EURASIAN JOURNAL OF EMERGENCY MEDICINE
Original Article
DOI: 10.4274/eajem.galenos.2020.42275
Eurasian J Emerg Med. 2022;21(3): 188-92

# The Effect of Severe Pain on Transmyocardial Repolarization Parameters in Renal Colic Patients

Meral Tandoğan, Emine Emektar, Seda Dağar, Yücel Yüzbaşıoğlu, Handan Özen Olcay, Tuba Şafak, Yavuz Katırcı, Yunsur Çevik

University of Health Sciences Turkey, Ankara Atatürk Sanatoryum Training and Research Hospital, Clinic of Emergeny Medicine, Ankara, Turkey

## Abstract

**Aim:** In this study, we evaluated changes in transmyocardial repolarization parameters in renal colic patients with severe pain. Our secondary aim was to evaluate the changes in these parameters after pain relief.

**Materials and Methods:** The study was a prospective observational study. Patients with known urolithiasis and severe pain and without any cardiac disease were included. A control group was created from healthy volunteers of similar age and sex. Electrocardiography (ECG) were taken at the time of admittance and one hour after pain relief. The data were analyzed with the Statistical Package for the Social Sciences 16 program.

**Results:** One hundred renal colic patients and 100 healthy volunteers were included in the study. Median age and sex of the patients in the patient group and the control group were similar. The heart rates and myocardial parameters of the patients were higher than those in the control group. In the patient group, heart rate, P wave duration, QTc, Tp-e interval and Tp-e/QTc rates were decreased in the ECGs that were taken after pain relief, and these differences were statistically significant ($p<0.005$ all values).

**Conclusion:** We observed several responses in the cardiovascular system due to acute pain. Myocardial parameters were prolonged during severe acute pain. Severe pain, such as that from the renal colic, may cause cardiac responses, such as arrhythmias.

**Keywords:** Pain, P wave, QT dispersion, Tp-e, Tp-e dispersion, Tp-e/QT ratio, renal colic

## Introduction

Pain is defined as a subjective, unpleasant and negative sensationunder the influence of stimuli that damagetissues or threaten malfunctions of systems (1). In addition to subjective effects inthe organ or tissue of origin, painmay cause several autonomic or hormonal responses. An important cause of emergent admittance is pain. Urolithiasis causes severe pain,andpatients renal colic are often admitted to the emergency department (ED) painthatthey define as the most severe pain of their life (2). The cardiovascular system can be affected directly (autonomic nervous system, heart rate, blood pressure, etc.) or indirectly (neuroendocrine and peripheral nervous systems), depending on the pain. Increased sympathetic tonus triggers coronary ischemia and arrythmia mechanisms; therefore, it may have directly harmful effects on the heart (3). Alpha receptors on the coronary arteries respond to sympathetic stimulation with vasoconstriction. This coronary arterial spasm may cause angina, myocardial ischemia, and even infarction (3,4). Additionally, autonomic changes induce several arrhythmias by increasing stimulation of pacemaker cells or production of stimulation from latent pacemakers in the heart (5,6). QT dispersion (max QT interval-min QT interval) is a crude and approximate measure of the abnormalities in repolarization (4,6). In clinical practice, for evaluating ventricular repolarization by electrocardiographic (ECG), measurement of the QT interval and correction of this measurement by using heart rate (QTc) are usually used.An increase in QT dispersion, which is an indicator of regional heterogeneity in myocardial repolarization, may cause severe arrhythmias and sudden cardiac death (4,6,7). Also the relationship between an increase in the Tpeak-Tend (Tp-e) interval, which is measured from the peak point to the end point of the T wave, increase in

**Corresponding Author:** Meral Tandoğan, M.D., University of Health Sciences Turkey, Ankara Atatürk Sanatoryum Training and Research Hospital, Clinic of Emergeny Medicine, Ankara, Turkey
**Phone:** +90 505 925 45 07 **E-mail:** drmeraltandogan33@gmail.com ORCID ID: orcid.org/0000-0002-5407-7092

**Received:** 09.08.2020
**Accepted:** 30.10.2020

**Cite this article as:** Tandoğan M, Emektar E, Dağar S, Yüzbaşıoğlu Y, Özen Olcay H, Şafak T, Katırcı Y, Çevik Y. The Effect of Severe Pain on Transmyocardial Repolarization Parameters in Renal Colic Patients. Eurasian J Emerg Med. 2022;21(3):188-92.

Tp-e/QTc rate, which is calculated from the division of the Tp-e interval from QTc, and life-threatening ventricular arrhythmias (7-9).

Several studies have investigated transmyocardial repolarization parameters in several diseases, but there have been studies about the effects of pain on these parameters (7,9-11). Therefore, in this study, we aimed to investigate changes in transmyocardial repolarization parameters in renal colic patients with severe pain. Our secondary aim was to investigate the changes in these parameters after pain relief.

## Materials and Methods

This study was planned as a prospective and observational clinical study. Ethical approval for the study was obtained from the Keçiören Training and Research Hospital Local Ethics Committee with the registration number 1668 on 25.04.2018. Patients and control groups were informed about the study protocol and all subjects were given written, informed consent according to the principles of the Declaration of Helsinki.

### Study Population

From May 1, 2018 to April 30, 2019, all foreknown nephrolithiasis patients between the ages of 18 and 50 years, without any pathologic cardiac conditions, that presented to the ED with flank pain and were diagnosed with reno-ureteral colic were included the study. Patients who were admitted to the ED with same back pain and dysuria that they had experienced before were accepted as renal colic, so they were diagnosed clinically. The visual analog scale (VAS) score was used to determine the severity of pain, and patients with a score of 40 or higher were included in the study. The scale used for the VAS was asked to score patients from painless to worst pain ever (0-100). All participants received a 12-lead ECG at a standard of 10 mm/mV amplitude and a paper speed of 25 mm/h. ECGs were taken 2 times, the first at the time of admission and the second after analgesic treatment. ECG was performed for the second time in patients whose VAS score decreased by 30 or more at the first hour after drug treatment. Patients who could not achieve a decrease of 30 or more in the VAS score after treatment were excluded from the study. Evaluation of the ECGs was made by two researchers who were blind to all steps of the study and each other. The researchers measured the P wave, P dispersion (Pd), QT interval (QT) and corrected QT interval (QTc), QT dispersion (QTd), Tp-e interval, and Tp-e/QTc. Dispersions were obtained from the numerical difference between maximum and minimum values. The QTc was calculated using Bazett's formula. Tp-e was described as the time between the peak of the T-wave and the end of the T-wave. Patients whose T-wave amplitude was less than 1.5 mm were excluded from the study. The Tp-e interval was measured using the "tangent" method (9). The Tp-e/QTc ratio was calculated for the precordial leads.

### Exclusion Criteria

The study excluded patients with any known cardiac conditions, including previous coronary surgery, acute coronary syndrome, severe mitral and aortic valve disease; those who were on drug therapy that prolongs QT (antiarrhythmic drugs, antidepressants, antipsychotics, etc.) before/at the time of admission; those who had electrolyte imbalances; and those who had previous ECG abnormalities, such as branch blocks, pathological Q-waves, or left-ventricular hypertrophy. Additionally, pregnant or lactating patients, and patients who did not agree to participate in the study were excluded from the study.

### Control Group

The control group was formed from healthy volunteers of similar age and gender, without any co-morbidity, not using any drugs including cardiac drugs, and without pain.

### Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS, Inc.; Chicago, IL, USA). Demographic data related to patients and control subjects were expressed as numbers, percentages, median values, and min-max values. The Kolmogorov-Smirnov test was used to assess the normal distribution of the variables. Nonparametric categorical parameters were analyzed using the chi-square test, and non-parametric-dependent ordinal parameters were analyzed using the Wilcoxon test. Independent nonparametric or parametric values were analyzed using the Mann-Whitney U test. P value $<0.05$ was considered statistically significant.

### Sample Size

The sample size was estimated with G*Power for Mac OS X (version 3.1.9.2; Universität Dusseldorf, Germany). During our study, a 2 msn change in QT between measurements was considered clinically significant. Accordingly, with a type-1 error of 5%, a type-2 error of 20% (power 80%) and a two-sided analysis, the sample size was determined as 90 patients. The standard deviation of QT values was retrieved from previous study groups and considered (12). Considering a possible protocol bias, adding 10% patients to each arm was planned; hence, 100 were determined as the minimum number of volunteers to be included per group.

## Results

Demographic findings are shown in Table 1. There was no difference between the pain group and the control grouping terms of gender or age ($p=0.28$ and $p=0.41$, respectively).

According to the ECG parameters heart, HR P wave duration, Pd, QT, QTc, and QTd was significantly higher in the pain group (p=0.012, p<0.001, p<0.001, p<0.001, p<0.001, p=0,047, respectively). Additionally, Tp-e interval and Tp-e/QTc ratio was significantly higher in the pain group than in the control group (for all parameters p<0.001). The ECG parameters of both the groups are shown in Table 2.

**Table 1. Demographic findings of the study and control groups**

| | Patient group (n=100) | Control group (n=100) |
|---|---|---|
| **Gender n (%)**<br>Male | 68 (68%) | 58 (58%) |
| **Age year median (min-max)** | 37 (19-50) | 34 (18-50) |
| **1. VAS median (min-max)**<br>**2. VAS median (min-max)** | 80 (50-100)<br>20 (0-60) | |

VAS: Visual analog scale, min-max: Minimum-maximum

**Table 2. Characteristics of ECG parameters associated myocardial repolarization in pain group and control group [all values presented as median (min-max)]**

| | Pain group (n=100) | Control group (n=100) | p value |
|---|---|---|---|
| HR, beat/min | 85 (71-110) | 70 (46-108) | 0.012 |
| P Wave, ms | 100 (84-128) | 92 (80-578) | <0.001 |
| Pd, ms | 28 (4-52) | 20 (8-100) | <0.001 |
| QT, ms | 382 (336-434) | 365 (328-404) | <0.001 |
| QTd, ms | 52 (16-124) | 36 (16-76) | <0.001 |
| QTc, ms | 424 (367-512) | 415 (348-470) | 0.047 |
| Tp-e, ms | 103 (80-152) | 86 (74-104) | <0.001 |
| Tp-e/QTc | 0.24 (0.19-0.33) | 0.20 (0.17-0.29) | <0.001 |

HR: Heart rate, ms: millisecond, Pd: P dispersion, QT: QT interval, QTc: Corrected QT, QTd: QT dispersion, Tp-e: T wave peak-to-end interval, min-max: Minimum-maximum, ECG: Electrocardiography

When it was compared both ECGs recorded at the admission and one hour after the treatment, it was seen that Pd, QT, QTd was similar in the first and second ECGs (p=0.119, p=0.821, p=0.661, respectively), but heart rate, P wave duration, QTc, and Tp-e interval and Tp-e/QTc was significantly higher in the first ECGs (p<0.001, p=0.01, p=0.003, p<0.001, p<0.001 respectively). The ECG parameters of the first and second ECGs in the pain group are shown in Table 3.

## Discussion

In this study we demonstrated two important findings. First, there were significant ECG changes, including prolonged P wave, Pd, QT, QTd, Tp-e interval and increased Tp-e/QTc ratio, which could be associated with cardiac rhythm disturbance, pain group. Second in the ECGs after the pain relief there we detected reductions in P wave, QTc, Tp-e interval and Tp-e/QTc ratio. In acute pain statement myocardial repolarization parameters prolongs. Especially in patients with pain-like renal colic, it can be seen in any cardiac influences like arrhythmias due to severe pain.

P wave dispersion is obtained as the difference between the widest and narrowest P-wave durations using 12 lead ECG and the role of predicting atrial fibrillation (AF) risk is well known (13). Pd is becoming an interesting topic with increasingly and has been examined in a broad range of clinical settings, including cardiovascular and non-cardiovascular diseases. Studies have exposed the relationship between prolonged P wave indices in paroxysmal AF, and recurrent AF after cardioversion or cardiothoracic surgery. Additionally, some cross-sectional studies have shown that individuals with hypertension, diabetes, stroke, obesity, and sleep apnea have prolonged P wave indices (13,14).

In the literature, we did not find any studies related to P wave or Pd in patients with pain. The urolithiasis was characterized

**Table 3. Characteristics of ECG parameters associated trans-myocardial repolarization in pain group in the presence of pain and the absence of pain [all values presented as median (min-max)]**

| | In the presence of pain | In the absence of pain | p value |
|---|---|---|---|
| HR, beat/min | 75 (51-110) | 70.5 (46-108) | <0.001 |
| P Wave, ms | 100 (84-128) | 98 (82-118) | 0.010 |
| Pd, ms | 28 (4-52) | 28 (4-48) | 0.191 |
| QT, ms | 382 (336-434) | 380 (324-436) | 0.821 |
| QTd, ms | 52 (16-124) | 52 (12-128) | 0.661 |
| QTc, ms | 424 (367-512) | 415 (359-488) | 0.003 |
| Tp-e, ms | 103 (80-152) | 96 (74-122) | <0.001 |
| Tp-e/QTc | 0.24 (0.19-0.33) | 0.23 (0.17-0.31) | <0.001 |

HR: Heart rate, ms: Millisecond, Pd: P dispersion, QT: QT interval, QTc: Corrected QT, QTd: QT dispersion Tp-e: T wave peak-to-end interval, min-max: Minimum-maximum, ECG: Electrocardiography

as severe pain. In the literature, there are studies that bring out a significant association between diseases characterized by painful crisis and symptoms of anxiety include excessive worry, autonomic hyperactivity, exaggerated response and muscle tension (15-17). Significant variations in cardiac atrial conduction were associated with systemic autonomic symptoms seen during anxiety episodes. Yavuzkir et al. (17) shown that P wave dispersion was prolonged in panic disorder patients (17). Moreover, in anxiety disorders, it has been shown that the arrhythmia and P-wave dispersion are associated with state anxiety more than trait anxiety. In our study, we think that the reason for high Pd values is a result of increased sympathetic autonomic response.

Pain causes several changes in the cardiovascular system due to the effects of the autonomic nervous system and neuroendocrine mechanisms (18,19). The relationship between pain and cardiac functions in healthy people has been investigated, and it is obvious that in healthy individuals, excessive pain might be a reason for cardiac autonomic imbalance and high risk of coronary disease due to increased sympathetic autonomic response (20). Besides hypertension and tachycardia, sympathetic discharge also produces mydriasis, diaphoresis, nausea/vomiting, diarrhea and vasoconstriction. In the literature also studies show the effects of the autonomic nervous system on the QT interval (21,22). The QT interval reflects the depolarization and repolarization in myocardial cells. The factors that increase depolarization or retard the repolarization of myocardial cells may prolong the measurement of QT interval. Additionally, genetic and non-genetic factors, besides electrolyte abnormalities and drugs, also affect QTc. Moreover, there are indirect evidence on the activity of the autonomic nervous system affects QTc (22). Pain also signals the hypothalamus and pituitary to release adrenocorticotropin hormone that stimulates the adrenal glands to release adrenalin with subsequent elevation of pulse and blood pressure (23). We did not meet any studies related to QT, QTc and QTd in patients with pain in the literature. In our study we find prolongation in myocardial repolarization parameters at the time of pain. This statement may arise from the effects of pain on heart as we mentioned above.

In addition to the prediction of QT, QTc, QTd in cardiac mortality, Tp-e, that is thought to be a measurement of the transmural dispersion of repolarization, has been determined as a predictor of ventricular arrhythmias and sudden death (24,25). QT and QTd cannot remain stable due to dynamic changes in heart rate in contrast to Tp-e/QT. Tp-e interval, and Tp-e/QT ratio can be an indicator of transmyocardial heterogeneity in ECG (10). If the Tp-e intervals prolong, that can be an opportunity for ventricular re-entries and following arrhythmias. Consequently, to predict the repolarization dispersion, comparison of the Tp-e/QT ratio and the Tp-e interval are commented as an indicator (11).

In this study, Tp-e interval and Tp-e/QT ratiowere higher in the patient group when than the control group. In our study, we think that in addition to the increased sympathetic autonomic response, the inflammatory process due to severe pain in renal colic patients plays a role in increased Tp-e interval and Tp-e/QT.

### Study Limitations

This study had some limitations. The endpoint of our study included only a short-term period; we did not follow patients for a longer period. Additionally, in the study, we did immeasure plasma catecholamine levels, so we did not evaluate the relationship between those levels and repolarization parameters. Another limitation of our study is that drugs used as analgesics may have affected transmyocardial repolarization parameters. ECG could not be performed during the painless periods of the patients.

## Conclusion

This study found that compared to the control group, patients had severe pain with renal colic, had increased myocardial repolarization parameters. Additionally, after the pain reduces, we find reductions in these parameters and heart rate. We believe that physicians should be aware of several cardiac events and related clinical signs, in patients with any cause of severe pain.

### Ethics

**Ethics Committee Approval:** Ethical approval for this study was obtained from Keçiören Training and Research Hospital Ethics Committee (protocol no: 042018/1668, date: 25.04.2018).

**Informed Consent:** Consent form was filled out by all participants.

**Peer-review:** Externally and internally peer-reviewed.

#### Authorship Contributions

Concept: M.T., S.D., H.Ö.O., Y.K., Y.Ç., Design: M.T., E.E., Y.Y., T.Ş., Y.K., Data Collection or Processing: S.D., Y.Y., H.Ö.O., T.Ş., Analysis or Interpretation: M.T., E.E., H.Ö.O., Y.K., Y.Ç., Literature Search: E.E., S.D., Y.Y., T.Ş., Writing: M.T., E.E., Y.K., Y.Ç.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

## References

1. Łabuz-Roszak B, Niewiadomska E, Kubicka-Bączyk K, Skrzypek M, Tyrpień-Golder K, Majewska A, et al. Prevalence of pain in patients with multiple sclerosis and its association with anxiety, depressive symptoms and quality of life. Psychiatr Pol. 2019;53:475-86.

2. Sasmaz MI, Kirpat V. The relationship between the severity of pain and stone size, hydronephrosis and laboratory parameters in renal colic attack. Am J Emerg Med. 2019;37:2107-10.
3. Stevens RA, Beardsley D, White JL, Kao TC, Teague PJ, Spitzer L. Does the choice of local anesthetic affect the catecholamine response to stress during epidural anesthesia? Anesthesiology. 1993;79:1219-26.
4. Afsar N, Fak AS, Metzger JT, Van Melle G, Kappenberger L, Bogousslavsky J. Acute stroke increases QT dispersion in patients without known cardiac diseases. Arch Neurol. 2003;60:346-50.
5. Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, et al. 2015 ACC/AHA/HRS Guideline for the management of adult patients with supraventricular tachycardia: executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart rhythm society.Circulation. 2016;133:e471-505.
6. Rahar KK, Pahadiya HR, Barupal KG, Mathur CP, Lakhotia M. The QT dispersion and QTc dispersion in patients presenting with acute neurological events and its impact on early prognosis. J Neurosci Rural Pract. 2016;7:61-6.
7. Emektar E, Çorbacıoğlu ŞK, Korucu O, Ramadan S, Uzunosmanoğlu H, Kan E, Çevik Y. The evaluation of a new marker of transmyocardial repolarization parameters in ischemic stroke patients; T peak-T end (T p-e), T p-e/QTc. Acta Neurol Belg. 2017;117:461-7.
8. Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, Dorantes Sánchez M, Dorticós 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;47:1828-34.
9. Akilli NB, Akinci E, Akilli H, Dundar ZD, Koylu R, Polat M, et al. A new marker for myocardial injury in carbon monoxide poisoning: T peak-Tend. Am J Emerg Med. 2013;31:1651-5.
10. 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.
11. Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, Dorantes Sánchez M, Dorticós Balea F, Zayas Molina R, et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors forventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol. 2006;47:1828-34.
12. Letsas KP, Weber R, Astheimer K, Kalusche D, Arentz T. Tpeak-Tend interval and Tpeak-Tend/QT ratio as markers of ventricular tachycardia inducibility in subjects with Brugada ECG phenotype. Europace. 2010;12:271-4.
13. Okutucu S, Aytemir K, Oto A. P-wave dispersion: what we know till now? JRSM Cardiovasc Dis. 2016;5:2048004016639443.
14. Magnani JW, Mazzini MJ, Sullivan LM, Williamson M, Elinor PT, Benjamin EJ. P-Wave Indices, Distribution and Quality Control Assessment (from the Framingham Heart Study). Ann Noninvasive Electrocardiol. 2010;15:77-84.
15. Okutucu S, Oto A. P-wave dispersion in different clinical situations: Expanding list with resembling mechanisms. JRSM Cardiovasc Dis. 2017;6:2048004017720369.
16. Henningsen P, Zimmermann T, Sattel H. Medically unexplained physical symptoms, anxiety, and depression: a meta-analytic review. Psychosom Med. 2003;65:528-33.
17. Yavuzkir M, Atmaca M, Dagli N, Balin M, Karaca I, Mermi O, et al. P-wave dispersion in panic disorder. Psychosom Med. 2007;69:344-7.
18. Drummond PD. The effect of pain on changes in heart rate during the Valsalva manoeuvre. Clin Auton Res. 2003;13:316-20.
19. Möltner A, Hölzl R, Strian F. Heart rate changes as an autonomic component of the pain response. Pain. 1990;43:81-9.
20. Demirtaş AO, Urgun OD. Can QT interval prolongation or dispersion detected in a positive exercise ECG test predict critical coronary artery disease? Arch Med Sci Atheroscler Dis. 2019;4:e7-12.
21. Diedrich A, Jordan J, Shannon JR, Robertson D, Biaggioni I. Modulation of QT interval during autonomic nervous system blockade in humans. Circulation. 2002;106:2238-43.
22. Busjahn A, Knoblauch H, Faulhaber HD, Boeckel T, Rosenthal M, Uhlmann R, et al. QT interval is linked to 2 long-QT syndrome loci in normal subjects. Circulation. 1999;99:3161-4.
23. Tennant F. The Physiologic Effects of Pain on the Endocrine System. Pain Ther. 2013;2:75-86.
24. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Decreased heart rate variability in men with phobic anxiety (data from the Normative Aging Study). Am J Cardiol. 1995;75:882-5.
25. Vrtovec B, Delgado R, Zewail A, Thomas CD, Richartz BM, RadovancevicB. Prolonged QTc interval and high B-type natriuretic peptide levels together predict mortality in patients with advanced heart failure. Circulation. 2003;107:1764-9.