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Association of trans-myocardial repolarisation parameters with size of the diffusion limitation area in acute ischaemic stroke

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ABSTRACT

Objectives. This study aimed to evaluate the relationship between transmyocardial repolarisation parameters and the size of the diffusion limitation area measured using diffusion weighted magnetic resonance imaging (DWMRI) in patients diagnosed with ischaemic stroke without known cardiac diseases.

Material and methods. The study was a prospective, observational clinical study. Patients without cardiac disease with acute ischaemic stroke were included in the study. Electrocardiography (ECG) was received from the patients. P, QT, QTc and Tp-e dispersions were calculated. All the patients had computerised brain tomography (CT) and then DWMRI carried out so as to calculate infarct areas.

Results. Seventy ischaemic stroke patients and 30 control patients were included in the study. All parameters except for QTc dispersion ($p = 0.88$) were higher in the stroke group than in the control group ($p < 0.05$ for all values). The infarct area calculated with DWMRI was divided into four groups according to quartiles, and QT, QTc, P, and Tp-e dispersions of patients were evaluated. Patients were found to have a prolonged dispersion as the infarct area expanded, and this difference was statistically significant ($p < 0.05$ for all values).

Conclusions. When we compared the patients with ischaemic stroke who had no known cardiac disease to those in the control group we found an increase in transmyocardial repolarisation parameters. As diffusion limitation areas grew larger, QT, QTc, P, and Tp-e dispersions increased. Physicians should be aware of dysrhythmias and sudden cardiac death in acute stroke and should observe these patients, especially those with larger stroke lesions.

Key words: stroke, diffusion-limitation area, trans-myocardial repolarisation parameters, electrocardiography

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Introduction

Strokes are among the most frequent and most important of all neurological disorders encountered during adulthood [1]. In the acute phase of a stroke, repolarisation abnormalities or ischaemic-like electrocardiographic changes can be observed [2]. Electrocardiographic abnormalities in patients with ischaemic and haemorrhagic strokes are a well-known problem which leads to diagnostic difficulties. In stroke patients, electrocardiographic changes have been observed without cardiac pathology [3]. The mechanism behind the electrocardiographic changes during an acute stroke has aroused great interest for years. It is thought that these changes could either be related to an underlying cardiac disorder, or indicate myocardial damage developing under acute stress. They might also result from neuro-hormonal interaction

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between the central nervous system and the cardiovascular system, which has been understood better in recent years [4, 5]. These abnormalities include ST segment changes (elevation or depression), changes in T waves, QT interval prolongation, and supraventricular or ventricular arrhythmias [2]. It has been reported that an increase in QT dispersion, which is regarded as an indicator of regional heterogeneity in myocardial repolarisation, leads to severe ventricular arrhythmias and sudden cardiac death [6, 7]. Even so, an increase in the Tpeak–Tend (Tp-e) interval from the peak of the T wave to the end, considered a new arithmogenic marker in ECG in recent times, has been shown to be related to life-threatening ventricular arrhythmias [8–10]. It has been demonstrated in previous studies that the above mentioned transmyocardial repolarisation parameters were extended in patients with a history of stroke [11–13].

In this study, we have evaluated the relationship between transmyocardial repolarisation parameters and the size of the diffusion limitation area measured using diffusion weighted magnetic resonance imaging (DWMRI) in patients diagnosed with ischaemic stroke without known cardiac diseases.

Material and methods

This study was a prospective and observational clinical study whose protocol was approved by the local ethics committee. The patients, who were aged over 18, were successively included in the study between 31 January and 1 June 2016 after they had received the diagnosis of an ischaemic stroke based on the clinical physical examination and the findings of imaging when they arrived at the emergency department within six hours of the first appearance of stroke symptoms. The exclusion criteria are set out in Table 1. The control group consisted of healthy subjects who were matched for age and sex, and had no malignancies, active infections, or coronary arterial disease.

Table 1. Exclusion criteria

Patients under 18 years of age
Patients with an accompanying acute coronary syndrome at admission
Those with a history of coronary arterial disease (stable / unstable angina, myocardial infarct)
Those undergoing a bypass operation
Those with transient ischaemic attack or lacunary infarct, and those who underwent haemorrhagic stroke
Pregnant women
Those with a history of cardiac medication (beta blocker, nitrate, calcium antagonist, digoxin)
Those who suffered cardiac embolism-related stroke
Patients with electrolyte disorders
Patients who had a branch block, pathological Q wave or atrial fibrillation, the criteria of left ventricle hypertrophy
Patients who refused to join in the study
Severe mitral or aortic valve disorder (stenosis or insufficiency)

All the patients were given detailed physical and neurological examinations, electrocardiography, imaging and echocardiographic imaging. Patients' neurological examinations were done according to the National Institutes of Health Stroke Scale (NIHSS).

The methods of imaging and their analyses

All the patients had computerised brain tomography (CT) and then DWMRI. Patients' CTs were obtained with a Toshiba (Japan) Activion 16 Detector tomography device, and DWMRI with a General Electric (USA) 1.5 Tesla closed MRI. All CTs and DWMRIs were evaluated by the same radiologist.

Measuring diffusion limitation area

Using a 1.5-T General Electric MR device, images with diffusion sensitivities of b 0 and b 1,000 s / mm^2 and 20 slice diffusion weighted images with a cross-sectional thickness of 5 mm were obtained. In cases with multiple acute infarct areas, the largest lesion was measured. On the iMAC medical image-processing system, the volumetric volume in cm^2 was automatically calculated from the images created with 1,000 s / mm^2 using the region of interest (ROI) from the widest outer edge of the lesion.

ECG

During the first hour, 12-channel ECGs were taken with a Nihon Kohden CardioFax GEN® (Japan) ECG device at 10 mm / mV and 25 mm / sec. ECG images were enlarged to 600-dpi resolution and read in Adobe Photoshop CS3 (USA). ECGs were assessed by two experts who were blinded to each other and the groups.

The QT interval was measured from the beginning of the QRS to the end of the T-wave in all derivations. QTc was calculated using the Bazzett formula ($QTc = QT / \sqrt{RR}$).

The Tp-e interval was determined from the T wave peak to the junction of the T wave with the isoelectric line junction. Tp-e was measured using the tangent method. P wave duration was measured from all leads. All dispersions were defined as the difference between the maximum and minimum duration in the measurements.

Statistical analysis

Analysis of the data was performed using the SPSS package program (version 15, Chicago, USA). The Shapiro-Wilk test was used to determine whether the distribution of continuous variables was normal. Descriptive statistics were expressed as mean ± standard deviation or median (quartiles) for continuous variables, and the number of cases (n) and (%) as categorical variables. Categorical variables were assessed by Chi-square test. Two independent sample t-tests were used to determine whether there was a statistically significant

Table 2. Demographic data of the patients

	Stroke patients	Control subjects	p value
Age, median (IQR 25–75%)	74 (68–82)	71 (68–80)	0.5
Gender, n (%)			
Female	25 (35.7)	13 (43.3)	0.5
Male	45 (64.3)	17 (56.7)	
Comorbidity, (%)			
Diabetes mellitus	7 (23.3)	28 (40)	0.16
Hypertension	14 (46.7)	42 (60)	0.15
COPD	4 (13.3)	4 (5.7)	0.23
Prior stroke, n (%)	13 (18.6)	—	
NIHSS score at admission, median (IQR 25–75%)	5 (0–31)	—	
Localisation, n (%)			
Right	41 (58.6)	—	
Left	23 (32.9)		
Bilateral	6 (8.6)		
Area, (cm^2)	1.5 (0.70–4.03)	—	

COPD — chronic obstructive lung disease; NHISS — national institutes of health stroke scale; IQR — inter-quartile range

Table 3. Characteristics of ECG parameters associated with trans-myocardial repolarisation in control subjects and stroke patients

	Stroke patients	Control subjects	p value
QT-min	386 (370–402)	365 (348–381)	< 0.05
QT-max	426 (398–458)	393 (370–409)	< 0.05
QT dispersion	39 (22–57)	25 (20–30)	< 0.05
QTc-min	441 (408–473)	398 (378–398)	< 0.05
QTc-max	490 (445–529)	441 (424–456)	< 0.05
QTc dispersion	44 (25–67)	42 (34–49)	0.88
P-min	67 (60–76)	65 (55–65)	< 0.05
P-max	90 (80–104)	76 (72–80)	< 0.05
P dispersion	21 (12–36)	15 (12–20)	0.017
Tp-e min	70 (62–76)	59 (52–69)	< 0.05
Tp-e max	90 (80–103)	73 (68–80)	< 0.05
Tp-e dispersion	20 (14–29)	13 (10–18)	< 0.05

ECG — electrocardiography

change in the mean values of the patient and control groups. Whether there was a statistically significant change in the median values and in the non-normal distribution data was examined using the Mann-Whitney U test. In the patient and control groups, Spearman correlation test was used to determine whether there was a statistically significant correlation between ECG measurements and infarct size. The Kruskal Wallis test was used to examine the significance of median values among the groups.

For $p < 0.05$, the results were considered statistically significant. However, Bonferroni correction was performed to check for Type I error in all possible multiple comparisons.

Results

Seventy ischaemic stroke patients, and 30 control patients with similar features, were included in the study. The mean age of stroke patients was 72 (68–80) years while that of the control group was 74 (68–82) years. 18.6% of the stroke patients had a stroke history. Patients' demographic data and characteristics are set out in Table 2.

When the transmyocardial parameters were evaluated in ECGs of patients and of the control group, all parameters except for QTc dispersion ($p = 0.88$) were higher in the stroke group than in the control group, and this difference was statistically significant ($p < 0.05$ for all values) (Tab. 3).

Table 4. Relationship between infarct areas and transmyocardial repolarisation parameters

	Correlation coefficient	p-value	Number of patients (n)
QT-min	0.543	< 0.05	70
QT-max	0.710	< 0.05	70
QT dispersion	0.608	< 0.05	70
QTc-min	0.442	< 0.05	70
QTc-max	0.651	< 0.05	70
QTc dispersion	0.636	< 0.05	70
P-min	0.083	0.49	70
P-max	0.486	< 0.05	70
P dispersion	0.517	< 0.05	70
Tp-e min	0.472	< 0.05	70
Tp-e max	0.689	< 0.05	70
Tp-e dispersion	0.663	< 0.05	70

Table 5. Parameters of transmyocardial repolarisation according to DWMRI-calculated infarct area quartiles

	DWMRI calculated infarct area quartiles (cm^2)				
	1 (< 0.70)	2 (0.71–1.50)	3 (1.51– 4.03)	4 (> 4.04)	p-value
Parameters	(n = 20)	(n = 19)	(n = 14)	(n = 17)	
QT dispersion	24 (20–38)	32 (20–40)	39 (24–47)	68 (52–76)	< 0.001
QTc dispersion	25.7 (22–42)	34 (24–58)	45 (33–49)	79 (65–86)	< 0.001
P dispersion	12 (10–20)	18 (12–28)	20 (7–27)	40 (36–44)	< 0.001
Tp-e dispersion	14 (10–20)	16 (14–24)	24 (20–24)	38 (34–50)	< 0.001

DWMRI — diffusion weighted magnetic resonance imaging

When the relationship between diffusion limitation areas and transmyocardial repolarisation parameters in the stroke patients was evaluated, a statistically significant similarity between the transmyocardial repolarisation parameters and diffusion limitation areas was found (correlation coefficients and p values are shown in Table 4) except for P-min (r = 0.083 and p = 0.49).

The diffusion limitation area calculated using DWMRI was divided into four groups according to quartiles and the QT, QTc, P, and Tp-e dispersions of patients were evaluated. Patients were found to have a prolonged dispersion as the diffusion limitation area expanded, and this difference was statistically significant ($p < 0.05$ for all values) (Tab. 5).

Discussion

According to the results of our study, transmyocardial repolarisation parameters were higher in patients with acute ischaemic stroke than in the control group. The transmyocardial repolarisation parameters in ischaemic stroke patients and the diffusion limitation areas measured with DWMRI were positively related. QT, QTc, P, and Tp-e dispersions were prolonged as the infarct areas expanded.

Ischaemic stroke is the most common of all stroke types. Markers and tests that can be used to determine prognosis, especially arrhythmia and the possibility of sudden death, in patients with frequent and high mortality strokes are helpful in the management of patients. Many studies have shown that cardiovascular abnormalities are caused by cerebral infarction, depending on its localisation and size [2, 14, 15]. Prolongation of the QT interval and enlargement of the QRS complex are electrical instability of the ventricular myocardium; ST-T changes, which are ischaemia-like changes, are the abnormalities most commonly observed on ECG [2]. Parameters such as QT, QTc, P, and Tp-e dispersions which can be used in the prediction of sudden death and arrhythmia and obtained only from a standard 12-lead ECG become increasingly attractive, due to their low cost and usefulness [6]. Measurements of these parameters in ECG reveal heterogeneity of cardiac repolarisation and useful parameters used in the definition of risky patients [6–8, 16, 17]. T wave peak-to-end point interval (Tp-e) measured in the ECG has recently been introduced into the literature, and is a parameter used to evaluate ventricular arrhythmogenity in many diseases [8, 9]. Studies comparing QT, QTc, and QTd for relatively long periods of time have shown that these studies yield reliable results at least as accurate as these measurements without signifying ventricular repolarisation [9].

It is thought that a stroke leads to ECG changes especially due to its effect on the autonomic nervous system, its capacity to cause haemodynamic changes, and to trigger catecholamine

release [18, 19]. For these reasons, cardiac involvement in cerebral lesions that have sustained certain areas of the brain for a long time has been the subject of studies. Since the hypothalamus and insulin have effects on the autonomic nervous system, various cardiac effects have been observed with the stimulation of these [18, 19]. We have already carried out a study in our own department. This, and other studies in the literature, have shown a prolonged range of transmyocardial repolarisation parameters that have been proven to be associated with ventricular arrhythmias and sudden cardiac death in stroke patients [13, 20, 21]. In addition, these parameters were evaluated not only for stroke, but also for stroke severity, type, localisation, and prognostic value. These parameters have been shown to be longer than stroke severity, ischaemic stroke in haemorrhagic stroke, and in patients with insula or brainstem involvement [13, 21-24]. The prognostic effect of QTc prolongation has been investigated in several studies. Most of these studies have shown that QTc prolongation adversely affects prognosis [11, 12].

There have been a number of studies evaluating the relationship between infarct area and QT dispersion in the literature; Pd, Tp-e interval, and Tp-e dispersion have not been identified in studies [22, 24]. In the study conducted by Chugh on patients with ischaemic and haemorrhagic stroke but without a cardiovascular disease history, patients with a large lesion on DWMRI were shown to have longer QTds on ECGs taken in the first 24 hours [22]. Also Avsar found the same result in a similar group of patients [24]. In our study, we showed that as the diffusion limitation area of the patients expanded, the myocardial repolarisation parameters were prolonged. Previous studies reported that Tp-e interval and Tp-e dispersion were longer in patients with long- and short-QT syndrome, Brugada syndrome, and myocardial infarction. [8, 25, 26]. Tp-e and Tp-e dispersions were validated in various cardiac conditions that led to sudden cardiac death [10].

We showed that trans-myocardial repolarisation parameters, including Pd, Tp-e and Tp-e dispersion, are longer in stroke patients, and especially in patients with a large diffusion limitation area.

We think that early attention should be paid to malignant ventricular arrhythmias and sudden cardiac death in these patients.

Limitations

Our study has some limitations. Firstly, our study comprised a relatively small sample size. Therefore, we believe that our results cannot be generalised to all populations. Secondly, none of the patients included in our study had arrhythmia during their entire hospital stay. This could have been due to the exclusion of patients with a known cardiac disease, cardiac drug use, and cardioembolic stroke in the aetiology.

Another limitation of our study was the absence of long-term follow-up of our patients. We have not evaluated the patients over a long time in terms of mortality, neurological status or cardiac intervention / implantation of pacemaker.

Finally, patients with other stroke types, including intracranial haemorrhages with fewer cases, were not included in the study. Patients were followed only during their hospitalisation period, and so could not be followed for long-term rhythm disturbances or mortality.

Conclusion

No studies in the literature have investigated the relationship between the diffusion limitation volume and other transmyocardial repolarisation parameters, including Pd, Tp-e interval and Tp-e dispersion in patients with ischaemic stroke. When we compared the patients with ischaemic stroke who had no known cardiac disease to those in the control group, we found an increase in these parameters. As diffusion limitation areas grew larger, QT, QTc, P, and Tp-e dispersions increased. We think that physicians should be aware of dysrhythmias and sudden cardiac death in ischaemic stroke patients and should observe these patients, especially those with larger stroke lesions.

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