon vardı.

Sonuç: Çalışmamız, GİA'da Tpe, Tpe-d ve Tpe/QT gibi ventriküler repolarizasyon parametrelerinin değişmediğini ancak hem AİS hem de AHS'un bu indeksleri arttırdığını ortaya çıkardı. Bu durum, akut inme hastalarında ventriküler aritmi riskindeki artışı açıklayabilir. Ayrıca akut inme hastalarında, EKG üzerinde V5 ve V6 leadleri ventriküler repolarizasyonu değerlendirmede uygun leadler gibi görünmektedir.

Anahtar Kelimeler: Akut serebrovasküler olay; geçici iskemik atak; Tpe aralığı; Tpe/QT oranı.

Introduction

Arrhythmic events and repolarization disorders are common in cerebrovascular events, even in the absence of concomitant cardiac disease (1). The existence of an intense vascular and neuronal connection between the two systems is accepted as the main reason why neurological and cardiovascular problems are so intertwined (2). It is effective in regulating the mechanical and

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electrical activity of the heart through the autonomic nervous system, sympathetic and parasympathetic systems. Neurons in the cerebral cortex, hypothalamus, midbrain, pons, and medulla contribute to autonomic control (3). It has been asserted that cardiovascular changes such as tachycardia, bradycardia, and atrioventricular conduction disorders that occur in cerebrovascular diseases emerge as a result of the involvement of these regions (4). In pathophysiology, neuronal effects caused by changes in myocardial cells, especially in membrane potentials and permeability due to calcium ions, damage to the autonomic nervous system that arrangements heart rhythm and rate, with the effect of catecholamines released into the general circulation come into prominence (1). Transient ischemic attack (TIA) is a subtype of acute cerebrovascular events such as acute ischemic stroke (AIS) and acute hemorrhagic stroke (AHS) (5). Although its pathophysiology is similar to ischemic stroke, it is considered to be the beginning of an ongoing ischemic process (6). Progression of the ischemic process can be prevented with early diagnosis and treatment. It has been shown that the frequency of cardiovascular events increases in TIA, though it is much less than in ischemic and hemorrhagic stroke (7,8). In addition to well-defined electrocardiographic parameters such as QTd, QTc and QT as an indicator of increased arrhythmia risk in recent years, new measurements like T peak-Tend (Tpe), Tpe/QT ratio and T pe dispersion (Tpe-d) have been suggested (9-11). QTc, total depolarization, and repolarization; QTd indicates global repolarization. It has been suggested that Tpe, Tpe-d, and Tpe/QTc ratio, which show transmural repolarization, are more valuable than previous parameters in determining the risk of arrhythmia (12). There are a limited number of studies evaluating Tpe, Tpe-d, and Tpe/QT ratio in acute ischemic and hemorrhagic stroke (13-15), nevertheless, within our knowledge, there is no study that included TIA and compared these three groups with each other or with a healthy control group. The aim of this study is to examine the change of new arrhythmia parameters, particularly Tpe, Tpe-d and Tpe/QT ratio, in patients with AIS, AHS and TIA compared to the healthy control group.

Materials and Methods

Study Design: This was an observational, cross-sectional study

Study Population: The study included 30 patients with AIS, 20 patients with AHS, and 30 patients with TIA, who applied to the Neurology and Emergency Department between February 2013 and July 2013, and 30 healthy individuals whose ECGs were taken for any reason and age and gender-matched as the control group. The patients were evaluated by at least two neurologists. The diagnosis was confirmed by neurologic examination, brain CT and diffusion MR imaging methods in the first 24 hours. The patients were divided into three groups as AIS, AHS and TIA. Subgroup analysis was performed according to the involvement of the insular cortex. The study was approved by local ethics committee conducted Meram Faculty of Medicine, Necmettin Erbakan University (date/approval number: 2013/406). The study was conducted in accordance with the ethical principles described by the Declaration of Helsinki. All participants were informed in detail about the study, and their verbal and written consents were obtained. Consent was obtained from the relatives of the patients who could not give verbal and written consent. Medical history of patients including previous stroke, systemic disease, family history, smoking, and drug use were obtained. Glucose, lipid parameters, TSH, B12, urea, creatine, Na, K, Ca levels, hemoglobin, and white blood cells (WBC) were analyzed from the samples taken. These examinations were performed between the first day at the earliest and the third day at the latest. Patients with history of cardiyovascular atherosclerosis and arrhythmia (such as atrial fibrillation, left or right bundle block and pacemaker) chronic lung disease, chronic renal failure, electrolyte or thyroid disorder, and patients with drug use affecting the conduction system, subarachnoid and intracranial hemorrhage due to trauma were excluded in the study.

Electrocardiographic Evaluation: ECG recordings of all participants were taken with a 12-lead Nihon-Kohden ECG-9132K device at a speed of 25 mm/s and an amplitude of 10 mm/mV. ECGs were reviewed by two cardiologists who were uninformed about the patients' clinical knowledge. For ECG analysis, we performed manual measurements of the values with a digital caliper using a special program. The measurement of each parameter was obtained from the average of three consecutive beats. The QT interval was calculated as the time from the start of the QRS wave to the end of the T wave. QTd was calculated by subtracting the minimum QT interval from the maximum QT interval.

Corrected QT (QTc) and corrected QT dispersion (QTcd) were obtained by using the Bazett formula ($QTc=QT/\sqrt{RR}$). QTc values greater than 440 ms for men and 460 ms for women were defined as prolonged QTc. The Tpe interval was measured in all precordial leads, and the Tpe interval was defined as the the interval from the peak of T wave to the end of T wave (Figure 1). In cases where the T wave was biphasic or negative, the lowest point of the T wave was taken. Leads with T wave amplitude <0.1 mV were not included in the analysis. 110 msec was taken as the critical threshold value for Tpe (13). Tpe-d was expressed as the difference between the maximum and minimum Tpe interval in the precordial leads.

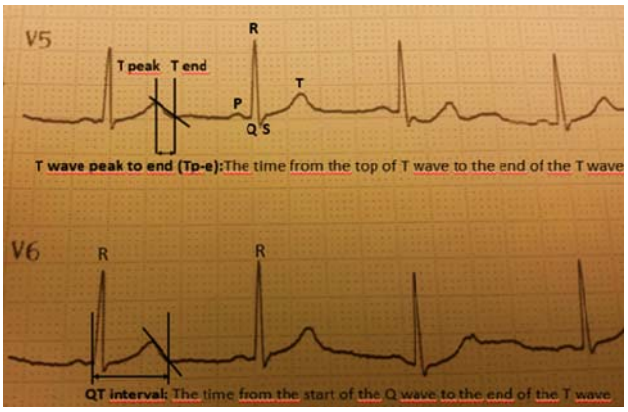

Figure 1: An image of measurement of electrocardiographic parameters

Table 1: Clinical features and laboratory findings of study groups

Variables	Control group (n=30)	TIA group (n=30)	Ischemic stroke group (n=30)	Hemorrhagic stroke group (n=20)	P
Age (years)	58.27 ± 10.45	58.10 ± 13.32	61.17 ± 14.14	65.05 ± 9.5	0.162
Women, n (%)	15 (50)	15 (50)	15 (50)	10 (50)	1.000
Men, n (%)	15(50)	15 (50)	15 (50)	10 (50)	1.000
Smoking, n (%)	3 (10)	4 (13.3)	5 (16.6)	1 (5)	0.630
BMI (kg/m²)	27.6 ± 7.9	26.8 ± 3.3	27.7 ± 3.7	28.1 ± 4.1	0.712
DM, n (%)	0 (0)	2 (6.6)	11 (36.6) [d,e]	5 (25) [a]	0.001
HT, n (%)	0 (0)	10 (33.3) [f]	15 (50) [d]	14 (70) [a,b]	0.001
SBP (mmHg)	124.1 ± 9.8	138.2 ± 12.3 [f]	143.3 ± 10.5 [d]	154.8 ± 23.4 [a,b,c]	0.001
DBP (mmHg)	72.6 ± 7.4	74.6 ± 9.8	84.5 ± 8.4 [d,e]	85.8 ± 12.9 [a,b]	0.001
Glucose (mg/dl)	99.5 ± 13.9	109.8 ± 32.7	131.6 ± 67.5	167.3 ± 71.1	0.120
Urea (mg/dl)	31.1 ± 7.2	31.9 ± 8.01	44.6 ± 26.7 [d,e]	41.8 ± 13.3	0.003
Creatinine (mg/dl)	0.77 ± 0.13	0.75 ± 0.10	0.78 ± 0.27	0.74 ± 0.20	0.852
Na^+ (mmol/L)	139.8 ± 2.1	139.4 ± 2.3	139.8 ± 4.3	139.7 ± 2.5	0.946
K^+ (mmol/L)	4.2 ± 0.4	4.1 ± 0.3	4.2 ± 0.4	4.3 ± 0.4	0.245
Ca^{++} (mg/dl)	9.03 ± 0.21	9.4 ± 0.23	9.1 ± 0.18	9.2 ± 0.23	0.761
Total Cholesterol (mg/dl)	190.9 ± 36.4	191.9 ± 42.4	193.2 ± 57.07	200.8 ± 49.9	0.895
Triglyceride (mg/dl)	149.8 ± 51.8	149.3 ± 53.5	140.8 ± 59.4	125.7 ± 48.1	0.398
LDL-Cholesterole (mg/dl)	112.4 ± 24.5	116.7 ± 31.06	127.7 ± 47.9	130.1 ± 39.7	0.242
HDL-Cholesterol (mg/dl)	39.8 ± 8.1	39.3 ± 8.2	43.5 ± 10.9	44.7 ± 14.3	0.178
TSH (mlU/ml)	1.6 ± 0.8	1.6 ± 1.0	1.4 ± 0.8	1.3 ± 0.7	0.664
B12 (pg/ml)	287.9 ± 22.1	260.2 ± 63.7	200.9 ± 98.5	191.8 ± 88.8	0.087
WBC (K/uI)	7.20 ± 1.86	7.3 ± 1.95	8.47 ± 2.24	10.96 ± 2.44 [a,b,c]	0.001
Hb (g/dl)	14.1 ± 1.7	14.1 ± 1.6	13.0 ± 1.8	13.6 ± 2.2	0.083

Statistics: One Way ANOVA: Scheffe post-hoc test **Abbreviations:** BMI: Body Mass Index, DBP: Diastolic blood pressure, DM: Diabetes mellitus, Hb: Hemoglobin, HT: Essential hypertension, SBP: Systolic blood pressure, TIA: Transient ischemic attack, TSH: Thyroid stimulating hormone, WBC: White blood cell, Data are presented as means ± SD **a:** Expresses statistical significance between hemorrhagic stroke and healthy subjects ($p<0.05$) **b:** Expresses statistical significance between hemorrhagic stroke and TIA ($p<0.05$) **c:** Expresses statistical significance between hemorrhagic stroke and ischemic stroke ($p<0.05$) **d:** Expresses statistical significance between ischemic stroke and healthy subjects ($p<0.05$) **e:** Expresses statistical significance between ischemic stroke and TIA ($p<0.05$) **f:** Expresses statistical significance between TIA and healthy subjects ($p<0.05$)

Table 2: Electrocardiographic findings of the study groups

Variables	Control group (n=30)	TIA Group (n=30)	Ischemic stroke group (n=30)	Hemorrhagic Stroke Group (n=20)	P
HR (beats/min)	73.6 ± 13.5	76.5 ± 15.9	74.7 ± 13.2	82.8 ± 15.6	0.152
DIQT	366.6 ± 25.3	369.6 ± 23.4	371.0 ± 25.0	372.2 ± 23.5	0.265
DIQTc	411.0 ± 28.6	414.0 ± 27.2	421.4 ± 28.5	424.0 ± 32.8	0.114
DIIQT	374.0 ± 27.2	378.6 ± 26.2	413.6 ± 23.1 [d,e]	415.0 ± 18.1 [a,b]	0.032
DIIQTc	412.0 ± 27.4	417.9 ± 28.1	454.4 ± 29.3 [d,e]	458.5 ± 32.9 [a,b]	0.021
DIIIQT	375.6 ± 23.5	379.0 ± 22.6	383.3 ± 24.0	385.5 ± 18.3	0.225
DIIIQTc	412.6 ± 28.4	416.6 ± 27.9	426.1 ± 32.5	431.4 ± 41.1	0.218
AVRQTc	415.7 ± 32.8	420.9 ± 30.5	423.3 ± 36.4	427.6 ± 35.0	0.301
AVLQTc	409.4 ± 33.4	417.4 ± 31.6	418.1 ± 26.2	425.5 ± 38.1	0.091
AVFQTc	415.3 ± 31.7	420.1 ± 27.8	425.9 ± 26.8	432.5 ± 34.7	0.104
V1QT	373.3 ± 29.4	379.3 ± 22.5	385.3 ± 24.5	385.0 ± 17.0	0.160
V1QTc	415.9 ± 33.9	421.4 ± 36.8	426.9 ± 27.9	431.4 ± 41.7	0.092
V2QT	376.0 ± 29.4	377.3 ± 28.6	389.6 ± 23.4	389.5 ± 22.8	0.096
V2QTc	419.5 ± 29.1	423.5 ± 32.7	431.2 ± 34.3	435.1 ± 37.3	0.102
V3QT	387.0 ± 26.4	379.6 ± 29.3	393.6 ± 21.7	389.5 ± 26.2	0.230
V3QTc	427.8 ± 27.9	425.8 ± 28.9	436.6 ± 33.0	439.9 ± 34.4	0.281
V4QT	388.0 ± 23.2	384.0 ± 31.2	392.0 ± 20.5	365.0 ± 78.6	0.125
V4QTc	427.1 ± 28.2	429.5 ± 29.2	435.3 ± 38.9	430.3 ± 99.7	0.939
V5QT	381.3 ± 28.7	380.0 ± 34.0	398.0 ± 23.6 [d,e]	407.5 ± 21.8 [a,b]	0.025
V5QTc	417.7 ± 33.4	421.8 ± 30.1	449.5 ± 33.6 [d,e]	459.4 ± 39.2 [a,b]	0.003
V6QT	383.6 ± 27.6	378.0 ± 33.9	392.3 ± 25.4	395.0 ± 27.4	0.522
V6QTc	422.1 ± 28.5	419.1 ± 28.4	446.2 ± 35.1[d,e]	453.8 ± 43.6 [a,b]	0.011
QTmax	388.3 ± 19.0	391.0 ± 23.1	419.0 ± 18.9 [d,e]	422.0 ± 18.7 [a,b]	0.034
QTcmax	418.2 ± 32.1	423.3 ± 29.4	450.2 ± 33.9 [d,e]	465.2 ± 36.8 [a,b,c]	0.009
QTmin	360.0 ± 23.3	354.0 ± 22.9	370.0 ± 18.2	357.5 ± 16.8	0.342

Statistics: One Way ANOVA: Scheffe post-hoc test **Abbreviations:** HR: Heart rate, QTmax: Maximum QT, QTmin: Minimum QT, TIA: Transient ischemic attack, QTc: Corrected QT, Data are presented as means ± SD **a:** Expresses statistical significance between hemorrhagic stroke and healthy subjects ($p<0.05$) **b:** Expresses statistical significance between hemorrhagic stroke and TIA ($p<0.05$) **c:** Expresses statistical significance between hemorrhagic stroke and ischemic stroke ($p<0.05$) **d:** Expresses statistical significance between ischemic stroke and healthy subjects ($p<0.05$) **e:** Expresses statistical significance between ischemic stroke and TIA ($p<0.05$) **f:** Expresses statistical significance between TIA and healthy subjects ($p<0.05$)

Tpe/QT ratio was obtained from precordial leads. If the Tpe/QT ratio is over 0.25, it was defined as an increased Tpe/QT ratio (9). Tpe/QTc was calculated as the ratio between Tpe max and QTc max. The interobserver and intraobserver variation coefficients for the Tpe/QT ratio were 3.1% and 3.6%, respectively, and those for the Tpe were 2.9% and 3.6%, respectively.

Statistical Analysis: Data were presented as mean ± standard deviation (s.d.), number, or percentage. The difference of parametric data between groups was evaluated with ANOVA test. The χ^2 (chi square) test was used to compare categorical variables. The relationship between the change of ECG parameters and other factors was evaluated with the "Pearson correlation" analysis. Differences between subgroups in post hoc analyses were evaluated with Scheffe test. For all tests, $p < 0.05$ was considered statistically significant. SPSS 15.0 package software was used for all statistical analyses.

Results

Our study was conducted on a total of 110 age- and sex-matched cases including 30 AIS (mean age 61.17 14.14 years; 15 women), 20 AHS (mean age65.05 ± 9.50 years; 10 women/10 men), 30 TIAs (mean age 58.10 ±13.32 years; 15 women) and 30 healthy control groups (mean age 58.27 ±10.45 years; 15 women).

Table 2: Continue: Electrocardiographic findings of the study groups

Variables	Control group (n=30)	TIA Group (n=30)	Ischemic stroke group (n=30)	Hemorrhagic stroke group (n=20)	P
QTcmin	388.2 ± 25.8	370.3 ± 26.2	399.1 ± 24.1	398.5 ± 34.6	0.251
QTd	28.3 ± 17.1	33.0 ± 14.4	49.0 ± 13.4 [d,e]	64.5 ± 12.9 [a,b,c]	0.006
QTcd	30.0 ± 20.7	38.0 ± 17.3	51.1 ± 17.1 [d,e]	66.7 ± 14.6 [a,b,c]	0.004
V1Tpe	79.0 ± 11.8	84.6 ± 11.3	87.6 ± 14.0	88.5 ± 13.1	0.026
V2Tpe	82.3 ± 8.2	90.3 ± 11.8	94.0 ± 18.4	95.5 ± 16.0	0.345
V3Tpe	94.6 ± 8.9	93.0 ± 8.3	99.3 ± 15.7	97.5 ± 18.6	0.311
V4Tpe	91.3 ± 43.1	90.6 ± 14.8	95.6 ± 12.7	90.5 ± 17.4	0.611
V5Tpe	86.3 ± 11.5	85.6 ± 8.5	101.0 ± 16.8 [d,e]	103.0 ± 15.5 [a,b]	0.001
V6Tpe	86.7 ± 8.8	87.6 ± 8.9	102.3 ± 13.6 [d,e]	105.0 ± 12.3 [a,b]	0.001
Tpe-max	98.6 ± 6.8	101.6 ± 12.0	110.6 ± 13.3 [d,e]	112.5 ± 13.3 [a,b]	0.011
Tpe-min	75.6 ± 9.3	77.3 ± 8.6	78.0 ± 9.8	79.0 ± 9.6	0.314
Tpe-d	23.0 ± 8.3	24.3 ± 12.7	32.6 ± 11.7 [d,e]	33.5 ± 11.3 [a,b]	0.022
V1Tpe/QT	0.21 ± 0.02	0.21 ± 0.02	0.22 ± 0.02	0.21 ± 0.03	0.421
V2Tpe/QT	0.22 ± 0.01	0.20 ± 0.02	0.22 ± 0.03	0.22 ± 0.03	0.354
V3Tpe/QT	0.23 ± 0.02	0.23 ± 0.01	0.22 ± 0.03	0.23 ± 0.03	0,418
V4Tpe/QT	0.21 ± 0.09	0.23 ± 0.02	0.22 ± 0.01	0.23 ± 0.62	0,252
V5Tpe/QT	0.23 ± 0.01	0.23 ± 0.02	0.26 ± 0.03 [d,e]	0.26 ± 0.02 [a,b]	0.007
V6Tpe/QT	0.23 ± 0.02	0.22 ± 0.02	0.26 ± 0.02 [d,e]	0.28 ± 0.02 [a,b]	0.005
Long QTc, n (%)	0 (0)	0 (0)	8 (26.6) [d,e]	7 (35) [a,b]	0.003
Long Tpe, n (%)	0 (0)	0 (0)	10 (33.3) [d,e]	8 (40) [a,b]	0.002
Long Tpe/QT ratio, n (%)	0 (0)	0 (0)	10 (33.3) [d,e]	8 (40) [a,b]	0.001

The demographic characteristics and clinical findings of the patients included in the study are summarized in Tables 1 and 2. Among all groups, no statistical significance was found in terms of age, gender, smoking, height, weight, BMI, creatine, Na^+, K^+, Ca^{++}, lipid parameters, TSH, B12, and Hb values ($p>0.05$). There was a statistically significant difference between the patient group and the control group in terms of the presence of DM and HT ($P<0.001$). When the correlation analysis between SBP and DBP, BMI, glucose, creatine, Hb, Urea, and ECG parameters in all groups were performed separately, it was observed that there was no statistically significant correlation between these variables and ECG parameters (Table 3). Along with the mean age was similar between the groups, there was a positive correlation between

Table 3: Correlation analysis between ECG parameters and age, BMI, gender, waist circumference, SBP, DBP, fasting blood glucose, creatinine, Hb, K, Urea and WBC

Variables	Tpe (r)	Tpe/QT Scale (r)	QTcmax (r)	QTd (r)
Age	0.21*	0.02	0.19*	0.22*
BMI	0.01	0.03	0.25*	0.28*
Gender	0.02	0.02	0.01	0.02
SBP	0.11	0.10	0.08	0.09
DBP	0.06	0.09	0.04	0.05
Glucose	0.03	0.01	0.01	0.02
Creatinine	0.04	0.01	0.05	0.06
Hb	0.04	0.02	-0.17	-0.02
K^{++}	-0.07	0.04	0.02	-0.13
Urea	0.03	0.01	0.02	0.01
WBC	-0.02	0.01	0.15	-0.14

Statistics: Pearson correlation, *= P<0.05 r: Pearson correlation coefficient **Abbreviations:** Hb: Hemoglobin, BMI: Body mass index, Tpe: Tpeak-Tend, DBP: Diastolic blood pressure, QTc: Corrected QT, SBP: Systolic blood pressure, WBC: White blood cell

Table 4: Comparison of ECG measurements according to insular cortex involvement

Variables	Insular cortex involvement (+) n (%)	Insular cortex involvement (-) n (%)	P
Long QTc	12 (70.6)	5 (29.4)	0.036
Long Tpe	15 (71.4)	6 (28.6)	0.024
Long Tpe/QT ratio	13 (72.2)	5 (27.8)	0.021

Statistics: Crosstab Chi-square test **Abbreviations:** QTc: Corrected QT, Tpe: Tpeak-Tend, Tpe/QT: Ratio of Tpeak-Tend to QT

age and Tpe (r= 0.21, p= 0.028), QTcmax (r= 0.19, p= 0.032) and QTd (r= 0.22, p= 0.013) (Table 3). DIIQTc, V5QT, V5QTc and V6QTc were significantly prolonged in the AHS and AIS compared to control and TIA (p<0.05). QTd was significantly increased in the AIS compared to control and TIA. V5Tpe, V6Tpe and Tpe-d were significantly prolonged in the AHS and AIS compared with control and TIA (103.0 ± 15.5 ms vs 86.3 ± 11.5 ms, p<0.001 and 85.6 ± 8.5 ms, p<0.001; 101.0 ± 16.8 ms vs. 86.3 ± 11.5 ms, p= 0.003 and 85.6 ± 8.5, p= 0.026). The V5Tpe/QT and V6Tpe/QT ratios were significantly increased in the AHS and AIS compared to the control and TIA (p<005). Tpe values of 10 (33.3%) patients in the AIS and 8 (40%) patients in the AHS were above 110 msec, which is considered the upper limit for malignant arrhythmias. While the Tpe/QT of none of the subjects in the control and TIA could exceed 0.25, which is considered the critical value for arrhythmias, the Tpe/QT of 10 (33.3%) patients in the AIS and 8 (40%) patients in the AHS was above this value. When QTc, Tpe, and Tpe/QT ratio were compared between groups, these three parameters were significantly increased in both the AHS and AIS compared to the other groups (p= 0.003, p= 0.002, and p= 0.001, respectively). The rate of increase in these parameters was similar between AHS and AIS (p>0.05). While 12 (70.6%) of 17 patients with prolonged QTc had insular cortex lesions, 15 (71.4%) of 21 patients with long Tpe and 13 (72.2%) of 18 patients with increased Tpe/QT had insular injury (Table 4). The number of patients with insular injury was statistically insufficient to analyze right and left insular cortex involvoment separately.

Discussion

In this observational study including patients with AIS, AHS, and TIA, we investigated how Tpe, Tpe-d and Tpe/QT, which are new indicators of ventricular arrhythmias, were affected in these patient groups. Although there are studies on the

variation of these indices in AIS and AHS patients, within our knowledge, there was no study in which TIA patients were included, and these three groups were compared with each other and with a healthy control group. Our study was the first in the literature with this feature. Additionally, certain leads were used when making index measurements in current studies. In our study, we performed a more detailed electrocardiographic analysis compared to previous studies by measuring all leads when evaluating the old arrhythmia parameters and in all precordial leads when evaluating the new parameters. Again in our study, in addition to the increase in old parameters such as QTc and QTd, a significant increase in new arrhythmia parameters such as Tpe, Tpe-d and Tpe/QT was detected in both AIS and AHS groups when compared with TIA and healthy control group. The increase in these indices was in the chest leads V5 and V6. No increase was detected in any of these indices in the TIA group when compared to the healthy control group. QTc, Tpe, and Tpe/QTc ratio were similarly increased in patients with insular cortex involvement. Dogan et al. examined the ECG changes and prognosis of 162 patients with AIS who had a stroke for the first time without known heart disease, and QTc prolongation was observed in 26% of the patients (16). The long QT rate of our AIS patients was 26.6% and was consistent with this study. Latha et al. found a long QTc rate in 35.7% of the patients in their studies on ischemic stroke patients. In another study, Fure et al. determined the long QTc rate as 36% (17,18). Patients with known heart conditions were included in both studies. Considering that cardiac disorders prolong the QT interval, this may be the reason why our number of long QTc patients is lower than in these studies. Van Bree MC et al. ascertained QT prolongation in 36% of patients with intracerebral hemorrhage (19). The long QT rate of our AHS patients was 35% and was consistent with this study. Rui Póvoa et al. stated a long QTc percentage of 43% in AHS patients. Patients with subarachnoid hemorrhage were also included in this study (20). This may explain the different long QT rates. Tpe and Tpe/QT were increased in 33.3% of AIS patients in our study. This rate was 40% in patients with hemorrhagic stroke. Tpe prolongation and increase in Tpe/QT were significantly higher in both groups compared to the control and TIA groups. Emektar et al. indicated increased Tpe and Tpe/QTc ratios in AIS patients, consistent with our study (13). Danese et al. remarked increased Tpe and Tpe/QTc in AHS patients compared to AIS (15). As a result of the study, they claimed that the hemorrhagic lesions were more severe and extensive compared to ischemia, and thus may have more involved the autonomic network. In our study, the most affected group was in the AHS group. However, ventricular repolarization indexes were increased in our AIS patients. There may be several reasons for our non-compliance with the patients with ischemic stroke in this study; the first is the difference in cut-off values, the second is the difference in patient demographics, and last, there is no comparison with the healthy control group. In both AIS and AHS patients, complex pathophysiological changes (such as catecholamine effect, Ca, K, and Na permeability change, the effect of neurons) causing ECG changes were probably not evident in TIA patients. This prediction also elucidates that QT, QTc, QTcd, Tpe-d and Tpe/QT ratio in TIA patients are similar compared to the control group. Shibazaki et al. investigated the levels of brain natriuretic peptide (BNP) in stroke and TIA patients with atrial fibrillation, and BNP levels were found to be significantly higher in stroke patients compared to TIA (21). Gokhan et al. evaluated the neutrophil-lymphocyte ratio (NLR), which has been prominent in the inflammatory process in stroke and TIA patients in recent years and found NLR to be significantly higher in stroke patients compared to TIA patients (22). In both studies, it was alleged that the pathophysiological process in stroke is more dramatic than in TIA, which is consistent with the hypothesis in our study. Another result of our study is that Tpe prolongation and increase in Tpe/QT ratio are observed in V5 and V6 chest lead as in QTc. Jesus Castro Hevia et al. found that the Tpe and Tpe / QT ratios increased in patients with Brugada syndrome, particularly in the V2 lead. Since Brugada syndrome is a disease affecting the right ventricle, Tpe and Tpe/QT ratio were significantly increased in the V2 lead, which sees the right ventricle best (23). Yamaguchi M et al. determined that these parameters were significantly prolonged in the V6 lead in patients with LQTS, a disease affecting the left ventricle (12). Wong KY et al. emphasized the importance of V6 lead in patients with ischemic stroke and stated that prolonged QT in this lead was a predictor of mortality (24). In acute cerebrovascular events, ion exchange and catecholamine effects are probably more reflected on the left ventricle. Thus, it can be said that Tpe and Tpe/QT ratios are elongated in leads V5 and

V6, which best reflect the transmural axis of the left ventricle in AIS and AHS patients. In our study, there was no significant difference between the groups in terms of BMI. BMI was positively correlated with QTc and QTd. Annabella Braschi et al. stated that QT, QTc and QTcd were prolonged in obese individuals when compared to individuals with normal BMI, but Tpe and Tpe/QT ratios were similar (25). David Clemente et al. noted that BMI had no effect on the Tpe and Tpe/QT ratio (26). According to these results, we can say that the increase in BMI affects ventricular global repolarization by affecting QTc and QTd, but its effect on transmural repolarization is uncertain. In our study, there was a significant relationship between the insular lesion and QTc, which is consistent with many other studies. Eckardt et al. found that QTc was prolonged in strokes involving the insular cortex (27). Dogan et al. observed that patients with ischemic and hemorrhagic stroke had more frequent repolarization abnormalities in insular cortex lesions (16). Giammello F et al. detected various electrocardiographic changes, including prolonged QT in isolated insular stroke (28). In the GENIC study, 493 consecutive patients with ischemic stroke and the control group were compared, and abnormal repolarization was observed in those with stroke involving the insular cortex. Repolarization abnormalities were observed more frequently particularly in right insular cortex involvements. The number of patients with insular cortex involvement was statistically insufficient to analyze right and left insular cortex involvement separately. Emektar et al. confirmed that QTc, Tpe, Tpe/QT ratio were increased in patients with acute stroke with insular cortex involvement compared to patients without involvement (13). Similarly, a significant correlation was found between the insular lesion and the Tpe and Tpe/QT ratio in our study. According to these results, it can be considered that insular cortex lesions affect both total repolarization and transmural dispersion of repolarization.

Study Limitations: This study had some limitations. This study had relatively small sample size and is single-center study. The incidence of arrhythmias and their relationship with arrhythmia markers were not assessed in this study. Due to the cross-sectional design, adverse cardiac events during clinical follow-up could not be evaluated. As we could not make an etiological classification, we could not determine which subtype of stroke was associated with ECG parameters. As the ECGs of the patients before the acute cerebrovascular event were not known, a comparison with the application ECGs could not be made. Hence, it could not be clearly stated which change is specific to stroke.

Conclusion

Our study demonstrates that TIA did not affect ventricular repolarization parameters, and acute stroke increased transmural repolarization in addition to global repolarization of the ventricle. In acute stroke patients, the increased frequency of ventricular arrhythmias may be explained by increased indexes of ventricular repolarization. Furthermore, in acute stroke patients, leads V5 and V6 on the ECG appear to be suitable leads for evaluating ventricular repolarization.

Ethical Approval: This study was approved by the Necmettin Erbakan University Faculty of Medicine Ethics Committee (date/approval number: 2013/406) and it was done according to the declaration of Helsinki.

Conflict of Interest: The authors declare that they have no conflict of interest for this study.

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References

1. Kaya A, Arslan Y, Ozdoğan O, Tokucoglu F, Sener U, Zorlu Y. Electrocardiographic Changes and Their Prognostic Effect in Patients with Acute Ischemic Stroke without Cardiac Etiology. Turk J Neurol 2018; 24:137-142.
2. Marina N, Teschemacher AG, Kasparov S, Gourine AV. Glia sympathetic activity and cardiovascular disease. Exp Physiol 2016;101:565-576.
3. Qin M, Zeng C, Liu X. The cardiac autonomic nervous system: A target for modulation of atrial fibrillation. Clin Cardiol. 2019;42: 644-652.
4. Chouchou F, Mauguière F, Vallayer O, Catenoix H , Isnard J, Montavont A, et al. How the insula speaks to the heart: Cardiac responses to insular stimulation in humans. Hum Brain Mapp 2019 ;40: 2611-2622.
5. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill

D, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2021; 52: 364-467.
6. Shelagh B Coutts. Diagnosis and Management of Transient Ischemic Attack. Cerebrovascular Disease 2017;23: 82-92.
7. Arslan Y, Demirtaş BS, Ekmekci C, Tokuçoğlu F, Zorlu Y. The significance of Holter electrocardiography in the etiological evaluation of transient ischemic stroke. Brain Circ. 2020;30: 191-195
8. Xuanmin Li, Yafang Wang, Xue Mi, Zhaona Qiao, and Yongmei Liang. Impaired heart rate recovery as a predictor for poor health-related quality in patients with transient ischemic attack, Medicine (Baltimore) 2019; 98: e16938.
9. Gupta P, Patel C, Patel H, Narayanaswamy S, Malhotra B, Green JT, et al. T(p-e)/QT ratio as an index of arrhythmogenesis. J Electrocardiol 2008; 41: 567-574.
10. Maury P, Sacher F, Gourraud JB, Pasquié JL, Raczka F, Bongard V, et al. Increased Tpeak-Tend interval is highly and independently related to arrhythmic events in Brugada syndrome. Heart Rhythm 2015;12: 2469-2476.
11. Lux RL. Basis and ECG measurement of global ventricular repolarization. J Electrocardiol 2017;50: 792-797.
12. Yamaguchi M, Shimizu M, Ino H, Terai H, Uchiyama K, Oe K, et al. T wave peak-to-end interval and QT dispersion in acquired long QT syndrome: a new index for arrhythmogenicity. Clin Sci (Lond). 2003;105: 671-676.
13. Emektar E, Çorbacıoğlu Ş, Korucu O, Ramadan S, Uzunosmanoğlu H, Kan E, et al. The evaluation of a new marker of transmyocardial repolarization parameters in ischemic stroke patients; T_{peak}–T_{end} (T_{p-e}), T_{p-e}/QT_c. Acta Neurologica Belg 2017; 117: 461-467
14. Bilge S, Tezel O, Acar YA, Cüce F, Karadaş Ö, Taşar M. Investigation of the Value of T peak to T end and QTc Intervals as Electrocardiographic Arrhythmia Susceptibility Markers in Acute Ischemic Stroke. Arch Neuropsychiatry 2020; 57:171-176.
15. Danese A, Cappellari M, Pancheri E, Mugnai G, Micheletti N, Tomelleri G et al. The dispersion of myocardial repolarization in ischemic stroke and intracranial hemorrhage. J Electrocardiol. 2018;51: 691-695.
16. Dogan A, Tunc E, Ozturk M, Kerman M, Akhan G. Electrocardiographic changes in patients with ischaemic stroke and their prognostic importance. Int J Clin Pract 2004;58: 436-440.
17. Stead LG, Gilmore RM, Bellolio MF, Vaidyanathan L, Weaver AL, Decker WW, et al. Prolonged QTc as a predictor of mortality in acute ischemic stroke. J Stroke Cerebrovasc Dis 2009;18: 469-474.
18. Fure B, Bruun Wyller T, Thommessen B. Electrocardiographic and troponin T changes in acute ischaemic stroke. J Intern Med 2006;259:592-597.
19. Van Bree MD, Roos YB, C van der Bilt IA, Wilde AA, Sprengers ME, de Gans K, et al. Prevalence and characterization of ECG abnormalities after intracerebral hemorrhage. Neurocrit Care 2010;12:50-55.
20. Povoa R, Cavichio L, de Almeida AL, Viotti D, Ferreira C, Galvao L, et al. Electrocardiographic abnormalities in neurological diseases. Arq Bras Cardiol 2003;80:351-358.
21. Shibazaki K, Kimura K, Iguchi Y, Aoki Y, Sakai K, Kobayashi K. Differences in brain natriuretic peptide value between transient ischemic attack and stroke patients with atrial fibrillation. Eur Neurol 2011;66:271-276.
22. S Gökhan, A Ozhasenekler, H Mansur Durgun, E Akil, M Ustündag, M Orak. Neutrophil lymphocyte ratios in stroke subtypes and transient ischemic attack. Eur Rev Med Pharmacol Sci 2013;17:653-657.
23. Castro Hevia J, Antzelevitch C, Tornes Barzaga F, Dorantes Sanchez M, Dorticos Balea F, Zayas Molina R, et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol 2006;47:1828-1834.
24. Wong KY, Mac Walter RS, Douglas D, Fraser HW, Ogston SA, Struthers AD. Long QTc predicts future cardiac death in stroke survivors. Heart. 2003;89:377-381.
25. Braschi A, Abrignani MG, Francavilla VC, Francavilla G. Novel electrocardiographic parameters of altered repolarization in

uncomplicated overweight and obesity. Obesity (Silver Spring). 2011;19(4):875-881.
26. Clemente D, Pereira T, Ribeiro S. Ventricular repolarization in diabetic patients: characterization and clinical implications. Arq Bras Cardiol. 2012;99(5):1015-1022.
27. Eckardt M, Gerlach L, Welter FL. Prolongation of the frequency-corrected QT dispersion following cerebral strokes with involvement of the insula of Reil. Eur Neurol 1999;42:190-193.
28. Giammello F, Cosenza D, Casella C, Granata F, Dell'Aera C, Fazio M. C, et al. Isolated Insular Stroke: Clinical Presentation. Cerebrovasc Dis 2020; 49:10-18.