

Ibutilide and novel indexes of ventricular repolarization in persistent atrial fibrillation patients

Panagiotis Korantzopoulos, Konstantinos P Letsas, Anna Kotsia, Giannis Baltogiannis, Kallirroï Kalantzi, Konstantinos Kyrilas, John A Goudevenos

Panagiotis Korantzopoulos, Anna Kotsia, Giannis Baltogiannis, Kallirroï Kalantzi, Konstantinos Kyrilas, John A Goudevenos, Department of Cardiology, University of Ioannina Medical School, 45110 Ioannina, Greece

Konstantinos P Letsas, Second Department of Cardiology, Evangelismos General Hospital of Athens, 10675 Athens, Greece
Author contributions: Korantzopoulos P, Letsas K and Goudevenos JA contributed to the conception and design of the study, drafting the article, final approval; Kotsia A, Baltogiannis G, Kalantzi K and Kyrilas K contributed to the acquisition of data, critical revision of the article, final approval.

Correspondence to: Panagiotis Korantzopoulos, MD, PhD, Department of Cardiology, University of Ioannina Medical School, Campus, PO Box 1186, 45110 Ioannina, Greece. p.korantzopoulos@yahoo.gr

Telephone: +30-26-51045654 Fax: +30-26-51007017

Received: February 10, 2013 Revised: May 15, 2013

Accepted: June 1, 2013

Published online: July 26, 2013

Abstract

AIM: To examine the effect of ibutilide on novel indexes of repolarization in patients with persistent atrial fibrillation (AF).

METHODS: We studied consecutive patients scheduled for elective electrical cardioversion. Intravenous ibutilide (1 + 1 mg) was administered before the electrical cardioversion while close electrocardiographic (ECG) monitoring was performed. ECG indexes such as corrected QT interval (QTc), the interval from the peak until the end of T wave (Tpe), and the Tpe/QT ratio were measured before ibutilide infusion and 10 min after the end of infusion.

RESULTS: The final study population consisted of 20 patients (mean age: 67.1 ± 9.9 years, 10 men). Six patients were cardioverted pharmacologically and did not proceed to electrical cardioversion. Two patients

developed short non-sustained episodes of torsades de pointes ventricular tachycardia. All but one of the aforementioned ECG indexes increased significantly after ibutilide administration. In specific, the QTc interval increased from 442 ± 29 to 471 ± 37 ms ($P = 0.037$), the Tpe interval in precordial leads from 96 ms (range 80-108 ms) to 101 ms (range 91-119 ms) ($P = 0.021$), the Tpe interval in lead II from 79 ms (range 70-88 ms) to 100 ms (range 87-104 ms) ($P < 0.001$), the Tpe/QT ratio in precordial leads from 0.23 ms (range 0.18-0.26 ms) to 0.26 ms (range 0.23-0.28 ms) ($P = 0.028$), and the Tpe interval dispersion from 25 ms (range 23-30 ms) to 35 ms (range 27-39 ms) ($P = 0.012$). However, the Tpe/QT ratio in lead II did not change significantly.

CONCLUSION: Ibutilide increases the duration and dispersion of ventricular repolarization. The prognostic value of Tpe and Tpe/QT in the setting of drug-induced proarrhythmia needs further study.

© 2013 Baishideng. All rights reserved.

Key words: Ibutilide; Ventricular repolarization; Arrhythmic risk; Proarrhythmia; Dispersion of repolarization; T peak-to-end; T peak-to-end/QT ratio

Core tip: In this pilot study we examined the effect of ibutilide on novel indexes of repolarization in patients with persistent atrial fibrillation scheduled for electrical cardioversion. Electrocardiographic (ECG) indexes such as corrected QT interval, the interval from the peak until the end of T wave (Tpe), and the Tpe/QT ratio were measured. We showed that ibutilide significantly increases the dispersion of ventricular repolarization as assessed by modern ECG markers such as Tpe interval and Tpe/QT ratio. These indexes may have a prognostic value with regard to drug-induced proarrhythmia.

Korantzopoulos P, Letsas KP, Kotsia A, Baltogiannis G, Kalantzi

K, Kyrilas K, Goudevenos JA. Ibutilide and novel indexes of ventricular repolarization in persistent atrial fibrillation patients. *World J Cardiol* 2013; 5(7): 242-246 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i7/242.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i7.242>

INTRODUCTION

Drug-induced proarrhythmia represents a significant problem that poses special risks in the implementation of drug therapy^[1]. Several antiarrhythmic drugs seem to have proarrhythmic potential^[2,3]. Ibutilide is a class III antiarrhythmic agent effective for pharmacological cardioversion of recent-onset atrial fibrillation (AF) or atrial flutter^[4,5]. It is administered intravenously and has a rapid onset of action^[5]. In addition, ibutilide pretreatment facilitates external electrical cardioversion of persistent AF^[6-8]. However, its QT-prolonging properties and the increased risk for torsades de pointes (TdP) ventricular tachycardia raise safety concerns and limit its widespread use^[5].

A well-known pathogenetic factor for malignant ventricular arrhythmias is the increased dispersion of repolarization which reflects the heterogeneity rather than the total duration of repolarization^[9]. The T peak-to-end (Tpe) interval and the Tpe/QT ratio represent novel electrocardiographic indexes of arrhythmic risk that possibly correspond to the spatial dispersion of ventricular repolarization^[9-11]. It has also been demonstrated that in the setting of acquired QT prolongation the Tpe/QT ratio is a better predictor of TdP compared to the corrected QT interval (QTc) interval and QT dispersion^[12]. Thus, in this pilot observational study we sought to investigate the impact of ibutilide pretreatment on the aforementioned electrocardiographic (ECG) indexes in the setting of persistent AF before electrical cardioversion.

MATERIALS AND METHODS

We screened consecutive patients with persistent AF scheduled for elective electrical cardioversion. Patients taking drugs or having conditions that affect the QT interval were excluded. In specific, exclusion criteria were recent acute coronary syndrome within the past 6 mo, recent percutaneous coronary intervention or cardiac surgery, congestive heart failure with New York Heart Association class > II, presence of nonsustained ventricular tachycardia on Holter monitoring, presence of bundle branch block, QRS duration > 120 ms, previous implantation of a pacemaker or a defibrillator, administration of antiarrhythmic drugs, administration of drugs that prolong the QT interval, thyroid dysfunction, renal failure, and electrolyte disturbances. All patients were on b-blockers and/or digoxin for rate control as well as on vitamin K antagonists for anticoagulation treatment.

The patients were admitted to the coronary care unit in the morning hours. After checking the laboratory examinations, intravenous ibutilide (1 mg for 10 min +

1 mg after 20 min if the patients were still in AF) was administered at a fasting state before the electrical cardioversion while close ECG monitoring was performed. ECG indexes such as QTc, the interval from the peak until the end of T wave (Tpe) and the Tpe/QT ratio were measured before ibutilide infusion and 10 min after the end of administration.

The ECG indexes were assessed at baseline in the supine position and calculated as described in our previous reports^[13-15]. Specifically, the QT and the QTpeak intervals were measured manually on ECG recordings at a paper speed of 50 mm/s. QT interval was assessed as the time between the first deflection of QRS and the point of return of the T wave to the isoelectric line. The Tpe interval was calculated as QT-QTpeak. The QT interval was measured in as many of the 12 leads as possible while Tpe interval was assessed in lead II and in the precordial leads^[10,13-15]. The Tpe interval and the Tpe/QT ratio were calculated using the corresponding values from each lead. The measurements were obtained in 5 consecutive complexes of each lead and the resulting average value was finally accepted. In order to avoid diurnal variations, all procedures were performed during the same time interval (from 9.00 am to 11.00 am). QT interval corrected for heart rate (QTc) was calculated using the Bazett's formula ($QTc = QT/RR^{0.75}$)^[16]. The Tpe and QTc reported values were the maximum obtained values. All measurements were performed by one experienced investigator (Korantzopoulos P) who was unaware of the clinical characteristics of the study participants. To identify intraobserver variability, the ECG tracings of 6 randomly selected patients were reexamined 10 d after the initial evaluation. Intraobserver variation was less than 5%.

Statistical analysis

Continuous variables are expressed as mean \pm SD, or as median (25th-75th percentile) if their values are not normally distributed. The examination of normality was performed by the Kolmogorov-Smirnov test. Categorical variables are presented as frequencies. Comparisons of the continuous variables performed using the paired *t*-test or the non-parametric Wilcoxon signed-rank test. A two-tailed *P* value < 0.05 was considered significant. All analyses were performed using the SPSS software (version 16.0; SPSS Inc., Chicago, IL, United States).

RESULTS

The final study population consisted of 20 patients (mean age: 67.1 ± 9.9 years, 10 men). The baseline clinical and demographic characteristics of the patients are presented in Table 1. The mean duration of persistent AF before the attempted electrical cardioversion was 3 mo while the patients had preserved left ventricular ejection fraction and marginally dilated left atria (Table 1).

Six patients were cardioverted pharmacologically and did not proceed to electrical cardioversion. Two patients

Table 1 Baseline and clinical characteristics of the study population

Patients' characteristics	Value
Age (yr)	67.1 ± 9.9
Men	50%
Duration of atrial fibrillation (d)	94 ± 51
Baseline heart rate (beats per minute)	87 ± 19
Hypertension	65%
Diabetes	30%
Coronary artery disease	25%
Left ventricular ejection fraction	58% ± 7%
Left atrial diameter (mm)	41.7 ± 4.3
Sodium (mEq/L)	139.0 ± 3.0
Potassium (mEq/L)	4.4 ± 0.4

developed short non-sustained episodes of TdP ventricular tachycardia a few minutes after the infusion of the second dose. All but one of the aforementioned ECG indexes increased significantly after ibutilide administration. In specific, the QTc interval, the Tpe interval in precordial leads, the Tpe interval in lead II, the Tpe/QT ratio in precordial leads, and the Tpe interval dispersion increased (Table 2). However, the Tpe/QT ratio in lead II did not change significantly (Table 2).

DISCUSSION

In this pilot study we demonstrated that ibutilide significantly increases the total duration of repolarization reflected by the QTc interval and more importantly the dispersion of ventricular repolarization as assessed by modern ECG markers such as Tpe interval and Tpe/QT ratio.

Ibutilide confers a high risk of TdP (up to 9% of cases), although most episodes are self-terminated and do not require electrical termination^[17]. However, its proarrhythmic potential may hamper its use in several clinical settings. Besides its use for pharmaceutical cardioversion of recent-onset AF or atrial flutter, ibutilide increases the success rates of electrical cardioversion of these arrhythmias, facilitates electrical cardioversion of refractory persistent AF, and lowers energy requirements during the procedure^[6-8,17,18]. Of note, ibutilide infusion must be followed by 3-4 h of ECG monitoring to exclude TdP^[5-8].

Ibutilide prolongs repolarization by inhibition of the rapidly activating component of the delayed rectifier potassium currents (I_{Kr}) and by selective enhancement of the slow inward sodium current^[19]. It should be pointed out that the heterogeneity of ventricular repolarization is a much more important parameter for proarrhythmia compared to the total duration of repolarization. For example, it is well known that amiodarone carries a very low risk for proarrhythmia despite its QT prolonging effects^[20]. This apparent paradox is explained by the fact that amiodarone prolongs the ventricular repolarization homogeneously and does not increase transmural dispersion of repolarization^[20].

Spatial dispersion of repolarization reflects the het-

Table 2 Electrocardiographic variables before and after ibutilide infusion

Variables	Before ibutilide	After ibutilide	P value
QTc (ms)	442 ± 29	471 ± 37	0.037
Tpe in lead II (ms)	79 (70-88)	100 (87-104)	< 0.001
Tpe in precordial leads (ms)	96 (80-108)	101 (91-119)	0.021
Tpe dispersion (ms)	25 (23-30)	35 (27-39)	0.012
Tpe/QT in lead II	0.22 (0.18-0.24)	0.24 (0.22-0.28)	0.12
Tpe/QT in precordial leads	0.23 (0.18-0.26)	0.26 (0.23-0.28)	0.028

The parameters are presented as means ± SD or as median values (25th-75th percentile). QTc: Corrected QT interval; Tpe: T peak-to-end.

erogeneity of repolarization which creates voltage gradients and thus promoting ventricular arrhythmias. Tpe interval represents a promising marker of total dispersion of ventricular repolarization (transmural, apicobasal, or global)^[10]. However, the Tpe/QT ratio appears to be a more sensitive arrhythmogenic index since it remains constant despite changes in the heart rate (dynamic changes in Tpe and QT interval occur in a proportional and parallel fashion)^[10,12,21]. Remarkably, an increased Tpe/QT ratio has been associated with arrhythmic events in patients with acquired long QT syndrome^[12], in patients with hypertrophic cardiomyopathy^[22], and in cardiac resynchronization therapy patients^[23]. Also, the Tpe interval is independently associated with sudden cardiac death in the general population^[24], as well as with mortality after acute myocardial infarction^[25]. In the setting of stable coronary artery disease where exercise-induced arrhythmias represent a specific problem, we recently demonstrated that Tpe/QT ratio significantly increases at peak exercise^[13]. Very recently we also showed that these novel indexes of dispersion of repolarization including Tpe/QT are increased in individuals with early repolarization^[14] and also after hemodialysis in patients with end-stage renal disease^[15].

Taking into account the aforementioned considerations we focused on the measurement of the novel indexes Tpe and Tpe/QT in order to investigate the effects of ibutilide administration on the dispersion of ventricular repolarization in patients with AF. Accumulating evidence suggests that the older index "QTc dispersion" does not actually reflect the dispersion of ventricular repolarization^[26] and therefore we did not assess this parameter. In experimental models such as in the rabbit left ventricular wedge preparation the estimation of transmural dispersion of repolarization represented by Tpe interval and Tpe/QT ratio proved to be a useful tool for the prediction of drug-induced QT prolongation and proarrhythmic potential^[27]. In this context, Yamaguchi *et al.*^[12] showed that Tpe/QT ratio is a better predictor of TdP compared to QTc interval and QT dispersion in the setting of acquired QT prolongation. With regard to ibutilide, Kannankeril *et al.*^[28] recently demonstrated that QT prolongation by the drug does not correlate to baseline QTc and does not differ between the 2 sexes. Given that

the QT prolongation by ibutilide is highly variable and does not accurately predict the occurrence of TdP the assessment of dispersion of ventricular repolarization may confer an advantage for this purpose.

Limitations

We feel that our study adds to the current knowledge of drug-induced proarrhythmia and its evaluation through novel ECG markers of dispersion of repolarization. However, some limitations are apparent. Firstly, the study population was small. Secondly, due to the limited number of patients it was not feasible to compare the indexes of repolarization between patients who suffered short episodes of TdP ($n = 2$) and patients who did not suffer any ventricular arrhythmia ($n = 18$). Thirdly, we have to acknowledge that our patients did not have significant comorbidities and especially they did not have significant LV dysfunction. The effect of ibutilide on ventricular repolarization may be more prominent in more advanced heart disease states. Finally, although we measurements of the ECG were obtained in 5 consecutive complexes of each lead and the resulting average value was finally accepted, we have to admit that the high variability of the RR intervals during AF poses specific problems in the accuracy of measurements.

In conclusion, ibutilide administration increases the duration and the dispersion of ventricular repolarization. Therefore, Tpe interval and Tpe/QT ratio may represent useful prognostic markers for the occurrence of TdP after ibutilide infusion. Undoubtedly, the prognostic role of these ECG indexes and their variations in the setting of drug-induced proarrhythmia needs further study.

COMMENTS

Background

Drug-induced proarrhythmia represents a significant problem that poses special risks in the implementation of drug therapy. Several antiarrhythmic drugs seem to have proarrhythmic potential. Ibutilide is a class III antiarrhythmic agent effective for pharmacological cardioversion of recent-onset atrial fibrillation (AF) or atrial flutter. It is administered intravenously and has a rapid onset of action. In addition, ibutilide pretreatment facilitates external electrical cardioversion of persistent AF.

Research frontiers

Electrocardiographic (ECG) indexes such as corrected QT interval, the interval from the peak until the end of T wave (Tpe), and the Tpe/QT ratio were measured.

Innovations and breakthroughs

In this pilot study authors examined the effect of ibutilide on novel indexes of repolarization in patients with persistent atrial fibrillation scheduled for electrical cardioversion. Authors showed that ibutilide significantly increases the dispersion of ventricular repolarization as assessed by modern ECG markers such as Tpe interval and Tpe/QT ratio. These indexes may have a prognostic value with regard to drug-induced proarrhythmia.

Peer review

According to this report 10% of the subjects developed short episodes of TdP and 30% were pharmacologically converted into sinus rhythm. It demonstrated the significant side effects and proarrhythmic profile of ibutilide. It has been nicely shown that the novel tools of Tpe interval and Tpe/QT are useful for the prediction of ibutilide-induced QT prolongation compared the classic QTc interval.

REFERENCES

- 1 **Kannankeril P**, Roden DM, Darbar D. Drug-induced long QT syndrome. *Pharmacol Rev* 2010; **62**: 760-781 [PMID: 21079043 DOI: 10.1124/pr.110.003723]
- 2 **Estrada JC**, Darbar D. Clinical use of and future perspectives on antiarrhythmic drugs. *Eur J Clin Pharmacol* 2008; **64**: 1139-1146 [PMID: 18762931 DOI: 10.1007/s00228-008-0555-x]
- 3 **Camm J**. Antiarrhythmic drugs for the maintenance of sinus rhythm: risks and benefits. *Int J Cardiol* 2012; **155**: 362-371 [PMID: 21708411 DOI: 10.1016/j.ijcard.2011.06.012]
- 4 **Camm AJ**, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Vardas P, Al-Attar N, Alfieri O, Angelini A, Blömstrom-Lundqvist C, Colonna P, De Sutter J, Ernst S, Goette A, Gorenek B, Hatala R, Heidbüchel H, Heldal M, Kristensen SD, Kolh P, Le Heuzey JY, Mavrakis H, Mont L, Filardi PP, Ponikowski P, Prendergast B, Rutten FH, Schotten U, Van Gelder IC, Verheugt FW. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012; **33**: 2719-2747 [PMID: 22922413 DOI: 10.1093/eurheartj/ehs253]
- 5 **Nair M**, George LK, Koshy SK. Safety and efficacy of ibutilide in cardioversion of atrial flutter and fibrillation. *J Am Board Fam Med* 2011; **24**: 86-92 [PMID: 21209348 DOI: 10.3122/jabfm.2011.01.080096]
- 6 **Oral H**, Souza JJ, Michaud GF, Knight BP, Goyal R, Strickberger SA, Morady F. Facilitating transthoracic cardioversion of atrial fibrillation with ibutilide pretreatment. *N Engl J Med* 1999; **340**: 1849-1854 [PMID: 10369847]
- 7 **Li H**, Natale A, Tomassoni G, Beheiry S, Cooper P, Leonelli F, Easley A, Barrington W, Windle J. Usefulness of ibutilide in facilitating successful external cardioversion of refractory atrial fibrillation. *Am J Cardiol* 1999; **84**: 1096-1098, A10 [PMID: 10569674]
- 8 **Naegeli B**, Straumann E, Bertel O. Ibutilide in persistent atrial fibrillation refractory to conventional cardioversion methods. *Int J Cardiol* 2005; **99**: 283-287 [PMID: 15749188]
- 9 **Antzelevitch C**. Role of spatial dispersion of repolarization in inherited and acquired sudden cardiac death syndromes. *Am J Physiol Heart Circ Physiol* 2007; **293**: H2024-H2038 [PMID: 17586620]
- 10 **Gupta P**, Patel C, Patel H, Narayanaswamy S, Malhotra B, Green JT, Yan GX. T(p-e)/QT ratio as an index of arrhythmogenesis. *J Electrocardiol* 2008; **41**: 567-574 [PMID: 18790499 DOI: 10.1016/j.jelectrocard.2008.07.016]
- 11 **Kors JA**, Ritsema van Eck HJ, van Herpen G. The meaning of the Tp-Te interval and its diagnostic value. *J Electrocardiol* 2008; **41**: 575-580 [PMID: 18954608 DOI: 10.1016/j.jelectrocard.2008.07.030]
- 12 **Yamaguchi M**, Shimizu M, Ino H, Terai H, Uchiyama K, Oe K, Mabuchi T, Konno T, Kaneda T, Mabuchi H. T wave peak-to-end interval and QT dispersion in acquired long QT syndrome: a new index for arrhythmogenicity. *Clin Sci (Lond)* 2003; **105**: 671-676 [PMID: 12857349]
- 13 **Korantzopoulos P**, Letsas KP, Christogiannis Z, Kalantzi K, Massis I, Millionis HJ, Pappas C, Goudevenos JA. Exercise-induced repolarization changes in patients with stable coronary artery disease. *Am J Cardiol* 2011; **107**: 37-40 [PMID: 21146683 DOI: 10.1016/j.amjcard.2010.08.038]

- 14 **Letsas KP**, Charalampous C, Korantzopoulos P, Tsikrikas S, Bramos D, Kollias G, Efremidis M, Sideris A. Novel indexes of heterogeneity of ventricular repolarization in subjects with early repolarization pattern. *Europace* 2012; **14**: 877-881 [PMID: 22186777 DOI: 10.1093/europace/eur390]
- 15 **Kalantzi K**, Gouva C, Letsas KP, Vlachopanou A, Foulidis V, Bechlioulis A, Katopodis KP, Goudevenos JA, Korantzopoulos P. The impact of hemodialysis on the dispersion of ventricular repolarization. *Pacing Clin Electrophysiol* 2013; **36**: 322-327 [PMID: 23305256 DOI: 10.1111/pace.12066]
- 16 **Goldenberg I**, Moss AJ, Zareba W. QT interval: how to measure it and what is "normal". *J Cardiovasc Electrophysiol* 2006; **17**: 333-336 [PMID: 16643414]
- 17 **Reiffel JA**. Cardioversion for atrial fibrillation: treatment options and advances. *Pacing Clin Electrophysiol* 2009; **32**: 1073-1084 [PMID: 19659629 DOI: 10.1111/j.1540-8159.2009.02441.x]
- 18 **Mazzocca G**, Corbucci G, Venturini E, Becuzzi L. Is pre-treatment with ibutilide useful for atrial fibrillation cardioversion when combined with biphasic shock? *J Cardiovasc Med (Hagerstown)* 2006; **7**: 124-128 [PMID: 16645372]
- 19 **Murray KT**. Ibutilide. *Circulation* 1998; **97**: 493-497 [PMID: 9490245]
- 20 **Antzelevitch C**. Role of transmural dispersion of repolarization in the genesis of drug-induced torsades de pointes. *Heart Rhythm* 2005; **2**: S9-S15 [PMID: 16253930]
- 21 **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**: 271-274 [PMID: 19897501 DOI: 10.1093/europace/eup357]
- 22 **Shimizu M**, Ino H, Okeie K, Yamaguchi M, Nagata M, Hayashi K, Itoh H, Iwaki T, Oe K, Konno T, Mabuchi H. T-peak to T-end interval may be a better predictor of high-risk patients with hypertrophic cardiomyopathy associated with a cardiac troponin I mutation than QT dispersion. *Clin Cardiol* 2002; **25**: 335-339 [PMID: 12109867]
- 23 **Barbhaiya C**, Po JR, Hanon S, Schweitzer P. Tpeak - Tend and Tpeak - Tend /QT ratio as markers of ventricular arrhythmia risk in cardiac resynchronization therapy patients. *Pacing Clin Electrophysiol* 2013; **36**: 103-108 [PMID: 23106253 DOI: 10.1111/pace.12031]
- 24 **Panikkath R**, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, Gunson K, Jui J, Chugh SS. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. *Circ Arrhythm Electrophysiol* 2011; **4**: 441-447 [PMID: 21593198 DOI: 10.1161/CIRCEP.110.960658]
- 25 **Erikssen G**, Liestøl K, Gullestad L, Haugaa KH, Bendz B, Amlie JP. The terminal part of the QT interval (T peak to T end): a predictor of mortality after acute myocardial infarction. *Ann Noninvasive Electrocardiol* 2012; **17**: 85-94 [PMID: 22537325 DOI: 10.1111/j.1542-474X.2012.00493.x]
- 26 **Rautaharju PM**. A farewell to QT dispersion. Are the alternatives any better? *J Electrocardiol* 2005; **38**: 7-9 [PMID: 15660341]
- 27 **Liu T**, Traebers M, Ju H, Suter W, Guo D, Hoffmann P, Kowey PR, Yan GX. Differentiating electrophysiological effects and cardiac safety of drugs based on the electrocardiogram: a blinded validation. *Heart Rhythm* 2012; **9**: 1706-1715 [PMID: 22710481 DOI: 10.1016/j.hrthm.2012.06.030]
- 28 **Kannankeril PJ**, Norris KJ, Carter S, Roden DM. Factors affecting the degree of QT prolongation with drug challenge in a large cohort of normal volunteers. *Heart Rhythm* 2011; **8**: 1530-1534 [PMID: 21420510 DOI: 10.1016/j.hrthm.2011.03.042]

P- Reviewers Kettering K, Liu T, Said S **S- Editor** Gou SX
L- Editor A **E- Editor** Lu YJ

