Original Article

Relation Between Index of Cardioelectrophysiological Balance and Stroke Severity in Patients with Acute Ischemic Stroke

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Abstract

Background: The index of cardioelectrophysiological balance (iCEB), measured as QT interval divided by QRS duration, has recently been defined as a new risk marker for arrhythmias. Increased or decreased iCEB is associated with malignant ventricular arrhythmias. **Aim:** In this study, we aimed to investigate the relationship between iCEB and stroke severity in patients with acute ischemic stroke. **Methods:** The study comprised 105 adult patients (males, 58; females, 47; 69 ± 15 years) with acute ischemic stroke. Nine patients were excluded. Patients were divided into two groups based on the calculated National Institutes of Health Stroke Scale (NIHSS) score (Group 1, NIHSS score <16; Group 2, NIHSS score ≥16). Demographic, clinical, and laboratory data for all patients were collected. Electrocardiography (ECG) was recorded from all patients on admission to the neurology care unit. iCEB (QT/QRS) was calculated from the 12-lead electrocardiogram. **Results:** There were no significant differences among the demographic parameters of patients. iCEB score was significantly higher in Group 2 patients than Group 1 patients (3.97 ± 0.61 vs 3.43 ± 0.57, $P = 0.0024$). **Conclusion:** Our results suggested that iCEB is associated with stroke severity on admission in patients with acute ischemic stroke. It is known that high iCEB is associated with torsade de pointes (TdP), ventricular tachycardia.

Keywords: *Arrhythmia, ECG, Index of Cardioelectrophysiological Balance, stroke*

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Introduction

Acute stroke is an important cause of morbidity, and mortality and cardiovascular complications are common after an acute stroke.[1,2] Several ECG abnormalities have been reported in patients following acute cerebrovascular events including QT interval prolongation, ST-segment deviation, and T-wave changes.[3] Autonomic nervous system dysregulation after acute cerebrovascular events possibly causes sympathetic activation resulting in cardiac arrhythmia. QT dispersion (QTd) has been proposed as an indirect ECG measure of the heterogeneity of ventricular repolarization.[4] Conflicting results have been reported on the prognostic value of QTd in patients following acute stroke.[5,6] Therefore, its association and predictive value in acute stroke remain controversial. Recently a new noninvasive marker index of cardioelectrophysiological balance (iCEB) between the depolarization and repolarization of the action potential was introduced as a potential risk predictor arrhythmia.[7] iCEB is measured as the QT interval divided by QRS duration, which plays an important role in arrhythmogenesis.

In this study, we aimed to investigate the relationship between iCEB and National Institutes of Health Stroke Scale (NIHSS) score in patients with acute ischemic stroke.

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Materials and Methods

Study participants and design

Patient selection

We prospectively studied consecutive 105 adult patients (males, 58; females, 47; mean age, 69 ± 15 years; range 40–89 years) with acute ischemic stroke (≤24 h of symptom onset) admitted to the neurology care unit, between October 2016 and November 2018. Nine patients were excluded. Demographic and baseline clinical data, including neurological deficit severity assessment with NIHSS on admission to the neurology care unit were recorded. Patient clinical data, history of cardiovascular risk factors, and stroke onset were determined, and neurologic examination was conducted at the time of admission. The diagnosis was made based on the neurologic examination and cranial imaging within 24 h of symptom onset. Patients with a well-defined time of ischemic stroke symptom onset were included in the study and those with any previous history of cerebrovascular disease (n = 2), documented atrial fibrillation (n = 3), congestive heart failure (n = 2), serious valvular heart disease (n = 1), and unmeasurable T-wave (n = 1) were excluded.

All patients underwent immediate computed tomography after being admitted to the emergency care unit. Troponin levels were measured and electrocardiogram (ECG) was recorded after admission to the neurology care unit. The study was approved by the Ethics Committee of our hospital and informed consent was obtained. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Echocardiographic examination

Two-dimensional echocardiography

All patients underwent comprehensive transthoracic echocardiography examinations, which were conducted according to the guidelines of the American Society of Echocardiography. An ultrasound system (Philips EPIQ 7C, Philips Healthcare, Andover, MA, USA) equipped with a multifrequency transducer (3–8 MHz) and tissue harmonic imaging capability was used. A single-lead electrocardiogram was continuously recorded. Patients were kept in the left lateral decubitus position. Images were obtained from the parasternal long- and short-axes, apical two- and four-chamber, and long-axis views. All echocardiograms included at least three cardiac cycles and were digitally stored for offline analysis. In addition to left ventricular ejection fraction (LVEF), end-systolic and end-diastolic volumes were measured from the apical two- and four-chamber views, using the standard biplane Simpson's technique. The interventricular septum, posterior wall thickness, left ventricle (LV) end-diastolic diameter, and left atrial anteroposterior diameter were measured from a parasternal long-axis view.[8] Echocardiographic parameters were calculated by a qualified physician, and echocardiographic examination was conducted by an investigator who was blinded to the patients' clinical information.

Analysis of QT, Tpe interval

All standard 12-lead ECGs were recorded at 25 mm/s speed and 10 mm/mv gain with Nihon Kohden ECG-9132K electrocardiograph (Nihon Kohden Corporation, Tokyo, Japan). A 12-lead resting ECG was recorded at admission in the neurology care unit for patients with an acute ischemic stroke and then was manually measured with a ruler. All ECGs were manually analyzed by an experienced cardiologist who was unaware of the clinical data. The QT interval was measured from the beginning of the QRS to the end of the T-wave. The end of the T-wave was defined as the point of return to the isoelectric line.[9] In cases where the T-wave was interrupted by a U-wave, the end of the T-wave was defined as the nadir between the T- and U-waves. In instances where the T-wave could not be reliably determined due to extremely low voltage (<0.1 mV), measurement of QT interval was not established and consequently, these leads were excluded from the analysis. In order to exclude the effects of the heart rate (HR) on the QT interval, the QT interval was corrected according to the Bazett formula (QTc = QT/square root of RR interval). QTd was defined as the difference between the maximum and minimum QT intervals. T peak to T end (Tpe) was measured with a ruler from the peak of the T-wave to its end; Tpe was corrected for heart rate. The criteria to determine the endpoint of the T-wave were similar to the aforementioned criteria considered for the QT measurement. iCEB was calculated by the ratio of QT/QRS, measured from the ECG recordings.[7]

Definition of stroke and assessment of stroke severity

According to the updated definition of stroke in the American Heart Association/American Stroke Association guidelines, ischemic stroke is diagnosed based on the combination of symptoms and/or signs of typical neurological dysfunction and imaging evidence of central nervous system infarction. Therefore, ischemic stroke is defined as a neurological dysfunction episode caused by focal cerebral, spinal, or retinal infarction on imaging.[10] NIHSS is a simple, valid, and reliable systematic assessment tool that measures acute stroke-related neurologic deficit.[11] The NIHSS score is a very important scale for clinical assessment as it enables the determination of appropriate treatment, prediction of lesion size, measurement of stroke severity,

and prediction of patient outcome in patients with acute ischemic stroke. The NIHSS comprises 11 different elements evaluating specific ability. Each ability is scored between 0 and 4, where 0 corresponds to normal functioning and 4 corresponds to complete impairment. A patient's NIHSS score is calculated by adding the score for each element of the scale; 42 is the highest score possible. A higher NIHSS score corresponds to greater impairment of cerebral function in a stroke patient.

The higher the NIHSS score, the higher the impairment of a stroke patient. According to NIHSS score, there are five stroke severity groups: NIHSS = 0 (no stroke), NIHSS = 1–4 (minor stroke), NIHSS = 5–15 (moderate stroke), NIHSS = 16–20 (moderate-to-severe stroke), and NIHSS = 21–42 (severe stroke). A baseline NIHSS score greater than 16 indicates a strong probability of patient disability and death.[11]

Stroke severity at admission to the neurology care unit was assessed by the NIHSS score by a neurologist. Patients were categorized into two groups; Group 1 comprised of patients with nonsevere stroke (NIHSS <16; n = 69), whereas Group 2 comprised of patients with severe stroke (NIHSS ≥16; n = 27).

Cerebral Infarct Volume Measurements

A neurolog computed the "cerebral infarct volume" in each patient by using Analyze 12.0, a software package for biomedical image analysis (Biomedical Imaging Resource, New York, NY, USA). The regions of interest were segmented using the Region Grow in the Volume Edit module, with manual removal of artifacts when necessary. The total volume was reported in milliliter.

Statistical analysis

Statistical analysis was conducted with the SPSS statistical package (Version 12.0; SPSS Inc., Chicago, IL, USA). All baseline parameters were analyzed. Continuous variables are expressed as mean ± SD and categorical variables are expressed as percentages. Intraobserver variability was calculated as the absolute difference between the two measurements as a percentage of their mean. Mann–Whitney U test and Chi-square test were used for comparison of data as appropriate. P values < 0.05 were considered statistically significant. Spearman's correlation was used to determine the relationship between NIHSS and clinical parameters. Multivariate analyses were performed.

Results

Baseline characteristics

The baseline characteristics of patients are summarized in Table 1. Clinical characteristics of groups were similar with respect to age, gender, hypertension, diabetes, smoking (P > 0.05). Systolic blood pressure (BP), diastolic BP, heart rate, dyslipidemia, infarct volume, and troponin levels in Group 2 patients were significantly higher than Group 1 patients (P < 0.05). Serum hemoglobin HbA1c and low-density lipoprotein cholesterol levels were significantly higher in Group 2 patients than Group 1 patients (P < 0.05).

Echocardiographic findings

Echocardiographic findings are summarized in Table 2. LV wall thickness and E/e' values were significantly higher in Group 2 patients than in Group 1 patients (P < 0.05). LVEF was significantly higher in Group 1 patients having lower NIHSS scores than in Group 2 patients having higher NIHSS scores.

Electrocardiographic findings

Group 2 patients showed significantly longer QTc, QTd, QTcd, Tpe, Tpe/QT, iCEB than Group 1 patients [Table 3]. Intraobserver variability of QTd is 3.2 ms and Tpe is 3.8 ms.

Correlation analysis performed to investigate the relationship between NIHSS score and clinical parameters showed a negative correlation between the NIHSS score and LVEF. In addition, there was a positive correlation between the NIHSS score and iCEB, age, heart rate, and E/e'. [Table 4]. Logistic regression

Table 1: Clinical characteristics of patients

Variables	Group 1 (NIHSS score <16) n=69	Group 2 (NIHSS score ≥16) n=27	P
Age (years)	67.5±13.6	69.2±16.8	0.736
Gender (F/M), n	39/30	15/12	0.652
Hypertension, n%	33 (49%)	15 (56%)	0.078
SBP (mmHg)	141.6±17.1	162.5±17.9	0.046
DBP (mmHg)	75.7±9.1	86.8±11.9	0.037
Heart Rate (bpm)	91±13	117±18	0.029
Diabetes Mellitus, n%	15 (23%)	7 (26%)	0.657
Smoking, n%	9 (13%)	4 (15%)	0.067
Dyslipidemia, n%	11 (16%)	5 (19%)	0.329
Infarct volume (mL)	17 mL±2.1	46 mL±3.8	0.027
Troponin (ng/L)	5.834	13.976	0.025
HbA1c (%)	6.18±1.41	9.97±1.69	0.035
Glucose (mg/dL)	139.3±36.8	191.6±47.9	0.042
Creatinine (mg/dL)	1.2±0.6	1.7±0.8	0.028
LDL cholesterol (mg/dL)	105.5±26.9	134.1±38.7	0.037
HDL cholesterol (mg/dL)	41.5±11.6	38.7±9	0.416

*DBP: Diastolic Blood Pressure, †F: Female, ‡HDL: High Density Lipoprotein, §LDL: Low Density Lipoprotein, ‖ M: Male, ¶SBP: Systolic Blood Pressure

Table 2: Echocardiographic parameters of patients

Variables	Group 1 (NIHSS score <16) *n*=69	Group 2 (NIHSS score ≥16) *n*=27	*P*
LV septal thickness, mm	11.3±1.7	12.6±1.5	0.032
LVDd (mm)	50.8±6.5	54.2±6.4	0.372
LV posterior Wall thickness, mm	10.6±1.4	12.1±1.7	0.025
LVDs (mm)	41.6±3.9	43.9±5.4	0.287
LVEDV (mL)	85.2±16.5	96.7±25.9	0.298
LVESV (mL)	42.3±11.6	44.9±13.8	0.462
LAD (mm)	38.4±4.2	43.5±4.7	0.547
RAD (mm)	31.2±3.6	33.8±3.5	0.389
RVDd (mm)	27.9±2.7	30.3±2.5	0.428
LVEF (%)	58.6±5.3	52.4±6.6	0.035
E/e'	8.3±3.2	10.7±3.1	0.027

*LAD: Left atrial diameter, †LV: Left Ventricle, ‡LVDd: Left ventricular diastolic diameter, ‖LVDs: Left ventricular systolic diameter, ¶LVEDV: Left ventricular end-diastolic volume, **LVEF: Left ventricular ejection fraction, ††LVESV: Left ventricular end-systolic volume, ‡‡NIHSS: National Institutes of Health Stroke Scale, §§RAD: Right atrial diameter, ‖‖RVDd: Right ventricular diastolic diameter

Table 3: Electrocardiographic parameters of patients

Variables	Group 1 (NIHSS score <16) *n*=69	Group 2 (NIHSS score ≥16) *n*=27	*P*
QTc (ms)	474±51.9	537±75.9	0.041
QTd (ms)	61.9±3.6	89.2±3.4	0.039
QTcd (ms)	63.6±2.7	91.4±3.6	0.032
Tpe (ms)	68±35	92±38	0.024
Tpe/QT	0.14±0.02	0.18±0.03	0.037
iCEB	3.43±0.57	3.97±0.61	0.0024

*iCEB: Index of Cardioelectrophysiological Balance, †QTc: corrected QT interval, ‡QTcd: QTc dispersion, §QTd: QT dispersion, ‖Tpe: Interval between the peak and the end of the T wave, ¶Tpe/QT: Tpe interval divided by the QT interval

analysis was performed to identify the potential predictors for stroke severity. Results of the multivariate analysis revealed that age, LV EF, infarct volume, and iCEB were the powerful predictors of severe ischemic stroke [Table 5].

Discussion

Acute stroke is characterized by profound autonomic dysregulation, including alterations in the autonomic reflex pathways, central autonomic neuroanatomical sites, and hormonal factors.[12] Stroke-related sympathetic activation is high in patients with higher NIHSS scores. There is a relationship between the central nervous system and the cardiovascular system during acute cerebrovascular disease.[13] The previous studies have reported that a relationship between acute

Table 4: Correlation between NIHSS score and clinical parameters in patients with acute ischemic stroke

Parameters	Sperman's correlation coefficient (*r*)	*P*
iCEB	0.571	0.032
LVEF	-0.314	0.038
E/e'	0.217	0.026
Age	0.320	0.042
Heart rate	0.419	0.023
Infarct volume	0.672	0.019

*iCEB: İndex of cardioelectrophysiological balance, †LVEF: Left ventricular ejection fraction, ‡NIHSS: National Institutes of Health Stroke Scale

Table 5: Multivariate logistic regression analysis between NIHSS score and clinical parameters in patients with acute ischemic stroke

Parameters	OR	95% CI	*P*
iCEB	0.561	0.328-0.840	0.004
LVEF	0.835	0.770-0.920	0.025
Age	1.218	1.090-1.465	0.030
Heart rate	1.130	0.972-1.223	0.453
Infarct volume	0.953	0.673-0.942	0.022

NIHSS: National Institutes of Health Stroke Scale, † LV GLS: Left ventricular global longitudinal strain, ‡ LVEF: Left ventricular ejection fraction

cerebrovascular disease and QT.[4,14] The effect of cerebrovascular events on the cardiovascular system is due to neurogenic myocardial stunning and changes in the autonomic nervous system (increased sympathetic control, reduced parasympathetic control). Significant imbalances between the repolarization and depolarization and of the heart may be associated with arrhythmic conditions. Lazar *et al.* found that a positive relationship between baseline QTd and NIHSS and modified ranking scores.[15]

The previous clinical studies show that prolonged QT interval is associated with arrhythmia risk.[3-6] However, there is some concern regarding the use of QT interval as the sole risk marker for arrhythmias. The absence of QT prolongation is no guarantee for a lack of proarrhythmia. Therefore, a search is ongoing for better or complementary risk markers. Recently iCEB was proposed as a new and noninvasive biomarker to predict the risk for both TdP and non-TdP VT/VF. It was suggested that an optimal balance between depolarization (QRS duration) and repolarization (QT interval) is crucial to preserve the electrical stability of the ventricles: deviating too much from this delicate balance may indeed be proarrhythmic.[7]

iCEB (QT/QRS) is a simple but effective ECG surrogate of the cardiac wavelength. Robyns *et al.* found that

the correlation between the effective refracter period measured during electrophysiologic study and the uncorrected QT interval, thus supporting the concept of this new marker as an ECG surrogate for cardiac wavelength.[7] Only limited data are available on cardiac wavelength as a risk stratifier, mainly due to the invasive nature to measure it. They found that iCEB is a readily measurable local estimate of the cardiac wavelength. iCEB is increased in situations that predispose to TdP. iCEB, measured from the ECG, could serve as an important, new and noninvasive biomarker for potential risks of cardiac arrhythmias beyond long QTs and TdP. Causes of prolonged QT-interval (inherited long QTs) are significantly increasing iCEB. Increasing iCEB is associated with TdPs.[16]

Therefore, iCEB might serve as a noninvasive and readily measurable marker to detect increased arrhythmic risk.[7] Sivri and Celik found that in addition to ventricular repolarization dispersion indices in end-stage renal disease patients, iCEB elevation and increasing values after hemodialysis session indicate the increased risk of TdP-mediated ventricular arrhythmia after hemodialysis.[17] However, to our knowledge, no studies in the literature have investigated the relationship between iCEB and stroke severity in acute ischemic stroke patients. In the present study, we found that iCEB score was significantly higher in Group 2 patients than Group 1 patients. In addition, infarct volume was significantly higher in Group 2 patients than Group 1 patients.

Stead *et al.* found an increased risk of early death in patients with acute ischemic stroke and a prolonged QTc interval at the time of emergency department presentation.[18] Marafioti *et al.* found that the QTc interval prolongation is mainly a marker of serious cerebral damage.[19] Villa *et al.* found that in patients with ischemic stroke and prolonged QTc interval, the risk of dying could be significantly higher than in patients with normal QTc interval.[20] In our study, we found that QT was significantly higher in Group 2 patients than Group 1 patients. The previous study found that a significant association between changes in QTd and stroke severity quantified by the National Institute of Health Stroke Scale (NIHSS).[21,22] Larger stroke lesions were associated with greater QTd in the early stages of stroke in the 2 studies.[23,24] Simula *et al.* found that right MCA ischemic stroke results in prolongation of QT interval.[25]

Hypertension, hyperlipidemia, and diabetes mellitus are important risk factors for atherosclerotic cerebrovascular disease. We found that blood pressure at admission is significantly higher in severe ischemic stroke patients. However, Bonardo *et al*. found that, in young patients with acute ischemic stroke, large infarct volume was not associated with high blood pressure at admission.[26] In our study, we found that LDL cholesterol and HbA1c were significantly higher in patients with higher NIHSS scores than in those with lower NIHSS scores. Hendrix *et al.* found that diabetes mellitus history is an important predictor of stroke severity.[27]

Irrespective of prior cardiovascular status, an acute phase of stroke markedly influences systemic BP, heart rate, LV function, and biochemical parameters (Glucose, troponin, creatinine).[28] In this study, we found that troponin levels were significantly higher in severe ischemic stroke patients. Chang *et al.* observed that cardiac biomarkers, particularly serum troponin levels, are associated with acute large vessel occlusion in patients with ischemic stroke.[29] Lindsberg and Roine observed that elevated blood glucose is common in the early phase of the stroke.[30] In our study, blood glucose levels were significantly higher in severe stroke patients on admission. Although up to one-third of severe acute ischemic stroke patients have diagnosed diabetes, probably a major proportion of patients have stress hyperglycemia mediated partly by the release of cortisol and norepinephrine.[30,31] In our study, we found that E/é value was significantly higher in severe stroke patients. Ryu *et al.* suggested that E/e' ratios were associated with arterial occlusion in AF-related stroke and may play a role in identifying patients at high risk of a severe stroke.[32] In this study, we found that creatinine levels were significantly higher in severe stroke patients. Mostofsky *et al.* suggesting that shared risk factors underlying vascular diseases including age, diabetes mellitus, hypertension, left ventricular hypertrophy may represent unique vascular pathogenesis resulting from reduced renal clearance. Renal function predicts survival in patients with acute ischemic stroke.[33]

Study limitations

Our study has several limitations. Although we excluded patients with a major cardiac history, it is possible that chronic heart failure was missed. However, we excluded patients with echocardiographic parameters that are compatible with chronic heart failure, such as segmental dyskinesis, dilated or hypertrophic cardiomyopathy, or severe valvular disease. Moreover, the elevation of cardiac troponin levels over time is in accordance with the current definition of stress cardiomyopathy. Therefore, we suggest that stress cardiomyopathy features should be studied in patients with acute ischemic stroke and without chronic asymptomatic heart failure.

Conclusions

The results of our study suggest that iCEB is associated with stroke severity on admission in patients with acute ischemic stroke. iCEB can help to evaluate arrhythmia risk in patients with acute neurologic diseases.

Ethical approval

The study was approved by the Ethics Committee of our hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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