

Ventricular repolarization wave variations during the amiodarone treatment course

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Abstract

The aim of this study was to assess ventricular repolarization wave variations during the amiodarone treatment course for patients with ventricular arrhythmias and atrial fibrillation.

Sixty-nine patients with ventricular arrhythmias and 9 patients with persistent atrial fibrillation were treated with intravenous injection of a 150 mg loading dose of amiodarone, followed by 1 mg/minute for 6 hours and 0.5 mg/minute for 48 hours. After the initial 24 hours of intravenous injection, amiodarone was also administered orally at a dose of 0.2 g tid for 1 week; followed by 0.2 g bid for 1 week and 0.2 g qd for maintenance. During the procedure, the heart rate, QT, QTc, QTd, QTcd TpTe, TpTe-c, TpTe-d, TpTe/QT, and QTp were measured on days 1, 3, 7, 10, 14, 17, and 20 of amiodarone treatment.

The control rate of arrhythmias was 91.0% (71/78). The heart rate dropped significantly on the 7th day after treatment initiation and reached the minimal value on day 14. The QT interval was prolonged from day 3; TpTe was prolonged from day 7 to day 14; QTp was prolonged from day 1 to day 20. The longest QT interval (441.2 ± 33.9 ms) and TpTe (95.0 ± 18.0 ms) occurred on day 14. QTc, QTd, QTcd, TpTe-c, TpTe-d, and TpTe/QT showed no significant changes throughout the treatment.

Amiodarone lowers the heart rate, prolongs QT and QTp intervals, and transiently prolongs TpTe. However, it has no effects on QTc, QTd, QTcd, TpTe-c, TpTe-d or TpTe/QT. Amiodarone prolongs QT interval evenly, showing no effects on repolarization dispersion. TpTe/QT is a better indicator of ventricular transmural repolarization dispersion compared with TpTe.

Abbreviations: EAD = early after depolarization, QTd = QT dispersion, TDR = transmural dispersion of repolarization.

Keywords: amiodarone, heart rate, QT, TpTe, TpTe/QT

1. Introduction

Cytological studies have shown that transmural dispersion of repolarization (TDR) and early after depolarization (EAD) are strong predictors of malignant arrhythmias. Application of QT dispersion (QTd) in evaluating TDR has not been fully recognized by the electrocardiography (ECG) academia. In recent years, TpTe (width from the T-wave peak to T-wave end) is considered to be related to TDR.^[1,2] The beginning of the T wave corresponds to the start of epicardial repolarization. When the T wave peaks, the epicardium achieves complete repolarization. There is a maximum potential difference between the endocardium and epicardium,^[3] which constitutes a vulnerable period that is sensitive to EAD, thereby leading to reentry and triggering malignant arrhythmias. It was suggested that TpTe prolongation in resting ECG is relevant to sudden cardiac

death.^[4] Elevated TpTe and TpTe/QT values in cardiac resynchronization therapy are related to defibrillation of ventricular arrhythmia events.^[5] However, the various findings are not entirely consistent. In vivo cardiac studies in pigs have shown that TpTe is not related to TDR.^[6] Ventricular repolarization heterogeneity is related to severe life-threatening arrhythmias. Amiodarone can effectively treat ventricular arrhythmias, especially ventricular tachycardia after myocardial infarction or secondary to chronic heart failure. It can reduce mortality caused by arrhythmias, thereby becoming an indispensable drug in antiarrhythmic treatments.^[7] Assessing the impact of amiodarone on ventricular repolarization wave can help understand the indexes of ventricular repolarization dispersion. A report on amiodarone in treating arrhythmias after acute myocardial infarction revealed that TpTe is prolonged by amiodarone.^[8] If TpTe reflects TDR, the question is therefore whether amiodarone leads to increase TDR heterogeneity. This is inconsistent with the clinical efficacy of amiodarone in ventricular arrhythmias. Therefore, this study aimed to assess the effect of amiodarone on ventricular arrhythmias and atrial fibrillation, as well as ventricular repolarization wave variations during the treatment course.

2. Methods and materials

2.1. Case selection

From January 2012 to June 2014, 78 patients were admitted in the Department of Cardiology. Of these, 14 cases were diagnosed with frequent premature ventricular contractions, 26 had nonsustained ventricular tachycardia, 29 had sustained ventricular tachycardia, and 9 presented with persistent atrial fibrilla-

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tion diagnosed by ECG and Holter monitor (24 hours). Patients with QT interval prolongation syndromes (QT > 0.44 seconds), bundle branch blocks, intraventricular blocks, and thyroid dysfunction were excluded. The patient population included 50 males ranging from 38 to 90 years of age (64.5 ± 10.8 years) and 28 females ranging from 48 to 80 years of age (62.7 ± 13.9 years). Causes included acute myocardial infarction (26 cases), old myocardial infarction and ischemic cardiomyopathy (21 cases), hypertensive heart disease (13 cases), alcoholic cardiomyopathy (1 case), dilated cardiomyopathy (5 cases), nonobstructive hypertrophic cardiomyopathy (1 case), hypertrophic obstructive cardiomyopathy (1 case), arrhythmogenic right ventricular cardiomyopathy (1 case), idiopathic ventricular tachycardia (4 cases), lone atrial fibrillation (3 cases), pericardial effusion (1 case), and myocarditis (1 case).

On December 20th 2011, the ethics committee of North China University of Science and Technology Affiliated Hospital approved the study protocol, and informed consent was provided by the patients.

2.2. Treatment protocol

All 78 patients were treated with intravenous injection and oral administration of amiodarone. Before using amiodarone, all cases had no previous treatment with antiarrhythmic drugs based on conventional clinical therapeutics such as β blockers, ACEI, and so on. The treatment protocol was as follows: intravenous injection of amiodarone (150 mg) for 10 minutes, followed by 1 mg/minute for 6 hours and 0.5 mg/minute for 48 hours. Concurrent oral administration of amiodarone was started 24 hours after intravenous injection at 0.2 g tid for 1 week, 0.2 g bid for 1 week, and finally 0.2 g qd. The treatment was maintained if effective and discontinued after 3 weeks if ineffective. Effectiveness standards were as follows: no sustained ventricular tachycardia, reduction of nonsustained ventricular tachycardia by at least 90%, and reduction of premature ventricular contraction by at least 80%. According to the protocol, 71 and 7 patients were assigned to the “effective” and “ineffective” groups, respectively. Heart rate, QT, QTc, QTd, QTcd, TpTe, TpTe-c, TpTe-d, TpTe/QT, and QTp were monitored on days 1, 3, 7, 10, 14, 17, and 20 of amiodarone treatment.

2.3. Detection methods

Synchronous 12-lead ECG (GE MAC1200ST) simultaneously recorded 12-lead surface ECG with a chart speed of 25 mm/second and a gain at 10 mV. Appointed staff (a deputy chief physician) measured at least 6 leads of each ECG, where chest leads were V3, V4, and V5, based on current recommendations.^[9,10] Each lead measured 3 values in a row, and the average value was recorded. The QT interval was measured from the start of the QRS complex to the intersection of the T-wave and equipotential line (tangent line of the lower slope of the T wave). If there was a U wave, the lowest point of the intersection between the T and U waves was considered the standard. Leads with difficult-to-confirm T-waves were excluded, and maximum (QTmax) and minimum (QTmin) QT intervals were measured, respectively. QTd (QT dispersion) = QTmax - QTmin. QT = (QTmax + QTmin)/2. QTc (heart rate corrected QT interval) = [QTc(max) + QTc(min)]/2. QTc(max) = QT(max)/ $\sqrt{R-R}$, QTc(min) = QT(min)/ $\sqrt{R-R}$. $\sqrt{R-R}$ = square root of the average R-R interval of 3 cardiac cycles. QTcd (QTc dispersion) = QTc(max) - QTc(min). The QTp interval was measured from the

beginning of the QRS complex to the focus of the vertical T wave peak to baseline. When inversion or bidirectional T-waves appeared, they were measured to the bottom. If the T-waves had double peaks, the 2nd peak was measured. TpTe was not measured by leads with T-wave amplitude < 1.5 mm. TpTe(max) and TpTe(min) were measured and recorded. TpTe-d (TpTe dispersion) = TpTe(max) - TpTe(min). TpTe-c (heart rate corrected TpTe) = [TpTe-c(max) + TpTe-c(min)]/2, TpTe-c(max) = TpTe(max)/ \sqrt{RR} , TpTe-c(min) = TpTe(min)/ \sqrt{RR} . QTp was the starting point of the QRS wave to the peak of the T wave = QT - TpTe.

2.4. Statistical methods

The SPSS12.0 statistical software was used for analyses. Normality of continuous data was assessed by the Kolmogorov-Smirnov test. Normally distributed data were displayed as mean ± standard deviation. ANOVA repeated measures were performed to evaluate variables at different time points and paired *t* test was used as the post-hoc test. *P* < .05 was considered statistically significant.

3. Results

3.1. Arrhythmia control and adverse events

The control rate of arrhythmias was 91.0% (71/78). Treatment was ineffective in 7 cases, including 2 cases of ischemic cardiomyopathy and atrial fibrillation and 1 case of persistent hypertension and atrial fibrillation, who failed to achieve sinus rhythm; 1 case of acute myocardial infarction and nonsustained ventricular tachycardia who died of fibrillation; 1 case of ischemic cardiomyopathy, who presented sustained ventricular tachycardia, was treated with electrical cardioversion and discontinued amiodarone due to prolonged QT interval; and 2 cases of idiopathic ventricular tachycardia. During the treatment, there were 15 cases of mild gastrointestinal reactions. A total of 3 cases (2 cases of acute myocardial infarction and 1 case of atrial fibrillation) discontinued amiodarone due to heart rate below 45 beats/minute; 3 cases discontinued amiodarone momentarily for the development of ventricular fibrillation and continued amiodarone after successful electrical cardioversion. No other adverse reaction was observed. After excluding patients with ineffective treatment or treatment intolerance, complete measurement data were available for 68 patients from postadmission day 1 to day 7, for 65 patients from day 10 to day 17, and for 62 patients on day 20.

3.2. Heart rates before and after amiodarone treatment

As shown in Table 1, heart rates were decreased significantly compared with pre-treatment values, starting on day 7th after treatment and reached the minimal value on day 14, then stabilized afterwards. Heart rates on day 14 were also significantly different from the values recorded for days 1 and 3.

3.3. QT intervals before and after amiodarone treatment

Compared with pretreatment values, QT intervals were significantly prolonged starting on day 3 after treatment, continued to prolong with treatment time, and peaked on day 14. QT intervals on day 14 were also significantly different from day 1 values.

Table 1
Effects of amiodarone on heart rate, QT, QTc, QTd, and QTcd during treatment for ventricular arrhythmias in the effective group.

Time	n	Heart rate, beat/min	QT, ms	QTc, ms	QTd, ms	QTcd, ms
Pretreatment	68	73 ± 12	383.8 ± 28.6	414.6 ± 26.3	48.0 ± 29.5	50.0 ± 32.9
Day 1	68	72 ± 14	399.6 ± 39.0	432.5 ± 28.0	56.9 ± 22.1	60.0 ± 32.9
Day 3	68	69 ± 11	415.8 ± 33.2*	444.4 ± 34.6	55.4 ± 27.0	71.2 ± 30.9
Day 7	68	63 ± 8*	428.9 ± 28.8*	430.8 ± 26.3	47.7 ± 33.5	50.0 ± 32.4
Day 10	65	62 ± 8**	435.4 ± 23.4**	431.2 ± 24.3	51.5 ± 27.3	50.0 ± 36.6
Day 14	65	60 ± 9**	441.2 ± 33.9**	438.5 ± 26.0	59.2 ± 26.6	60.0 ± 26.1
Day 17	65	64 ± 7*	418.9 ± 36.7*	425.4 ± 26.9	57.7 ± 14.8	57.5 ± 15.8
Day 20	62	62 ± 8*	423.1 ± 28.7*	426.3 ± 27.9	51.7 ± 26.6	51.7 ± 28.9
F		4.191	6.554	1.576	0.576	0.723
P		.005	<.001	.167	.748	.633

*Statistically significant difference compared with pretreatment, P < .05.

**Statistically significant difference compared with day 1, P < .05.

3.4. TpTe, TpTe-c, TpTe-d, QTp, and TpTe/QT before and after amiodarone treatment

As shown in Table 2, TpTe was significantly prolonged from day 7 to day 14. However, no differences were observed on days 17 and 20, compared with day 1. The QTp interval was also significantly prolonged from day 1 to day 20. No significant differences were observed in TpTe-c, TpTe-d, and TpTe/QT before and after treatment, indicating that amiodarone transiently prolonged TpTe while had no impact on TpTe-c, TpTe-d, and TpTe/QT.

3.5. QTc, QTd, and QTcd before and after amiodarone treatment

As shown in Table 1, there were no statistically significant differences in QTc, QTd, and QTcd from day 1 to day 20, implying that amiodarone did not affect QTc QTd and QTcd.

4. Discussion

Amiodarone is a safe and effective treatment for organic cardiomyopathy and arrhythmias, with a successful rate of 76% to 94%.^[11,12] The electrophysiological effects of amiodarone are complex. It blocks fast sodium channels, L-type calcium channels, and Ikr; reduces sino-atrial node automaticity and atrioventricular conduction; decreases automaticity and conduction of Purkinje fibers; and prolongs ADP, effective refractive period, QRS complex, and QT interval.

In vitro studies have shown that the antiarrhythmic effects of amiodarone are related to TDR reduction in the myocardium.^[13] Dispersion is the expression of different ion flows between the myocardial wall, but no clinical evidence has been reported. The reason may be that ECG monitoring of cardiac electrical activity is an effective method, and the relationship between ECG morphology and cardiac repolarization heterogeneity has not been fully clarified. Using QTd to evaluate heterogeneity is not consistently accepted, although it is used to evaluate the dispersion index of the entire heart.

This study illustrated that upon oral administration of amiodarone after intravenous treatment, QTp was prolonged first, followed by QT (prolonged on the 3rd day) and TpTe (prolonged on the 7th day); the heart rate was reduced. QTc, QTd, QTcd, TpTe-c, TpTe-d, and TpTe/QT showed no significant changes throughout the treatment. These findings suggested that the clinical use of oral amiodarone after intravenous administration results in prolonged QT interval, which was most obvious for QTp; TpTe was only transiently prolonged, and no significant effect was observed on repolarization dispersion.

Intravenous and oral amiodarone treatments are different in pharmacokinetics and electrophysiological effects. Intravenous amiodarone acts fast, taking effect within a few minutes; the plasma half-life of amiodarone was short. However, oral amiodarone has large apparent volume of distribution, taking several weeks to reach the steady state of blood concentration, with overt individual differences in bioavailability. After

Table 2
Effects of amiodarone on TpTe, TpTe-c, TpTe-d, QTp, and TpTe/QT during treatment for ventricular arrhythmias in the effective group.

Time	n	TpTe, ms	TpTe-c, ms	TpTe-d, ms	QTp, ms	TpTe/QT
Pretreatment	68	77.3 ± 14.9	83.8 ± 13.9	25.4 ± 19.5	305.7 ± 35.0	0.20 ± 0.04
Day 1	68	72.7 ± 16.0	78.2 ± 14.0	29.2 ± 18.6	345.0 ± 28.9*	0.18 ± 0.35
Day 3	68	81.9 ± 12.7	86.1 ± 16.5	27.7 ± 14.8	343.6 ± 34.5*	0.20 ± 0.03
Day 7	68	91.9 ± 13.9**	93.5 ± 13.9	27.7 ± 19.2	347.3 ± 40.2*	0.22 ± 0.03
Day 10	65	89.2 ± 15.9**	88.4 ± 17.6	25.0 ± 15.8	349.3 ± 38.13*	0.21 ± 0.04
Day 14	65	95.0 ± 18.0**	94.1 ± 15.7	23.9 ± 12.6	352.9 ± 49.3*	0.22 ± 0.04
Day 17	65	80.8 ± 15.3	82.9 ± 15.9	17.5 ± 11.6	346.2 ± 32.6*	0.19 ± 0.04
Day 20	62	81.3 ± 14.3	76.0 ± 20.7	20.0 ± 12.3	340.7 ± 39.4*	0.20 ± 0.04
F		3.653	1.747	2.731	3.112	1.446
P		.003	.122	.069	.009	.209

*Statistically significant difference compared with pretreatment, P < .05.

**Statistically significant difference compared with day 1, P < .05.

intravenous injection, plasma drug concentration decreases rapidly. This is not because its elimination half-life is short, but due to amiodarone redistribution in tissues from plasma. Indeed, it was reported that the clinical efficacy of amiodarone is positively correlated with myocardial drug concentration and not with plasma concentration.^[6] Intravenous amiodarone has reduced effects on the heart rate and QT, while oral amiodarone significantly decreases the heart rate and prolonged the QT interval. Since amiodarone is clinically safe and has few arrhythmogenic effects, it is widely used for the treatment of ventricular arrhythmias caused by various causes, drug cardioversion in atrial fibrillation, and sinus rhythm maintenance in paroxysmal atrial fibrillation and ventricular rate control in critically ill patients with atrial fibrillation. The recommended drug regimen for clinical use is amiodarone, 150 mg, intravenous injection for 10 minutes, followed by 1 mg/kg for 6 hours, and then reduced to 0.5 mg/kg for maintenance. In patients with high risk recurrence, 24 hours after intravenous amiodarone, oral amiodarone 0.2 g tid is added for 1 week, 0.2 g bid for 1 week, and 0.2 g qd. The pharmacokinetics and electrophysiological effects of oral amiodarone after intravenous administration are more complicated. This study showed that addition of oral preparations after intravenous administration led to decreased heart rate, and the QT interval was most obviously prolonged at the 14th day, suggesting that oral amiodarone after intravenous administration requires about 2 weeks to reach the steady-state of myocardial drug concentration and therapeutic effects, which is faster than direct oral load medication for 3 to 4 weeks.

TpTe, the period from the T-wave peak to the T-wave end, is related to TDR. The beginning of the T wave corresponds to the beginning of epicardial repolarization. When the T wave peaks, the epicardium achieves complete repolarization. At this time, M cells are still repolarized. There is a maximum potential difference between the endocardium and epicardium; this is a vulnerable period which is sensitive to EADs, inducing ventricular arrhythmias.^[3]

Therefore, TpTe, associated with TDR, is considered a predictor of arrhythmias. It was shown that TpTe is an EEG parameter and predictor of ventricular tachycardia occurrence and associated sudden death in patients with coronary diseases.^[4,14] In addition, TpTe prolongation is considered a risk factor for the occurrence of torsades de pointes in acquired long QT syndrome,^[15] and is associated with the risk of spontaneous and induced ventricular tachycardia in organic heart disease.^[16]

Smetana et al^[18] used amiodarone to treat arrhythmias after acute myocardial infarction, and revealed prolonged TpTe compared with the placebo control. This observation conclusion contradicted our clinical findings that amiodarone is a safe and effective antiarrhythmic drug, as TpTe is currently considered an indicator of transmural dispersion of the ventricular wall and a risk factor for arrhythmia. It was possible that TpTe was associated with heart rate changes. Smetana claimed that the TpTe prolongation by amiodarone in patients with acute myocardial infarction is heart rate dependent. The TpTe/QT interval was less affected by the heart rate and may become an alternative indicator of TpTe.^[17] In addition, amiodarone prolonged the duration of action potential to achieve antiarrhythmic effects, and simultaneously prolonged the QRS, QTp, QT, and TpTe intervals. Compared with other antiarrhythmic drugs, there may be differences in the extent of prolonging various parts of the action potential, resulting in reduced arrhythmogenic effects.

In the early stage of ischemia in patients with coronary heart disease, delayed myocardial activation is mainly inner-wall delay

and not delayed along different parts of the epicardium.^[18] It remains unclear whether TpTe in ECG reflects the local transmural dispersion of the myocardium or overall dispersion of the heart. In vivo cardiac studies in pigs have shown that TpPe is not related to transmural dispersion, but is rather an indicator of overall dispersion of the heart.^[6,19] Therefore, TpPe might represent a combination of overall dispersion of the heart and transmural dispersion.

When TpTe prolongation exceeds 100 ms, it is generally considered to be related to arrhythmias.^[19] In this study, the maximum prolongation of TpTe was 95 ms on day 14, which did not reach the dangerous level of 100 ms. In addition, compared with selective class III antiarrhythmic medications, amiodarone extended TpTe but reduced it after depolarization; therefore, it did not increase the risk of arrhythmias. Kim et al^[20] assessed implantable cardioverter defibrillator electrogram and found no significant change in TpTe before discharge of clinical events. Smetana et al^[21] reported shortened TpTe in patients that died from cardiovascular diseases compared with those that survived. Thus, TpTe as a clinical indicator of TDR should be further explored.

The present study is not without limitations. Patients with various types of disease entities were included in the present study and the small sample size limited further subgroup analysis. Acute myocardial infarction and revascularization both affect TpTe.^[22,23] Accordingly, this study could not rule out the potential impacts of different diseases on TpTe.

Author contributions

Funding acquisition: Hong Zhao.

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References

- Taggart P, Sutton PM, Opthof T, et al. Transmural repolarisation in the left ventricle in humans during normoxia and ischaemia. *Cardiovasc Res* 2001;50:454–62.
- Antzelevitch C, Sicouri S, Litovsky SH, et al. Heterogeneity within the ventricular wall. Electrophysiology and pharmacology of epicardial, endocardial, and M cells. *Circ Res* 1991;69:1427–49.
- Antzelevitch C. T peak-Tend interval as an index of transmural dispersion of repolarization. *Eur J Clin Invest* 2001;31:555–7.
- Panikkath R, Reinier K, Uy-Evanado A, et al. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. *Circ Arrhythm Electrophysiol* 2011;4:441–7.
- Barbhaiya C, Po JR, Hanon S, et al. Tpeak – Tend and Tpeak – Tend /QT ratio as markers of ventricular arrhythmia risk in cardiac resynchronization therapy patients. *Pacing Clin Electrophysiol* 2013;36:103–8.
- Xia Y, Liang Y, Kongstad O, et al. 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.
- Claro JC, Candia R, Rada G, et al. Amiodarone versus other pharmacological interventions for prevention of sudden cardiac death. *Cochrane Database Syst Rev* 2015;12:Cd008093.
- Smetana P, Pueyo E, Hnatkova K, et al. Effect of amiodarone on the descending limb of the T wave. *Am J Cardiol* 2003;92:742–6.
- Wolk R, Mazurek T, Lusawa T, et al. Left ventricular hypertrophy increases transepical dispersion of repolarisation in hypertensive patients: a differential effect on QTpeak and QTend dispersion. *Eur J Clin Invest* 2001;31:563–9.

- [10] Emori T, Antzelevitch C. Cellular basis for complex T waves and arrhythmic activity following combined I(Kr) and I(Ks) block. *J Cardiovasc Electrophysiol* 2001;12:1369–78.
- [11] Song MF. Clinical investigation of amiodarone in the treatment of chronic heart failure with ventricular arrhythmias. *Med Innov China* 2009;6:61–2.
- [12] Ma YC, Ma X, Liu MX, et al. Clinical observation of amiodarone in the treatment of heart failure complicated by ventricular arrhythmias in senile patients. *Chin J Difficult Complicat Cases* 2004;3:142–3.
- [13] Sicouri S, Moro S, Litovsky S, et al. Chronic amiodarone reduces transmural dispersion of repolarization in the canine heart. *J Cardiovasc Electrophysiol* 1997;8:1269–79.
- [14] Lubinski A, Kornacewicz-Jach Z, Wnuk-Wojnar AM, et al. The terminal portion of the T wave: a new electrocardiographic marker of risk of ventricular arrhythmias. *Pacing Clin Electrophysiol* 2000;23(11 Pt 2):1957–9.
- [15] Topilski I, Rogowski O, Rosso R, et al. The morphology of the QT interval predicts torsade de pointes during acquired bradyarrhythmias. *J Am Coll Cardiol* 2007;49:320–8.
- [16] Watanabe N, Kobayashi Y, Tanno K, et al. Transmural dispersion of repolarization and ventricular tachyarrhythmias. *J Electrocardiol* 2004;37:191–200.
- [17] Gupta P, Patel C, Patel H, et al. T(p-e)/QT ratio as an index of arrhythmogenesis. *J Electrocardiol* 2008;41:567–74.
- [18] Taggart P, Sutton PM, Opthof T, et al. Inhomogeneous transmural conduction during early ischaemia in patients with coronary artery disease. *J Mol Cell Cardiol* 2000;32:621–30.
- [19] Janse MJ, Sosunov EA, Coronel R, et al. Repolarization gradients in the canine left ventricle before and after induction of short-term cardiac memory. *Circulation* 2005;112:1711–8.
- [20] Kim JW, Pak HN, Park JH, et al. Defibrillator electrogram T wave alternans as a predictor of spontaneous ventricular tachyarrhythmias in defibrillator recipients. *Circ J* 2009;73:55–62.
- [21] Smetana P, Schmidt A, Zabel M, 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.
- [22] Haarmark C, Hansen PR, Vedel-Larsen E, et al. The prognostic value of the Tpeak-Tend interval in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *J Electrocardiol* 2009;42:555–60.
- [23] Cetin M, Zencir C, Cakici M, et al. Effect of a successful percutaneous coronary intervention for chronic total occlusion on parameters of ventricular repolarization. *Coron Artery Dis* 2014;25:705–12.