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QTc, Tp-e Interval and Tp-e/QTc Ratio Changes in Hypoxia Due to Hypertensive Pulmonary Edema-Case Control Study

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Abstract

Aim: As far as we have investigated, although there are researches on QT and QTc interval, there are no studies evaluating T wave peak-to-end distance (Tp-e interval), the ratio of Tp-e to QT and QTc used in the evaluation of cardiac arrhythmia risk and ventricular repolarization changes in patients with hypoxia due to hypertensive pulmonary edema. Therefore, in this study was aimed to study whether there is a change in Tp-e interval, the ratio of Tp-e to QTc in hypoxia due to hypertensive pulmonary edema.

Materials and Methods: Forty patients diagnosed with hypertensive pulmonary edema in the emergency room were included in the study retrospectively. Forty patients with similar age and gender distribution were included in the study as a control group. All patients underwent 12-lead electrocardiography (ECG). In addition to the routine measurements, Tp-e interval, the ratio of Tp-e to QTc were measured in ECG. Study data were grouped as patients with and without hypoxia

Results: Mean age for patients was 68.60±15.25. QTc interval, Tp-e interval and Tpe/QTc values were found to be significantly higher in hypoxia caused by hypertensive pulmonary edema ($p<0.001$ for each). QTc interval, Tp-e interval and Tpe/QTc ratio showed significant negative correlation with hypoxia levels.

Conclusion: In patients with hypertensive pulmonary edema, Tp-e interval and Tp-e/QTc rates are increased significantly compared to those without hypertensive pulmonary edema, and these measurements can be used more effectively in the close follow-up of cardiac fatal arrhythmias.

Keywords: Tp-e/QTc ratio, arrhythmia, emergency medicine, hypoxia

Introduction

Hypertensive pulmonary edema is an important cause of mortality and morbidity, which is frequently encountered in the emergency room and often occurs as a result of acute heart failure. It may occur due to conditions such as diastolic and systolic dysfunction, myocardial ischemia, acute mitral regurgitation (1), and may cause cardiac rhythm disorders with resulting hypoxia (2). In addition, it is stated that resulting hypoxia can prolong the QT interval (3,4). Prolonging of QT interval increases the risk of developing ventricular arrhythmias and sudden cardiac death (3). As far as is known, although there are studies showing that hypoxia prolongs the QTc interval, there are no other studies studying hypoxia-related changes in Tp-e interval and Tp-e/QTc rates, which are indicators of ventricular arrhythmia.

There are multiple electrocardiographic (ECG) measurements related to ventricular repolarization, which are associated with the risk of ventricular arrhythmia. These measurements used are QT and QTc interval, QT and QTc dispersion and T wave peak-to-end distance (Tp-e interval). Among these parameters, QT and QTc are indicators of ventricular depolarization in addition to repolarization. However, Tp-e is more indicative

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of ventricular repolarization, and may be more meaningful especially in repolarization assessment. The ratio of Tp-e to QT and QTc obtained are associated with the ventricular transmural dispersion that occurs during repolarization (5). An increased Tp-e interval shows abnormal spread in ventricular repolarization and is associated with an increased risk of ventricular arrhythmia (6). Literature research shows there is no research related to the Tp-e interval, the ratio of Tp-e to QT and QTc used in the assessment of ventricular repolarization in those with hypoxia detected in the emergency department.

It was aimed to evaluate the changes in QTc, Tp-e interval, ratio of Tp-e to QTc in patients with hypoxia due to hypertensive pulmonary edema compared to patients without pulmonary edema and hypoxia in the emergency room.

Materials and Methods

Records of patients who applied to the University of Health Sciences, Adana City Research and Training Hospital Emergency Medicine Clinic between July 1, 2019 and December 31, 2019, and who are diagnosed with hypertensive lung edema after evaluation of vital signs, physical examination and radiological imaging were examined retrospectively. Electrocardiography (ECG) recordings obtained from the files of these patients were examined. A total of 40 patients were enrolled as the patient group. Arterial blood pressure values, physical examination findings, and radiological imaging results of the patients admitted to the emergency department for various reasons were examined and found to be healthy. ECG recordings of these patients without hypertensive lung edema were obtained. Forty outpatients who were found to be healthy were enrolled as the control group.

Exclusion criteria for all patients included in the study and control group were all medical treatments known to extend or shorten QT and QTc distance, known syncope or sudden cardiac arrest history in the patients or their family, presence of acute or chronic systemic or local infection, being in the pediatric age group (<18 years), inability to perform Tp-e and QTc measurements on ECG, presence of known diabetes mellitus, medium-advanced valvular disease, electrolyte deficiency, and having the diagnosis of chronic liver disease or chronic renal failure. This research complies with Helsinki Declaration and ethics approval was obtained from Adana City Training and Research Hospital Clinical Researches Ethics Committee (decision no: 629, date: 04.12.2019).

12-lead ECG and laboratory results of all patients were obtained from the files. From the demographic variables of the patients, age, sex, pulse, blood pressure, oxygen saturation values of all patients were recorded from the archived files. From the routine biochemistry parameters, renal function tests, serum electrolytes, liver function tests were recorded.

12-Lead Electrocardiographic Evaluation

Firstly, 12-lead ECG obtained by MAC 2000 ECG Machine (GE medical systems information technologies, Inc., WI, USA) with a sinus rhythm of 25 mm/sec and 1 mv/10 mm standard calibration was obtained from the files. The time from QRS to the point where the T wave returns to the isoelectric line was calculated for the QT time. QTc in patients with heart rate between 60-100/minute was calculated using the Bazett Formula (QTc=QT/√R–R). QTc in patients with heart rate outside the range of 60-100/minute was calculated using Frederica Formula (QTc=QT/RR 1/3). The Tp-e interval was defined as the time from the peak of the T wave to the point where the T wave interconnected with the isoelectric line. Measurements were made primarily from V5. If V5 was unsuitable for measurement (amplitude <1.5 mm), measurements were taken from V4 or V6 (7). Tp-e/QTc ratio was calculated based on these measurements. All ECG examinations in sinus rhythm were evaluated by a cardiologist with at least 5 years of experience in electrophysiology and ≥2,000 arrhythmia patients annually, while unaware of the clinical status of the patient.

Statistical Analysis

All analyzes were performed using SPSS 22.0 (Chicago, IL, USA) statistical software package. Using the Kolmogorov-Smirnov test, it was determined whether continuous variables distribution was normal. Continuous variables in data were presented as mean ± standard deviation, and categorical as numbers and percentages. Continuous variables showing normal distribution was compared using the Student t-test, whereas the Mann-Whitney U test is used to compare differences between two independent groups when the dependent variable is either ordinal or continuous, but not normally distributed. Categorical variables were compared using chi-square (χ^2) test. The kappa coefficient was used to examine the interobserver variability of all ECG measurements. Pearson's and Spearman's correlation analysis was used to determine the presence of a relationship between countable parameters. Statistical significance level was set as $p<0.001$.

Results

The study data was conducted as two groups; patient and control. ECG measurements were taken successfully from all patients.

When demographic data were compared according to the study groups, age and sex were similar. Laboratory results were also similar (Table 1).

Table 1. Comparison of demographic and laboratory findings between hypertensive pulmonary edema and control group			
	Patients with hypertensive pulmonary edema (n=40)	**Patients without hypertensive pulmonary edema (n=40)**	**p value**
Age (years)	68.60±15.25	67.60±7.77	0.607
Systolic blood pressure (mmHg)	189.75±21.90	169.63±16.23	<0.001
Diastolic blood pressure (mmHg)	104.75±9.33	96.50±6.90	<0.001
Heart rate (pulse/minute)	121.75±11.45	76.50±11.25	<0.001
Pulse-oximeter (%)	82.55±5.39	97.03±5.33	<0.001
Urea (mg/dL)	35.07±5.74	32.50±7.82	0.098
Creatinine (mg/dL)	0.90±0.18	0.74±0.20	<0.001
Sodium (mEq/L)	138.50±2.84	138.50±2.21	0.999
Potassium (mEq/L)	4.53±0.35	4.33±0.49	0.043
Glucose (mg/dL)	141.67±18.20	110.22±13.57	<0.001
ALT (u/L)*	20.20±8.47	18.80±9.17	0.481
AST (u/L)**	28.17±10.02	23.13±6.59	0.010
Significant values are shown in bold. *ALT: Alanine aminotransferase, **AST: Aspartate aminotransferase, n: Number			

Table 2. Comparison of ventricular repolarization parameters between hypertensive pulmonary edema and control group			
	Patients with hypertensive pulmonary edema (n=40)	**Patients without hypertensive pulmonary edema (n=40)**	**p value**
QTc interval time (ms)	483.05±8.91	415.90±12.77	<0.001
Tp-e interval time (msn)	108.85±9.38	60.13±7.80	<0.001
Tp-e/QTc ratio	22.51±1.54	14.42±1.43	<0.001
Tp-e: T wave peak-to-end distance, QTc: Corrected QT, n: Number			

When ventricular repolarization parameters were examined according to the study groups, QTc interval, Tp-e interval and Tp-e/QTc values were significantly higher in patients with hypoxia (Table 2).

Table 3 shows the correlation of QTc, Tpe-interval and Tpe/QTc measurements with the systolic and diastolic blood pressure, and pulse-oximeter values. All three measurements were positively correlated with systolic and diastolic blood pressure, and were negatively correlated with pulse-oximeter oxygen saturation levels (Table 3). In linear regression analysis, hypoxia significantly related to QTc, Tpe-interval Tpe/QTc measurements (Table 4). In linear regression analyses, QTc, Tpe-interval and Tpe/QTc ratio were independently associated with pulse-oximeter oxygen saturation levels. In Scatterplot analyses of pulse-oxymeter oxygen saturation levels with QTc interval, Tp-e interval and Tp-e/QTc ratios, R^2 linear values were 0.722, 0.696 and 0.690 respectively (Figures 1-3).

Discussion

The most important result of our research was that in patients with hypoxia due to hypertensive pulmonary edema, the rate of QTc, Tp-e interval and Tp-e/QTc were significantly higher than the control group. As far as known, findings of our research are the first in the literature to show an increase in ventricular repolarization parameters Tp-e interval and Tp-e/QTc in patients with hypertensive pulmonary edema. Our study also supports previous studies showing QT and QTc prolongation in hypoxic patients.

Depolarization of ventricular myocardium occurs from the endocardial region towards the epicardial region. Depolarization occurs before ventricular repolarization. There is dispersion between the endocardial and epicardial region. The interval between the T wave peak and the end distance is called the Tp-e interval, and this is associated with transmural ventricular repolarization (5,7). It has been showed to be associated with

Table 3. Correlation of QTc, Tp-e-interval and Tp-e/QTc ratio with blood pressure and pulse-oximeter						
	QTc		Tp-e-interval		Tp-e/QTc ratio	
	r	p value	r	p value	r	p value
Systolic blood pressure (mmHg)	0.431	<0.001	0.423	<0.001	0.417	<0.001
Diastolic blood pressure (mmHg)	0.391	<0.001	0.378	<0.001	0.376	0.001
Pulse-oximeter (%)	-0.775	<0.001	-0.759	<0.001	-0.757	<0.001
QTc: Corrected QT						

Table 4. A Linear regression analysis for pulse-oximeter significantly correlated with QTc, Tp-e-interval and Tp-e/QTc ratio						
	QTc		Tp-e-interval		Tp-e/QTc ratio	
	β	p	β	p	β	p
Pulse-oximeter	-0.775	<0.001	-0.759	<0.001	-0.757	<0.001
R-square for QTc, Tp-e interval and Tp-e/QTc ratio as 651, 787, 707, respectively. QTc: Corrected QT						

arrhythmias in the Tp-e interval and the ratio of this interval to the QT interval in the presence of many cardiac pathological conditions, and poses a high risk for sudden cardiac death (8-11). The association of increased Tp-e interval and Tp-e/QTc ratios with arrhythmias and sudden cardiac death was thought to stem from the dispersion in the ventricular myocardium between the epicardial and endocardial region, causing the slow conduction of these two anatomic regions, which could cause arrhythmias associated with re-entries, one of the most common causes of arrhythmias.

Hypertensive pulmonary edema is a clinical condition caused by increased hydrostatic pressure or capillary permeability, resulting in decreased oxygen delivery to tissues due to ventilation/perfusion mismatch (12). Even short hypoxemia periods are reported to be associated with prolonged sinusal pauses, transient A-V blocks, multifocal ventricular extrasystoles, and ventricular tachycardia (13). Hypoxia changes the plateau phase of the action potential of L-type Ca^{++} channels, which is the main pathway of calcium flow into cells, therefore may result in cardiac arrhythmias (14). There are studies evaluating the QT and QTc interval, one of the ventricular repolarization parameters that can lead to arrhythmias due to hypoxia, and similar to ours, these studies show that prolongation in QTc is an independent risk factor for hypoxia (3,4). On the other hand, there is no research evaluating the ratio of Tp-e interval, Tp-e/QT and Tp-e/QTc in hypoxic patients with hypertensive lung edema. Increase in ventricular repolarization parameters such as QT and QTc duration, QTc dispersion, Tp-e interval and Tp-e/QTc have been shown risk determinants for ventricular arrhythmias and death (6,15). In our study, the Tp-e/QT and Tp-e/QTc ratio increases significantly in patients with hypoxia.

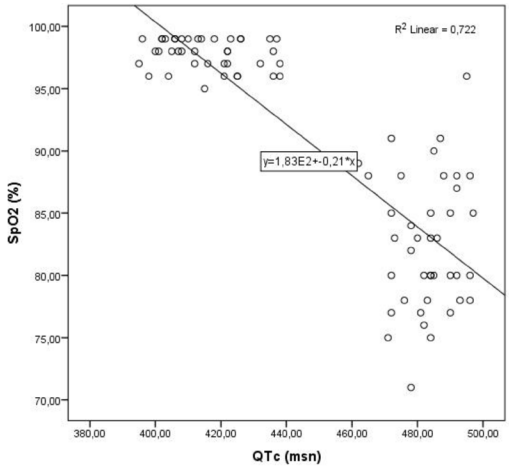

Figure 1. Analysis of Scatterplot for the relationship between SpO_2 and QTc interval

QTc: Corrected QT

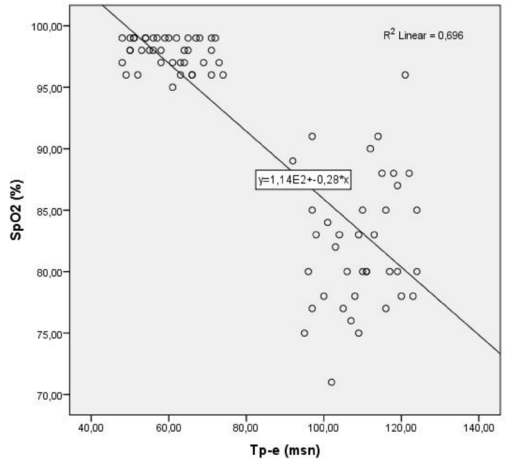

Figure 2. Analysis of Scatterplot for the relationship between SpO2 and Tp-e interval

QTc: Corrected QT

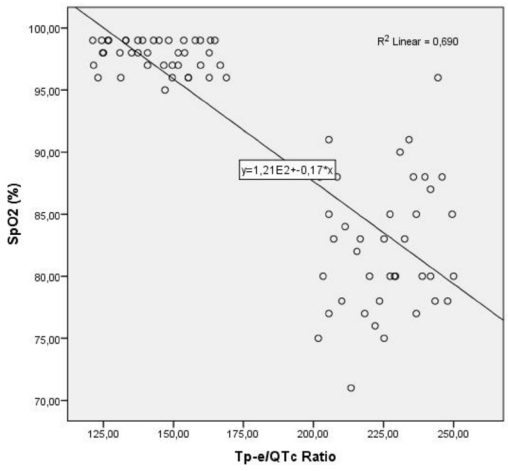

Figure 3. Analysis of Scatterplot for the relationship between SpO_2 and Tp-eQTc ratio

QTc: Corrected QT

Hypoxia with hypertensive pulmonary edema, besides prolonged QTc distance, changes in Tp-e and Tp-e/QTc parameters are precursors of ventricular dispersion and repolarization as a result of hypoxia. This shows the importance of monitoring patients with hypertensive pulmonary edema under strict observation accompanied by rhythm monitoring, due to cardiac complications that may arise from hypoxic conditions. According to this research, it may be effective to use the Tp-e and Tp-e/QTc ratio in addition to QT and QTc intervals for assessing ventricular repolarization.

Study Limitations

This research has some limitations. One of these was the retrospective design of the search. The number of patients is limited to 40. Conducting prospective studies with more patients may produce more meaningful results.

Conclusion

Tp-e interval and Tp-e/QTc rates are significantly increased in hypoxic patients with hypertensive pulmonary edema. In addition to QT and QTc evaluation during routine ECG evaluation in patients with hypertensive pulmonary edema in the emergency departments, it should be noted that Tp-e-interval and Tp-e/QTc ratios, which are among other ventricular repolarization parameters, could be observed more frequently due to increased probability of cardiac arrhythmias in patients with an increase in these values. However, since this information obtained in our study is shown for the first time, studies involving new and more patients are required.

Ethics

Ethics Committee Approval: This study was approved by Adana City Training and Research Hospital Clinical Researches Ethics Committee (decision no: 629, date: 04.12.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A., H.K., F.K., Concept: A.A., S.B., B.Ş.A., Design: A.A., S.B., B.Ş.A., Data Collection and/or Processing: M.G., Ö.Y., Analysis and/or Interpretation: A.A., F.İ., Literature Search: A.A., Ö.Y., S.B., S.S., Writing: A.A., Ö.Y., S.S.

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References

1. Sanjay KG, John CP, Abdel-Mohsen N, Karen F, Dalane WK, Kevin MR, et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med. 2001;344:17-22.
2. Hool LC. Acute hypoxia differentially regulates K^+ channels. Implications with respect to cardiac arrhythmia. Eur Biophys J. 2005;34:369-76.
3. Frédéric R, Claire R, Vincent P, David D, Frédéric C, Martin G, et. al. Effect of acute hypoxia on QT rate dependence and corrected QT interval in healthy subjects. Am J Cardiol. 2003;91:916-9.
4. Fabio P, Sara C, Susanna M, Fabio C. Effect of acute hypoxia on QTc interval in respiratory patients undergoing fitness to fly tests. Thorax. 2011;66:725-6.
5. Kongstad O, Xia Y, Liang Y, Hertevig E, Ljungström E, Olsson B, et al. Epicardial and endocardial dispersion of ventricular repolarization. A study of monophasic action potential mapping in healthy pigs. Scand Cardiovasc J. 2005;39:342-7.
6. Porthan K, Viitasalo M, Toivonen L, Havulinna AS, Tikkanen JT, Vaananen H, et al. Predictive value of electrocardiographic T Wave morphology parameters and T-Wave peak to T-Wave end interval for sudden cardiac death in the general population clinical perspective. Cir Arrhythm Electrophysiol. 2013;6:690-6.
7. Xia Y, Liang Y, Kongstad O, Holm M, Olsson B, Yuan S. Tpeak-Tend interval as an index of global dispersion of ventricular repolarization: evaluations using monophasic action potential mapping of the epi and endocardium in swine. J Interv Card Electrophysiol. 2005;14:79-87.
8. Chua KCM, Rusinaru C, Reinier K, Uy-Evanado A, Chugh H, Gunson Karen, et al. Tpeak-to-Tend interval corrected for heart rate: A more precise measure of increased sudden death risk? Heart Rhythm. 2016;13:2181-5.
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;41:567-74.
10. Smetana P, Schmidt A, Zabel M, Hnatkova K, Franz M, Huber K, et al. Assessment of repolarization heterogeneity for prediction of mortality in cardiovascular disease: peak to the end of the T wave interval and nondipolar repolarization components. J Electrocardiol. 2011:44:301-8.
11. Szymanski FM, Karpinski G, Platek A, Puchalski B, Filipak KJ. Long QT interval in a patient after out-of-hospital cardiac arrest with hypocalcaemia, undergoing therapeutic hypothermia. Am J Emerg Med. 2013;31:1722.e1-3.
12. Murray JF. Pulmonary edema: pathophysiology and diagnosis. Int J Tuberc Lung Dis. 2011;15:155-60.
13. Davies SW, Wedzicha JA. Hypoxia and the heart. Br Heart J. 1993;69:3-5.

14. Macdonald WA, Hool LC. The effect of acute hypoxia on excitability in the heart and the L-type calcium channel as a therapeutic target. Curr Drug Discov Technol. 2008;5:302-11.
15. Keating MT, Sanguinetti MC. Molecular and cellular mechanisms of cardiac arrhythmias. Cell. 2001;104:569-80.