AJEM-42275: Research Article

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

Meral Tandoğan, Emine Emektar, SEDA Dağar, Yucel Yuzbasioglu, Handan Özen Olcay, Tuba Şafak, Yavuz Katırcı, Yunsur Cevik
University of Health Sciences, Keçiören Training and Research Hospital

Introduction
In this study, we aimed to evaluate changes of 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 ages and sex. Electrocardiographies (ECG) were taken at the time of admittance and one hour after pain relief. The data were analyzed with the SPSS 16 program.
Results
100 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 renal colic, may cause cardiac responses, such as arrhythmias.

Keywords: Pain, P wave, QT dispersion, T p-e, T p-e dispersion, T p-e/QT ratio; Renal Colic
Short Title in English: effect of pain in 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).Inaddition to subjective effects inthe organ or tissue of origin, painmay cause several autonomic or hormonal responses. An important cause of emergent admittances is pain. Urolithiasis causes severe pain,andpatients with renal colic are often admit to the emergency department (ED) with painthatthey define as the most severe pain of their lives (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 tosympathetic stimulation with vasoconstriction. This coronary arterial spasm may cause angina, myocardial ischemia, and even infarction(3, 4).In addition, autonomic changes induce several arrythmias 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 the evaluation of ventricular repolarization by ECG, measurement of the QT interval and correction of this

measurement by using heart rate (QTc) are usually used.An increase of QT dispersion, which is an indicator of regional heterogeneity in myocardial repolarization, may cause severe arrythmias 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 Tp-e/QTc rate, which is calculated by the division of the Tp-e interval by QTc, and life-threatening ventricular arrythmias (7–9).

Several studies haveinvestigatedtransmyocardial repolarization parameters in several diseases, but there has beenno study about effects of pain on these parameters (7, 9–11). Therefore, in this study we aimed to investigate changes of 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 clinicalstudy. Ethical approval for study was obtained from the 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 a 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, who did not have any pathologic cardiac conditions, that presented to the ED with flank pain and were diagnosed with reno-ureteral colicwereincluded inthe study. Patients who were admitted to the ED with the same back pain and dysuria thattheyhad 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 visual analog scale 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 1st 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 values and minimum values. The QTc was calculatedusingBazett's formula. The Tp-e was described as the time between the peak of the T-wave and theend 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 by using the "tangent" method (9). The Tp-e/QTc ratio was calculated in the precordial leads.

Exclusion Criteria

The study excluded patientswithany 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,suchasbranch blocks, pathological Q-waves, or left-ventricular hypertrophy. In addition, pregnant or lactating patients, andpatientswhodidnotagree 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 analyses

Statistical analyses were performed using 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 KolmogrowSmirnowtest was used to assess the normal distribution of the variables. Nonparametric categorical parameters were analyzed using the Chi-square test, and nonparametric 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).Duringour study a 2msn 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 groups.

Results

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

According to the ECG parametersheart rate, P wave duration, Pd, QT, QTc, and QTd were 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 were significantly higher in the paingroup than in the control group (For all parameters $p <0.001$). The electrocardiographic parameters of both the groups are shown in Table 2.

When it was compared both two ECGs recorded at the admission and one hour after the treatment, it was seen thatPd, QT, QTd were similar in 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 were significantly higher in the first ECGs($p<0.001$, $p=0.01$, $p=0.003$, $p<0.001$, $p<0.001$ respectively). The electrocardiographic parameters of 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-eintervaland increased Tp-e/ QTc ratio, which could be associated with cardiac rhythm disturbance, in 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 any cardiac influences like arrythmias 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 exposed the relationship between prolonged P wave indices in paroxysmal AF, and recurrent AF after cardioversion or cardiothoracic surgery. In addition, some cross-sectional studies exposed 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 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.Yavuz et al shown that P-wave dispersion was found to be prolonged in panic disorder patients (17). Moreover, in anxiety disorders it has been shown that arrhythmia and P-wave dispersion is associated with state anxiety more than trait anxiety (17). 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 cardiovascular system by the effects of 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 of 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, diarrheaandvasoconstriction. In the literature also there are studies that shows the effects of autonomic nervous system on QT interval (21, 22). The QT interval reflects the depolarization and repolarization in myocardial cells. The factors that increase depolarization or retard repolarization of myocardial cells may prolong measurement of QT interval. In addition, genetic and non-genetic factors besides electrolyte abnormalities and drugs also affect QTc. Moreover, there are indirect evidences about activity of autonomic nervous system affects QTc (22). Pain also signals the hypothalamus and pituitary to release adrenocorticotropin hormone (ACTH) which 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 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 arrythmias 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 the present study, Tp-e interval and Tp-e/QT ratiowere higher in the patient groupwhen compared with 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 role inincreasedTp-e interval and Tp-e/QT.

Limitations

The present study had some limitations. Endpoint of our study included only a short-term period;we did not follow patients for longer period. Additionally, in the study, we did not measure 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.

Conclusions

The present study found that compared to the control group, patients have 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 think that physicians should be aware of several cardiac events and related clinical signs, in patients with any cause of severe pain.

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Table 1 Demographic findings of the study and control groups

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

VAS: Visual analog scale

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, Tp-e: T wave peak-to-end interval,

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, Tp-e: T wave peak-to-end interval