World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/esps/
wjc@wjgnet.com
doi:10.4330/wjc.v5.i6.175

World J Cardiol 2013 June 26; 5(6): 175-185
ISSN 1949-8462 (online)

REVIEW

Mechanisms of drug-induced proarrhythmia in clinical practice

Arkadia Konstantopoulou, Spyros Tsikrikas, Dimitrios Asvestas, Panagiotis Korantzopoulos, Konstantinos P Letsas

Arkadia Konstantopoulou, Spyros Tsikrikas, Dimitrios Asvestas, Konstantinos P Letsas, Second Department of Cardiology, Laboratory of Cardiac Electrophysiology, Evangelismos General Hospital of Athens, 10676 Athens, Greece
Panagiotis Korantzopoulos, Department of Cardiology, University Hospital of Ioannina, 45500 Ioannina, Greece
Author contributions: Konstantopoulou A and Asvestas D reviewed the literature, and helped to draft the manuscript; Tsikrikas S reviewed the literature, organized the different sections of the paper and helped to draft the manuscript; Korantzopoulos P and Letsas KP critically revised the manuscript; all authors have read and approved the final manuscript.
Correspondence to: Konstantinos P Letsas, MD, FESC, Second Department of Cardiology, Laboratory of Cardiac Electrophysiology, Evangelismos General Hospital of Athens, 45-47, Ipsilantou st., 10676 Athens, Greece. k.letsas@mail.gr
Telephone: +30-210-6843854 Fax: +30-210-6513317
Received: January 17, 2013 Revised: May 11, 2013
Accepted: May 18, 2013
Published online: June 26, 2013

Abstract

Drug-induced proarrhythmia represents a great challenge for those involved in the development of novel pharmaceuticals and in the regulatory bodies for drug approval as well as for the prescribing clinicians. Our understanding of the mechanisms that underlie drug-induced proarrhythmia has grown dramatically over the last two decades. A growing number of cardiac and non-cardiac agents have been shown to alter cardiac repolarization predisposing to fatal cardiac arrhythmias such as ventricular tachycardia or ventricular fibrillation and sudden cardiac death. These agents may induce the phenotype of long QT syndrome and less commonly of short QT syndrome and Brugada syndrome (BS). Although, genetic susceptibility underlie drug-induced proarrhythmia in certain cases, current data are limited regarding this topic. The present review surveys the current published literature on the mechanisms and the offending medical agents that predispose to drug-induced long QT syndrome, short QT syndrome and BS. Drug-induced proarrhythmia should be considered as a predictor of sudden cardiac death and should prompt critical re-evaluation of the risks and benefits of the suspicious medication. Survivors of drug-induced proarrhythmia and family members require careful examination and possibly genetic testing for the presence of a channelopathy. Treating physicians are advised to follow the lists of agents implicated in drug-induced proarrhythmia in order to minimize the risk of arrhythmia and sudden cardiac death.

Key words: Drugs; Sudden cardiac death; Long QT syndrome; Short QT syndrome; Brugada syndrome

Core tip: A growing number of cardiac and non-cardiac agents have been shown to alter cardiac repolarization predisposing to the most dangerous cardiac arrhythmias such as ventricular tachycardia or ventricular fibrillation and sudden cardiac death. These agents may induce the phenotype of long QT syndrome and less commonly of short QT syndrome and Brugada syndrome. Treating physicians are advised to follow the lists of agents implicated in drug-induced proarrhythmia in order to minimize the risk of arrhythmia and sudden cardiac death.

Konstantopoulou A, Tsikrikas S, Asvestas D, Korantzopoulos P, Letsas KP. Mechanisms of drug-induced proarrhythmia in clinical practice. *World J Cardiol* 2013; 5(6): 175-185 Available from: URL: http://www.wjgnet.com/1949-8462/full/v5/i6/175.htm DOI: http://dx.doi.org/10.4330/wjc.v5.i6.175

INTRODUCTION

A growing number of cardiac and non-cardiac agents

have been shown to alter cardiac repolarization predisposing to fatal cardiac arrhythmias such as ventricular tachycardia or ventricular fibrillation and sudden cardiac death (SCD). SCD accounts for approximately 50% of all deaths from cardiovascular diseases, and this proportion remains the same despite the overall decrease in cardiovascular mortality the last decades. In the past 30 years ventricular tachycardia or fibrillation was thought to be the most common cause of out-of hospital cardiac arrest, accounting for approximately three-quarters of cases, the rest 25% caused by bradyarrhytmias or asystole[1-9]. More recent studies suggest that the incidence of ventricular fibrillation or ventricular tachycardia as the first recorded rhythm in out-of-hospital cardiac arrest has declined to less than 30%, presumably due to the decline of coronary artery disease mortality[10,11]. An exception may exist in the setting of drug-induced proarrhythmias where the most common rhythm is polymorphic ventricular tachycardia termed torsades de pointes (TdP) or ventricular fibrillation. A national survey in England about sudden unexpected cardiac deaths have demonstrated that postmortem examination fails to identify a cause in 4% of sudden deaths in the 16-64 age group, yielding a default diagnosis of sudden arrhythmic death syndrome[6]. Recent data have shown that SCD occurs in the absence of coronary heart disease or other cardiomyopathy in about 5%-10% of cases. Certain primary electrical diseases such as the long QT syndrome, the short QT syndrome, the Brugada syndrome (BS), and the catecholaminergic polymorphic ventricular tachycardia may be underling cause of SCD in this group of subjects without overt structural heart disease[6,8,9,12]. Apart from the congenital form of these syndromes, accumulating data have shown that an increasing number of drugs commonly prescribed in routine clinical practice are implicated in acquired forms of long QT, short QT, and BS predisposing to SCD in the absence of structural heart disease. Drug-induced proarrhythmia is a growing challenge for the clinicians and for those involved in the development of novel pharmaceuticals and in the regulatory bodies charged with evaluating and monitoring drug safety. The present review describes the underlying mechanisms of drug-induced proarrhythmia and presents the drugs that predispose to this potentially life-threatening condition.

DRUG-INDUCED LONG QT SYNDROME

Several cardiac and non-cardiac agents have been shown to prolong cardiac repolarization (QT interval) predisposing to TdP and SCD[13-19]. Drug-induced QT interval prolongation is considered the most frequent cause of withdrawal or relabeling of marketed drugs in the last decade[15,16]. In a survey in United Kingdom and Italy, non-cardiac agents that have pro-arrhythmic potential (defined as QT interval prolongation or TdP) represented 3% and 2% of total prescriptions in both countries, respectively[19]. Antimicrobials and psychotropic drugs are the most common non-cardiac drugs involved in drug-induced QT interval prolongation, which in the vast majority of cases are prescribed by non-cardiologists. The prescription of non-cardiac QT-prolonging agents has been associated with a significantly increased risk of SCD in the general population. The risk of death has been reported to be higher in women and in recent starters[20]. Drugs implicated in QT interval prolongation and TdP are listed in Table 1. This list can be accessed *via* the internet (www.torsades.org, www.qtdrugs.org, www.longqt.org, www.sads.org). The incidence of drug-induced TdP in the general population is unknown[15,16]. In addition, the likelihood of drug-induced TdP is difficult to be predicted in routine clinical practice. Most of our understandings are derived from epidemiological studies, case reports, clinical studies during drug development, and post-marketing surveillance. Nevertheless, the absolute total number remains very low (less than one in 100000)[15].

Table 1 Drugs implicated in acquired long QT syndrome

Category	Drugs
Antianginal	Bepridil
Antiarrhythmic	Disopyramide, procainamide, quinidine, mexiletine, propafenone, flecainide, d,l-sotalol, amiodarone, dronedarone, bretylium, dofetilide, ibutilide, azimilide, ajmaline
Anticancer	Tamoxifen, lapatinib, vandetanib, nilotinib, arsenic trioxide
Antifungal	Itraconazole, ketoconazole, fluconazole, voriconazole
Antimicrobial	Erythromycin, clarithromycin, azithromycin, spiramycin, telithromycin, levofloxacin, moxifloxacin, sparfloxacin, gatifloxacin, grepafloxacin, gemifloxacin, ofloxacin, trimethoprim-sulfamethoxazole, pentamidine, quinine, chloroquine, mefloquine, halofantrine
Antiviral	Foscarnet
Antihistamine	Astemizole, diphenhydramine, ebastine, terfenadine, hydroxyzine
Antidepressant	Doxepin, venlafaxine, fluoxetine, desipramine, imipramine, clomipramine, paroxetine, sertraline, citalopram, escitalopram
Antipsychotic	Chlorpromazine, prochlorperazine, trifluoperazine, fluphenazine, felbamate, haloperidol, thioridazine, droperidol, mesoridazine, pimozide, risperidone, quetiapine, ziprasidone, lithium, chloral hydrate, pericycline, sertindole, sulopride, zimeldine, maprotiline, tiapride
Antimigraine	Naratriptan, sumatriptan, zolmitriptan
Bronchodilators	Albuterol, salmeterol
Diuretics	Indapamide, thiazide, furosemide
Gastrointestinal stimulants	Cisapride, metoclopramide, domperidone
Hormones	Octreotide, vasopressin
Immunosuppressives	Tacrolimus
Others	Probucol, methadone, cocaine, amantadine, aconitine, veratridine, vincamine, terodiline, budipine, tizanidine, organophosphorus compounds

The full list can be accessed *via* the internet (www.torsades.org, www.qtdrugs.org, www.longqt.org, www.sads.org).

ECG MARKERS OF VENTRICULAR REPOLARIZATION IN LONG QT SYNDROME

The QT interval is considered as the electrocardiographic

(ECG) index of ventricular repolarization. Correct measurement of the QT interval is of paramount importance for the diagnosis of drug-induced QT interval prolongation. Most physicians, including many cardiologists, cannot recognize a long QT interval. Viskin *et al*[21] have shown that correct classification of the QT interval as either "long" or "normal" was achieved by 96% of QT experts and 62% of arrhythmia experts, but by less than 25% of cardiologists and non-cardiologists. The QT interval is measured from the beginning of the QRS complex to the end of the T-wave on the surface ECG. Despite the fact that there are no sufficient data regarding which lead or leads to use for QT interval measurement, lead Ⅱ is considered the most appropriate because the vectors of repolarization result in a long single wave rather than discrete T- and U waves[22]. U waves should be ignored in QT measurements. However, whether total repolarization time should include the entire QU complex still remains a subject of controversy. The QT interval is influenced by the heart rate. Rate acceleration normally leads to QT shortening, whereas bradycardia leads to QT lengthening. The RR interval preceding the QT interval should be measured for rate correction. Several formulas may be used to correct the QT interval (QTc). The most commonly used formulas are Fridericia's cube root formula (QTc = QT/RR1/3) and Bazett's square root formula (QTc = QT/RR1/2). Although the Bazett's formula is widely accepted, it overestimates the QT interval during tachycardia and underestimates it during bradycardia. Fridericia's equation is preferred at extremes of physiological heart rate[23-25]. Individualised regression formulae are often preferred. Apart from heart rate, the duration of the QT interval is also influenced by the gender (females display longer QT intervals), autonomic tone, drugs, genetic abnormalities, electrolyte disorders (hypokalemia, hypomagnesemia, hypocalcemia), cardiac (congestive heart failure, cardiac hypertrophy) or metabolic diseases (starvation, anorexia nervosa, drug-interactions) and changes of cardiac afterload[24]. These intra-patient variations in the QT interval cannot be captured on a single twelve-lead ECG, which may be taken to evaluate the effect of a drug on the QT interval. Isolated measurements of the QT interval without reference to these QT dynamics can lead to inaccurate estimations of the risk of TdP. For these reasons, the intra-patient variability in the QT interval can be appreciated by examining ambulatory Holter recordings. QTc values greater than 450 ms in men and 470 ms in women are considered abnormal. Values ranging between 430-450 ms in men and 450-470 ms in women are considered borderline[24]. A recent scientific statement from the American Heart Association and the American College of Cardiology Foundation recommends that a QTc over the 99th percentile should be considered abnormally prolonged. Estimated 99th percentile QTc values for otherwise healthy postpubertal individuals are 470 ms for men and 480 ms for women. A QTc > 500 ms is considered abnormal and dangerous for both males and females[26].

In the setting of prolonged QRS duration (bundle branch block, pre-excitation, paced rhythm) the total QT interval will be increased. One method to adjust the QT measurement after the development of bundle brunch block is to subtract the difference of the QRS duration before and after the block. Another method is to measure the JT interval from the J point, which is the end of QRS complex to the end of T-wave. The most important issue is to apply the same adjustment method consistently when a patient is being monitored over time[26]. The current standard practice of periodic manual measurement of the QT interval and even the use of electronic callipers has drawbacks. Errors can occur in determining the beginning or end of QT interval, in the application of a heart rate formula, and from inconsistency in the choice of lead for QT measurement. Automated measurement by electrocardiographs is preferred over manual measurement[26].

The QTc interval is the best available predictor of TdP episodes[25]. The majority of drug-induced TdP occur with QTc values of more than 500 ms[27]. Data from patients with congenital long QT syndrome (LQTS) have shown that a QTc interval greater than 500 ms is related to an increased risk for arrhythmic events[28]. However, there is not a clear, linear incremental relationship between QTc prolongation and the risk of TdP, and therefore, there is no established threshold below which prolongation of the QTc interval is considered free of proarrhythmic events[29-32]. Notably, some agents that substantially prolong the QTc interval produce very low rates of clinical TdP, while other agents with much smaller QTc effects are considerably more proarrhythmic. A typical example is amiodarone[14]. In terms of QTc change from baseline on treatment, it has been recommended that an increase of 30 ms is a potential cause for concern and that a 60 ms increase is a definite cause for concern[27]. Additionally, QT dispersion (defined as the difference between the maximum and minimum QT interval of the twelve-leads) greater than 100 ms is considered abnormal[32].

An increased transmural dispersion of repolarization (TDR) is probably the best predictor of TdP, but this is measurable only in preclinical studies of limited availability[29-32]. Increased TDR by reflecting the intrinsic heterogeneities within the myocardium is postulated to contribute to the development of TdP by increasing the vulnerable window during repolarization, facilitating propagation of early afterdepolarizations (EADs). The TDR can be measured indirectly using novel ECG markers, such as the Tpeak-end interval and the Tpeak-Tend/QT ratio. In isolated ventricular wedge preparations, the peak of the T-wave was shown to coincide with epicardial repolarization and the end of the T-wave with repolarization of the M-cells, so that the Tpeak-Tend the interval as well as the Tpeak-Tend dispersion of the precordial leads provides a measure of TDR[33-36].

The Tpeak-Tend interval has been reported to be prolonged in congenital LQTS and to predict TdP in acquired LQTS[37]. Yamaguchi *et al*[38] have demonstrated

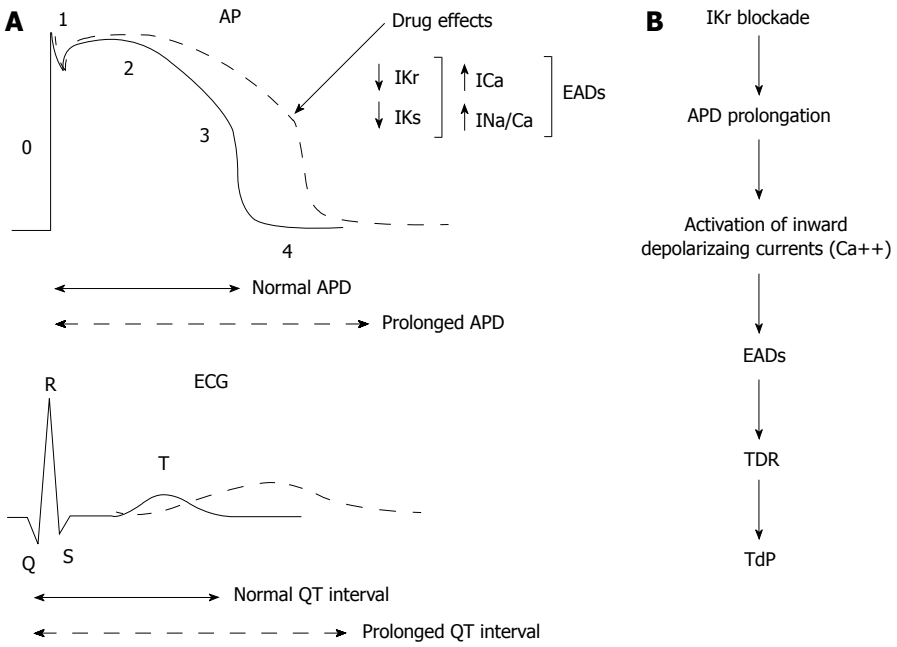

Figure 1 Relationship between the phases of ventricular transmembrane action potential and the surface electrocardiogram. A: A reduction of outward currents (IKr, IKs) during phase 2 and 3 leads to action potential duration (APD) prolongation and QT interval prolongation. Activation of inward depolarizing currents (ICa, INa/Ca) may then give rise to early afterdepolarizations (EADs) and torsades de pointes (TdP). B: This scheme is showing that APD prolongation caused by IKr blockade is not the sole determinant for TdP. Transmural dispersion of repolarization (TDR) is required in order to form a zone of functional refractoriness in the mid myocardial layer, which is probably the basis of the re-entry that is sustaining TdP. ECG: Electrocardiographic.

that the Tpeak-Tend/QT ratio is a better predictor of TdP as compared to QTc interval and QT dispersion in patients with acquired LQTS. In their study, a Tpeak-Tend/QT ratio greater than 0.28 was strongly associated with risk of developing TdP. T-wave alternans, defined as a change in amplitude or polarity of the T-wave on alternating beats, have been also considered as a precursor of TdP in LQTS[39]. T-wave alternans is thought to result from alternation of the M-cell action potential duration (APD), leading to exaggeration of TDR during alternate beats[33,40-42].

MECHANISMS OF DRUG-INDUCED QT INTERVAL PROLONGATION AND TDP: THE COMBINED ROLE OF LONG QT INTERVAL AND TDR

The knowledge of the different phases of the cardiac action potential is important for understanding the pathogenesis of drug-induced LQTS[18]. Figure 1 illustrates the normal cardiac action potential in ventricular myocytes. Phase 4 represents the resting membrane potential (-85 to -95 mV) as determined by the inward rectifier IK1 potassium current. Phase 0 of the cardiac action potential is the rapid depolarization phase. Depolarization of a sufficient area of a given cell membrane allows the rapid influx of sodium ions into the cell. The fast influx of sodium demonstrates a positive feedback, allowing even more INa channels to open and more sodium to enter the cell more rapidly, thereby depolarizing the cell to a point at which it overshoots the membrane potential to +20 to +30 mV. Phase 1 is the early rapid repolarization phase that results from potassium ions being driven out of the cell and the membrane potential returning to near 0 mV. Ito is a potassium current (transient outward current) that is rapidly activated at this phase. Phase 2 is the plateau period. Net potential derives from competition between outward currents of potassium efflux and chloride influx and inward currents from the L-type calcium channels (ICa-L). At the end of the phase 2, calcium entry slows and calcium is removed from the cell by the Na/Ca exchanger pump. Two important potassium currents participating in ventricular repolarisation are the components of the delayed rectifier current, IKr (rapid) and IKs (slow). Phase 3 is the rapid phase of final repolarization and is determined by competition between time-dependent deactivation of the ICa-L channels versus the IKr and IKs channels.

The majority of non-cardiac QT-prolonging agents exhibit direct electrophysiological effects on the rapidly activating delayed rectifier IKr current encoded by the human ether-a-go-go related gene (HERG, now termed KCNH2)[13-19]. An increase in ICa or late INa current may also prolong the APD. Many drugs act on multiple cardiac ion channels (IKr, IKs, INa, ICa) leading to a more complex shift of action potential morphology. As shown in Figure 1, IKr and/or IKs blockade leads to a delay in phase 3 of repolarization of the action potential (reflected as QT interval prolongation on surface ECG). These phenomena are more readily induced in M-cells from the mid ventricular myocardium. Compared to subendocardial or subepicardial cells, the M-cells show much more pro-

nounced action potential[29-31,43-46]. This feature of M-cell is due to weaker repolarizing current during phases 2 and 3 secondary to smaller IKs and a larger late INa and INa/Ca compared to epicardial and endocardial cells. These ionic distinctions sensitize M-cells to a variety of pharmacological agents and pathophysiological states. Agents that block IKr, IKs or increase ICa-L or late INa generally produce a much greater prolongation of the APD of M-cells than of epicardial or endocardial cells. Activation of inward depolarizing currents (most likely L-type ICa or INa/Ca exchange current) may then give rise to EADs that appear as depolarizing oscillations in membrane voltage during phases 2 and 3 of the action potential. Phase 2 may be interrupted due to augmented opening of the L-type ICa channels, while phase 3 interruptions are facilitated by the INa/Ca exchanger pump which exchanges 3 Na ions for 1 Ca ion, producing an inward current when extruding Ca from the cytoplasm. EADs that reach the threshold voltage cause ventricular extrasystoles.

As previously mentioned, there are agents that significantly prolong the QTc along with very low rates of clinical TdP[29-31]. This indicates that the QTc interval is not the sole or optimal determinant for arrhythmogenesis. TDR has been proposed to play a key-role in both acquired and congenital LQTS[29,44]. Amiodarone is a well-known class Ⅲ antiarrhythmic agent. Despite QTc interval prolongation, the drug exhibits a very low torsadogenic activity (< 1%)[47]. Chronic administration of amiodarone produces a greater prolongation of APD in epicardium and endocardium compared to M-cells, thereby reducing TDR[48]. Sodium pentobarbital is another agent that blocks multiple currents and prolongs the QT interval but reduces TDR[41]. Both amiodarone and pentobarbital produce a homogeneous APD lengthening and the EADs does not occur. On the contrary, d-sotalol causes a significant increase in M-cell APD in relation to the epicardial cell layer. This amplified TDR explains the high incidence of TdP observed with d-sotalol[40]. Bepridil and ranolazine are anti-anginal agents that both prolong the QT interval by blocking multiple ion channels but have very different torsadogenic properties. Bepridil amplifies TDR creating the substrate for a sustained TdP[49]. In contrast to bepridil, TDR was decreased with ranolazine and EADs could not initiate TdP, despite the dose-dependent increase in QT interval[50]. Cisapride, another agent that blocks both inward and outward currents, produces a biphasic concentration-dependent prolongation of the QT interval. A parallel biphasic dose-response relationship is seen for TDR, peaking at 0.2 μmol/L, and it is only at this concentration that TdP is observed. Higher concentrations of cisapride further prolong the QT interval and reduce TDR thereby preventing TdP induction[51]. These data suggest that the propensity of a drug to increase TDR across the ventricular wall is more important than the prolongation of the QTc interval in determining the substrate for TdP. The resultant heterogeneity in ventricular repolarization creates a zone of functional refractoriness in the mid myocardial layer, which is probably the basis of the re-entry by sustaining the TdP[29,44]. A "short-long-short" sequence (an extrasystole, followed by a post-extrasystolic pause) precedes the onset of TdP in most cases[52]. The "short-long-short" sequence provides a repolarization delay which in animal models is necessary to allow the late-plateau depolarizing currents (*e.g.*, ICa-L channel and INa/Ca exchanger current) to initiate EADs[53]. Compounds that block the late INa suppress the EADs and prevent TdP[50,54]. The anatomic origin of these extrasystoles can also be traced to late-repolarizing Purkinje fibers or M-cells[29].

Pharmacokinetic interactions with drugs known to inhibit cytochrome P450 isoenzymes (CYP3A4 or CYP2D6) may enhance the torsadogenic potential of certain agents by decreasing their clearance[15,16,18]. CYP3A4 activity can be inhibited by a wide variety of drugs including some macrolide antibiotics, antifungals, cimetidine, fluoxetine, protease inhibitors, and amiodarone. In addition, many non-drug factors including age, smoking, hepatic disease, genetic polymorphisms and grapefruit juice may lead to CYP3A4 inhibition[14]. Finally, cytochrome P450 CYP2D6 is functionally absent in approximately 7% of white and black individuals (poor metabolizer group) because of loss of function gene variants[55,56].

DRUG-INDUCED SHORT QT SYNDROME

The short QT syndrome (SQTS), a new highly arrhythmogenic syndrome affecting young and healthy individuals without structural heart disease, is associated with a predisposition to atrial fibrillation and SCD[57,58]. The definition of the short QT interval varies significantly in the literature. In a recent review of 61 cases with SQTS, the mean and median QTc values of the overall cohort were 306.7 ± 26.5 ms and 310 ms (IQR: 293-320 ms), respectively[59]. Other ECG findings include the absence of the ST-segment and the presence of tall, narrow, and symmetrical T-waves[57,58]. The diagnosis of SQTS is usually made in patients with a short QTc interval who present with additional clinical findings, such as syncope, episodes of atrial fibrillation, polymorphic ventricular tachycardia or ventricular fibrillation, or a family history of unexplained SCD[57,58]. In particular, in the cohort described by Gollob *et al*[59], the presence of symptoms associated with SQTS, including SCD, aborted cardiac arrest, syncope, and atrial fibrillation, occurred in 35 of the 61 (57.4%) subjects. There were 5 cases of SCD and 15 of aborted cardiac arrest, whereas an isolated, unexplained syncope occurred in an additional 9 subjects. Atrial fibrillation was experienced in 18% (11 of 61) of cases within the cohort.

Although the true prevalence is unknown, the congenital SQTS appears to be relatively rare[57,58]. Gain-of-function mutations in potassium channel genes (*KCNH2*, *KCNQ1* and *KCNJ2*) and loss-of-function mutations in CACNA1C, CACNB2, and CACNA2D1 have been reported as the genetic basis of this syndrome[60-66].

Limited data exist regarding the incidence and the

underlying mechanisms of drug-induced QT/QTc shortening. This is due to the fact that there has been relatively little research in this area compared to drug-induced QT/QTc prolongation. Although more work is required to elucidate the mechanism(s) of action of compounds which shorten QT/QTc, there are at least two mechanisms that have been demonstrated; activation of the IK_r current and of the ATP-sensitive potassium current (IK_{ATP})[67]. In both cases, there is an increase in the repolarizing currents leading to a shortening of the APD and resulting in reduction of ventricular refractory periods and shortening of QT interval. Although inherited SQTS is a recent acquisition, the existence of an acquired short QT interval has been known for a long time. Acquired short QT intervals can be secondary to hypercalcemia, hyperkalemia and other situations such as increased acetylcholine and catecholamine plasma levels, hyperthermia, alterations of the autonomic tone, acidosis and increased heart rate. The industry-wide survey (53 total responses representing 45 different companies) indicates that the number of compounds that induce QT/QTc shortening has increased over the last 5 years with 51% of responses reporting QT/QTc shortening in pre-clinical studies and 22% a corresponding clinical experience. The reason for the increase is not clear but there is a clear business impact with 13% (7/56) of these compounds being discontinued in the pre-clinical phase due to QT/QTc shortening[68].

Rufinamide, a recently approved anticonvulsant indicated for Lennox-Gastaut syndrome which has a prevalence of 1 per 10000 of population, had a QT shortening effect > 20 ms at peak concentrations when compared with placebo rates of 5%-10%. The FDA, in contrast to the European labeling which advices use of judgment, contraindicates its use in patients with familiar SQTS and recommends caution when administering with other drugs that shorten the QT interval[69]. In a recent observational study, QTc interval shortening following oral rufinamide administration was not associated with significant clinical adverse effects. However, the ability of rufinamide to significantly shorten the QT interval portends a potential arrhythmogenic risk that may best be guarded against by periodic ECG recordings[70].

DRUG-INDUCED BS

The BS is a primary electrical disease characterized by coved type ST-segment configuration in right precordial leads, the absence of structural heart disease, and a high risk of ventricular tachycardia/ventricular fibrillation and SCD[71-73]. The clinical phenotype is 8 to 10 times more prevalent in males than in females[72,73]. BS typically manifests with syncope or SCD, occurring in the third and fourth decade of life, and usually at rest or during sleep[71-73]. The diagnosis of Brugada sign is strictly based on the recommendations of the Second Expert Consensus Conference on BS[73]. According to this report, three types of ECG repolarisation patterns in right precordial leads (V_1-V_3) have been recognized. Type 1 is considered diagnostic and is characterized by a coved ST-segment elevation $\geqslant$ 2 mm followed by a negative T-wave in more than one right precordial leads (Figure 2). Type 2 ST-segment elevation displays a saddleback configuration with a high take-off ST-segment elevation of $\geqslant$ 2 mm, a trough displaying $\geqslant$ 1 mm ST-segment elevation, and either a positive or biphasic T-wave. Type 3 has either a saddleback or coved appearance with an ST-segment elevation of $\leqslant$ 1 mm. The diagnosis of BS requires the presence of type 1 ECG pattern with at least one of the recognized diagnostic criteria: syncope, prior cardiac arrest, documented or inducible polymorphic ventricular tachycardia or ventricular fibrillation, a family history of sudden death, 45 years old, or type 1 Brugada pattern and/or nocturnal agonal respiration[73]. The ECG features of BS are often concealed requiring a pharmacological challenge (sodium channel blocking test) with a Class I antiarrhythmic agent (ajmaline, flecainide, procainamide) to unmask the characteristic ST-segment elevation in the right precordial leads. The diagnosis of BS is afterwards considered positive when the baseline type 2 or type 3 ST-segment elevations converted to the diagnostic type 1 pattern (ST-segment elevation $\geqslant$ 2 mm). In a Consensus report published this year, only 2 ECG types are considered: type 1 which is identical to the classic type 1 ECG pattern of the other Consensus (coved pattern) and type 2 that joins ECG patterns 2 and 3 of previous Consensus (saddleback pattern)[74]. In this new type 2 ECG, the high take-off is $\geqslant$ 2 mm with respect to the isoelectric line and is followed by ST-segment elevation $\geqslant$ 0.05 mV with positive or flat T-wave in V2 and T-wave variable in V1[74].

Mutations of the *SCN5A* gene leading to loss of function of the INa by different mechanisms is the most common genotype found among these patients (20% of BS cases; range 11%-28%)[75]. To date, almost 300 mutations in *SCN5A* gene have been described in association with BS[75]. Putative mutations were also found in calcium channel genes (*CACNA1C*, *CACNB2b* and *CACNA2D1*)[60]; sodium channel β-subunit genes (*SCN1B*, *SCN3B*)[76]; glycerol-3 phosphate dehydrogenase 1-like enzyme (GPD1L) and MOG1, which affects trafficking of sodium channels[77,78]; and in genes that affect transient outward current (Ito) (KCNE3, KCND3 and KCNE5) in single cases and families with BS[79,80].

MECHANISMS OF DRUG-INDUCED BS

The pathophysiology of the BS is only partially resolved. There are 2 principal hypotheses on the pathophysiologic basis of BS: the "depolarization hypothesis", namely right ventricular conduction delay, and the "repolarization hypothesis", namely transmural dispersion of right ventricular action potential morphology, driven by the loss of the spike and dome action potential morphology at right ventricular epicardium[81,82]. So far, both repolarization and depolarization abnormalities are thought to be related to the development of ventricular fibrillation in

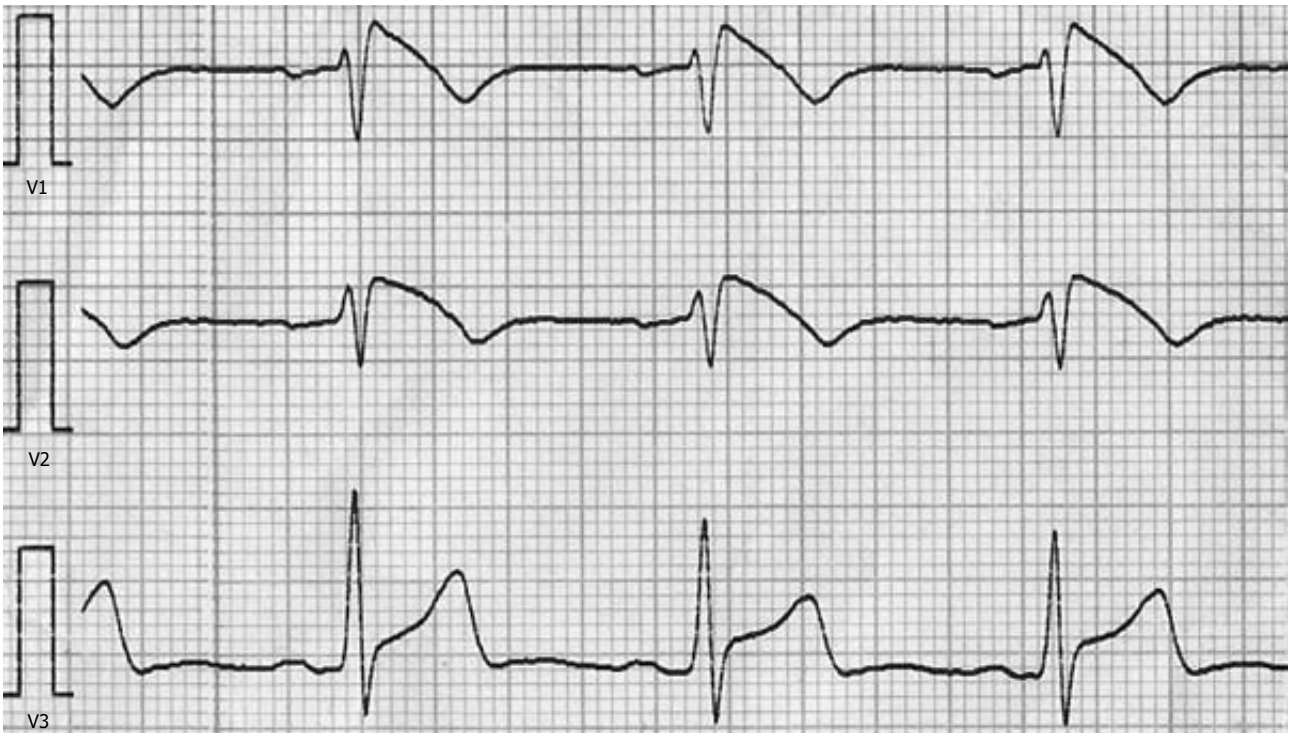

Figure 2 Diagnostic type 1 electrocardiographic pattern of Brugada syndrome.

BS patients[83].

The seminal work by Yan and Antzelevitch[84] had clearly demonstrated regional heterogeneities in action potential characteristics between the right and left ventricles, as well among epicardium, mid-myocardium and endocardium. A loss of the action potential dome at the epicardium but not at the endocardium creates a transmural voltage gradient that may be responsible for the ST-segment elevation. The Ito current seems to have an important role in the Brugada ECG pattern, evidenced by the fact that the right ventricle has a higher density of this channel compared with the left ventricle and it is suggested that the thinner endocardium of the right ventricle relative to its epicardium results in a more marked spike and dome pattern in this region[73,75,84]. This mechanism properly accounts for not only the ST-segment elevation but also for the premature ventricular contraction ("phase 2 re-entry") and re-entrant substrate for ventricular fibrillation in BS. Recent studies strongly support the depolarization hypothesis[85-88]. Postema *et al*[86] have shown conduction slowing and abnormal conduction velocity restitution in the right ventricle (with no significant regional differences) of patients with BS. Using a non-contact endocardial mapping technique, Lambiase *et al*[87] have demonstrated significant regional conduction delay, reduction in activation gradient and formation of lines of functional conduction block in the anterolateral free wall of the right ventricular outflow tract compared with the right ventricular body and apex of BS patients. Fractionated electrograms in the right ventricle, possibly due to subtle structural abnormalities, have been also reported in patients with BS[88]. In both mechanisms, a reduction in INa or other depolarizing and repolarizing ion currents have a central role. The cells with impaired sodium channel function may fail to propagate the action potential, resulting in localized conduction block. These cells have also a shorter refractory period and recover excitability from the surrounding cells. The combination of localized conduction block and a shortened refractory period provide the substrate for localized "phase 2 re-entry".

An increasing number of drugs have been reported to induce type 1 ECG pattern of BS and/or (fatal) arrhythmias in BS patients (Table 2). Postema *et al*[89] have initiated a website (www.brugadadrugs.org) to ensure worldwide availability on safe drug use in BS patients. As previously mentioned, Class I antiarrhythmic agents (ajmaline, flecainide, procainamide, pilsicainide, propafenone) unmask the diagnostic type 1 ECG pattern of BS. Calcium channel blockers and β-blockers have also been implicated in the acquired form of BS. Psychotropic agents are commonly implicated in drug-induced BS. Tricyclic antidepressants (TCA) have a quinidine-like antiarrhythmic action which effects repolarization. The most common adverse cardiovascular effects of 4s are slowing of intraventricular conduction, manifested by prolongation of PR and QRS intervals, QT prolongation, TdP and postural hypotension[90]. The primary mechanism of these ECG changes is likely to be sodium channel antagonism. TCAs cause a decrease in the maximum rate of rise (Vmax) of phase 0 of the action potential in canine Purkinje fibres. The shortened APD may therefore induce an intramyocardial electrical gradient, the Brugada ECG pattern and possibly the substrate for re-entry. Lithium is a commonly used drug in the treatment

Table 2 Agents implicated in drug-induced Brugada electrocardiographic pattern

Category	Drugs
Antiarrhythmic	Ajmaline, flecainide, pilsicainide, procainamide, propafenone
Antidepressant	Amitriptyline, nortriptyline, clomipramine, desipramine, imipramine, doxepin, dosulepine, maprotiline, lithium, fluoxetine, paroxetine, fluvoxamine,
Antipsychotic	Loxapine, trifluoperazine, cyamemazine, perphenazine, thioridazine
Anti-epileptic	Oxcarbazepine
Anesthetics/analgesics	Bupivacaine, propofol
Antihistamines	Diphenhydramine, dimenhydrinate
Other substances	Cocaine, alcohol, metoclopramide, acetylcholine, ergonovine maleate, edrophonium

The full list can be accessed *via* the internet (www.brugadadrugs.org).

of depressive and bipolar affective disorders. Cardiac side effects have been described at both therapeutic and toxic serum levels in adult patients. Lithium has been associated with non-specific T-wave abnormalities (inverted, flattened, or bifid T-waves), conduction defects and rhythm disturbances. The possible mechanism of action in unmasking patients with underlying BS is that lithium chloride causes a potent INa blockade in a concentration-dependent manner[91]. Selective serotonin-reuptake inhibitors have also been implicated in drug-induced BS[92,93].

The type 1 ECG pattern of BS has been also elicited in patients treated with first-generation antihistamines, anaesthetics, and cocaine[94]. Exposure to long-acting local anaesthetic, bupivacaine, has been reported to induce ECG manifestations of BS and ventricular tachycardia in an otherwise silent carrier of an *SCN5A* mutation[95]. Propofol is the commonest anaesthetic used in modern medicine and few significant side effects. However, there have described cases of SCD in patients with high doses of propofol infusion have been described when given for several days a condition termed "propofol infusion syndrome". Vernooy *et al*[96] described six patients with "propofol infusion syndrome" who developed a Brugada-like ECG pattern and died within hours of irrecoverable electrical storm. Some cases of unexpected SCD due to cocaine in young otherwise healthy individuals have occurred. Cocaine-induced BS has been reported in previous case reports[97-99]. In addition to indirect sympathomimetic actions, cocaine has a potent INa blocking effect resembling that of flecainide[100].

CONCLUSION

A continuously rising number of cardiac and non-cardiac agents have been implicated in proarrhythmia and SCD. Abnormalities in repolarization and/or depolarization of cardiac cells through changes in ion channels and myocardial zones are the main pathophysiological mechanisms manifested as long QT, short QT and BS in routine clinical practice. Drug-induced proarrhythmia should always be considered as a predictor of SCD and should prompt critical revaluation of risks and benefits of the suspicious medication. In clinical practice, adverse effects of QT-prolonging drugs can be prevented by not exceeding the recommended dose, by restricting the dose in patients with pre-existing risk factors and avoiding concomitant administration of agents that inhibit the metabolism of known drugs that prolong the QT interval. Survivors of drug-induced TdP and family members of drug-induced TdP fatalities require careful examination and possibly genetic testing for the presence of congenital LQTS-associated channelopathies. Similarly, drugs that shorten the QT interval should be avoided. Sodium channel blocking test, family screening for BS, and possibly genetic analysis may be performed in a subject with an acquired form of Brugada ECG phenotype by non-cardiac agents. Although the most appropriate treatment in BS is under discussion, avoidance of potential proarrhythmic drugs is an important part of prophylactic treatment. Rigorous treatment of fever, a well known trigger of arrhythmic events in BS, is also advised in subjects with acquired BS ECG pattern by non-cardiac agents[73]. Treating physicians are advised to follow the lists of agents implicated in drug-induced proarrhythmia in order to minimize the risk of arrhythmia and SCD.

REFERENCES

1 **Myerburg RJ**, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. *Circulation* 1992; **85**: I2-10 [PMID: 1728501]
2 **Myerburg RJ**, Kessler KM, Castellanos A. Sudden cardiac death: epidemiology, transient risk, and intervention assessment. *Ann Intern Med* 1993; **119**: 1187-1197 [PMID: 8239250 DOI: 10.7326/0003-4819-119-12-199312150-00006]
3 **Myerburg RJ**, Interian A, Mitrani RM, Kessler KM, Castellanos A. Frequency of sudden cardiac death and profiles of risk. *Am J Cardiol* 1997; **80**: 10F-19F [PMID: 9291445 DOI: 10.1016/S0002-9149(97)00477-3]
4 **Gorgels AP**, Gijsbers C, de Vreede-Swagemakers J, Lousberg A, Wellens HJ. Out-of-hospital cardiac arrest--the relevance of heart failure. The Maastricht Circulatory Arrest Registry. *Eur Heart J* 2003; **24**: 1204-1209 [PMID: 12831814 DOI: 10.1016/S0195-668X(03)00191-X]
5 **Josephson M**, Wellens HJ. Implantable defibrillators and sudden cardiac death. *Circulation* 2004; **109**: 2685-2691 [PMID: 15184292]
6 **Bowker TJ**, Wood DA, Davies MJ, Sheppard MN, Cary NR, Burton JD, Chambers DR, Dawling S, Hobson HL, Pyke SD, Riemersma RA, Thompson SG. Sudden, unexpected cardiac or unexplained death in England: a national survey. *QJM* 2003; **96**: 269-279 [PMID: 12651971 DOI: 10.1093/qjmed/hcg038]
7 **Myerburg RJ**, Junttila MJ. Sudden cardiac death caused by coronary heart disease. *Circulation* 2012; **125**: 1043-1052 [PMID: 22371442 DOI: 10.1161/CIRCULATIONAHA.111.023846]
8 **Myerburg RJ**, Castellanos A. Emerging paradigms of the epidemiology and demographics of sudden cardiac arrest. *Heart Rhythm* 2006; **3**: 235-239 [PMID: 16443542]
9 **Junttila MJ**, Castellanos A, Huikuri HV, Myerburg RJ. Risk markers of sudden cardiac death in standard 12-lead electrocardiograms. *Ann Med* 2012; **44**: 717-732 [PMID: 21745092]
10 **Cobb LA**, Fahrenbruch CE, Olsufka M, Copass MK. Changing incidence of out-of-hospital ventricular fibrillation,

1980-2000. *JAMA* 2002; **288**: 3008-3013 [PMID: 12479765]
11 **Weisfeldt ML**, Everson-Stewart S, Sitlani C, Rea T, Aufderheide TP, Atkins DL, Bigham B, Brooks SC, Foerster C, Gray R, Ornato JP, Powell J, Kudenchuk PJ, Morrison LJ. Ventricular tachyarrhythmias after cardiac arrest in public versus at home. *N Engl J Med* 2011; **364**: 313-321 [PMID: 21268723]
12 **Behr E**, Wood DA, Wright M, Syrris P, Sheppard MN, Casey A, Davies MJ, McKenna W. Cardiological assessment of first-degree relatives in sudden arrhythmic death syndrome. *Lancet* 2003; **362**: 1457-1459 [PMID: 14602442]
13 **van Noord C**, Eijgelsheim M, Stricker BH. Drug- and non-drug-associated QT interval prolongation. *Br J Clin Pharmacol* 2010; **70**: 16-23 [PMID: 20642543]
14 **Heist EK**, Ruskin JN. Drug-induced proarrhythmia and use of QTc-prolonging agents: clues for clinicians. *Heart Rhythm* 2005; **2**: S1-S8 [PMID: 16253926]
15 **Roden DM**. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004; **350**: 1013-1022 [PMID: 14999113]
16 **Kannankeril P**, Roden DM, Darbar D. Drug-induced long QT syndrome. *Pharmacol Rev* 2010; **62**: 760-781 [PMID: 21079043]
17 **Heist EK**, Ruskin JN. Drug-induced arrhythmia. *Circulation* 2010; **122**: 1426-1435 [PMID: 20921449]
18 **Barnes BJ**, Hollands JM. Drug-induced arrhythmias. *Crit Care Med* 2010; **38**: S188-S197 [PMID: 20502173]
19 **De Ponti F**, Poluzzi E, Montanaro N, Ferguson J. QTc and psychotropic drugs. *Lancet* 2000; **356**: 75-76 [PMID: 10892792]
20 **Straus SM**, Sturkenboom MC, Bleumink GS, Dieleman JP, van der Lei J, de Graeff PA, Kingma JH, Stricker BH. Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death. *Eur Heart J* 2005; **26**: 2007-2012 [PMID: 15888497]
21 **Viskin S**, Rosovski U, Sands AJ, Chen E, Kistler PM, Kalman JM, Rodriguez Chavez L, Iturralde Torres P, Cruz F FE, Centurión OA, Fujiki A, Maury P, Chen X, Krahn AD, Roithinger F, Zhang L, Vincent GM, Zeltser D. Inaccurate electrocardiographic interpretation of long QT: the majority of physicians cannot recognize a long QT when they see one. *Heart Rhythm* 2005; **2**: 569-574 [PMID: 15922261]
22 **Garson A**. How to measure the QT interval--what is normal? *Am J Cardiol* 1993; **72**: 14B-16B [PMID: 8256749 DOI: 10.1016/0002-9149(93)90034-A]
23 **Viskin S**, Justo D, Halkin A, Zeltser D. Long QT syndrome caused by noncardiac drugs. *Prog Cardiovasc Dis* 2003; **45**: 415-427 [PMID: 12704598]
24 **Yap YG**, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart* 2003; **89**: 1363-1372 [PMID: 14594906 DOI: 10.1136/heart.89.11.1363]
25 **Algra A**, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. *Circulation* 1991; **83**: 1888-1894 [PMID: 2040041 DOI: 10.1161/01.CIR.83.6.1888]
26 **Drew BJ**, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, Philippides GJ, Roden DM, Zareba W. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *J Am Coll Cardiol* 2010; **55**: 934-947 [PMID: 20185054]
27 **Bednar MM**, Harrigan EP, Ruskin JN. Torsades de pointes associated with nonantiarrhythmic drugs and observations on gender and QTc. *Am J Cardiol* 2002; **89**: 1316-1319 [PMID: 12031739]
28 **Priori SG**, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003; **348**: 1866-1874 [PMID: 12736279]
29 **Antzelevitch C**. Cellular basis and mechanism underlying normal and abnormal myocardial repolarization and arrhythmogenesis. *Ann Med* 2004; **36** Suppl 1: 5-14 [PMID: 15176418 DOI: 10.1080/17431380410032553]
30 **Antzelevitch C**, Shimizu W. Cellular mechanisms underlying the long QT syndrome. *Curr Opin Cardiol* 2002; **17**: 43-51 [PMID: 11790933 DOI: 10.1097/00001573-200201000-00007]
31 **Roden DM**. Cellular basis of drug-induced torsades de pointes. *Br J Pharmacol* 2008; **154**: 1502-1507 [PMID: 18552874]
32 **Bednar MM**, Harrigan EP, Anziano RJ, Camm AJ, Ruskin JN. The QT interval. *Prog Cardiovasc Dis* 2001; **43**: 1-45 [PMID: 11269621]
33 **Antzelevitch C**, Sicouri S, Di Diego JM, Burashnikov A, Viskin S, Shimizu W, Yan GX, Kowey P, Zhang L. Does Tpeak-Tend provide an index of transmural dispersion of repolarization? *Heart Rhythm* 2007; **4**: 1114-1116; author reply 1116-1119 [PMID: 17675094]
34 **Antzelevitch C**. Drug-induced spatial dispersion of repolarization. *Cardiol J* 2008; **15**: 100-121 [PMID: 18651395]
35 **Antzelevitch C**, Oliva A. Amplification of spatial dispersion of repolarization underlies sudden cardiac death associated with catecholaminergic polymorphic VT, long QT, short QT and Brugada syndromes. *J Intern Med* 2006; **259**: 48-58 [PMID: 16336513]
36 **Shimizu W**, Aiba T, Antzelevitch C. Specific therapy based on the genotype and cellular mechanism in inherited cardiac arrhythmias. Long QT syndrome and Brugada syndrome. *Curr Pharm Des* 2005; **11**: 1561-1572 [PMID: 15892662 DOI: 10.2174/1381612053764823]
37 **Kanters JK**, Haarmark C, Vedel-Larsen E, Andersen MP, Graff C, Struijk JJ, Thomsen PE, Christiansen M, Jensen HK, Toft E. T(peak)T(end) interval in long QT syndrome. *J Electrocardiol* 2008; **41**: 603-608 [PMID: 18822425]
38 **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]
39 **Grabowski M**, Karpinski G, Filipiak KJ, Opolski G. Images in cardiovascular medicine. Drug-induced long-QT syndrome with macroscopic T-wave alternans. *Circulation* 2004; **110**: e459-e460 [PMID: 15520328]
40 **Yan GX**, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. *Circulation* 1998; **98**: 1928-1936 [PMID: 9799215 DOI: 10.1161/01.CIR.98.18.1928]
41 **Shimizu W**, Antzelevitch C. Cellular and ionic basis for T-wave alternans under long-QT conditions. *Circulation* 1999; **99**: 1499-1507 [PMID: 10086976 DOI: 10.1161/01.CIR.99.11.1499]
42 **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]
43 **Gupta A**, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. *Am Heart J* 2007; **153**: 891-899 [PMID: 17540188]
44 **Antzelevitch C**. Role of transmural dispersion of repolarization in the genesis of drug-induced torsades de pointes. *Heart Rhythm* 2005; **2**: S9-15 [PMID: 16253930 DOI: 10.1016/j.hrthm.2004.09.011]
45 **Yan GX**, Shimizu W, Antzelevitch C. Characteristics and distribution of M cells in arterially perfused canine left ventricular wedge preparations. *Circulation* 1998; **98**: 1921-1927 [PMID: 9799214 DOI: 10.1161/01.CIR.98.18.1921]
46 **Antzelevitch C**, Shimizu W, Yan GX, Sicouri S, Weissenburger J, Nesterenko VV, Burashnikov A, Di Diego J, Saffitz J, Thomas GP. The M cell: its contribution to the ECG and to normal and abnormal electrical function of the heart. *J Cardiovasc Electrophysiol* 1999; **10**: 1124-1152 [PMID: 10466495 DOI: 10.1111/j.1540-8167.1999.tb00287.x]
47 **Drouin E**, Lande G, Charpentier F. Amiodarone reduces transmural heterogeneity of repolarization in the human heart. *J Am Coll Cardiol* 1998; **32**: 1063-1067 [PMID: 9768733]
48 **van Opstal JM**, Schoenmakers M, Verduyn SC, de Groot SH, Leunissen JD, van Der Hulst FF, Molenschot MM, Wellens

HJ, Vos MA. Chronic amiodarone evokes no torsade de pointes arrhythmias despite QT lengthening in an animal model of acquired long-QT syndrome. *Circulation* 2001; **104**: 2722-2727 [PMID: 11723026 DOI: 10.1161/hc4701.099579]

49 **Yoshiga Y**, Shimizu A, Yamagata T, Hayano T, Ueyama T, Ohmura M, Itagaki K, Kimura M, Matsuzaki M. Beta-blocker decreases the increase in QT dispersion and transmural dispersion of repolarization induced by bepridil. *Circ J* 2002; **66**: 1024-1028 [PMID: 12419934 DOI: 10.1253/circj.66.1024]

50 **Antzelevitch C**, Belardinelli L, Zygmunt AC, Burashnikov A, Di Diego JM, Fish JM, Cordeiro JM, Thomas G. Electrophysiological effects of ranolazine, a novel antianginal agent with antiarrhythmic properties. *Circulation* 2004; **110**: 904-910 [PMID: 15302796]

51 **Di Diego JM**, Belardinelli L, Antzelevitch C. Cisapride-induced transmural dispersion of repolarization and torsade de pointes in the canine left ventricular wedge preparation during epicardial stimulation. *Circulation* 2003; **108**: 1027-1033 [PMID: 12912819]

52 **Kay GN**, Plumb VJ, Arciniegas JG, Henthorn RW, Waldo AL. Torsade de pointes: the long-short initiating sequence and other clinical features: observations in 32 patients. *J Am Coll Cardiol* 1983; **2**: 806-817 [PMID: 6630761 DOI: 10.1016/S0735-1097(83)80226-5]

53 **January CT**, Riddle JM. Early afterdepolarizations: mechanism of induction and block. A role for L-type Ca2+ current. *Circ Res* 1989; **64**: 977-990 [PMID: 2468430 DOI: 10.1161/01.RES.64.5.977]

54 **Fedida D**, Orth PM, Hesketh JC, Ezrin AM. The role of late I and antiarrhythmic drugs in EAD formation and termination in Purkinje fibers. *J Cardiovasc Electrophysiol* 2006; **17** Suppl 1: S71-S78 [PMID: 16686685]

55 **Schulze-Bahr E**. Susceptibility genes & amp; modifiers for cardiac arrhythmias. *Prog Biophys Mol Biol* 2008; **98**: 289-300 [PMID: 19351519]

56 **Priori SG**, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome: clinical impact. *Circulation* 1999; **99**: 529-533 [PMID: 9927399 DOI: 10.1161/01.CIR.99.4.529]

57 **Gaita F**, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R, Grossi S, Richiardi E, Borggrefe M. Short QT Syndrome: a familial cause of sudden death. *Circulation* 2003; **108**: 965-970 [PMID: 12925462 DOI: 10.1161/01.CIR.0000085071.28695.C4]

58 **Giustetto C**, Di Monte F, Wolpert C, Borggrefe M, Schimpf R, Sbragia P, Leone G, Maury P, Anttonen O, Haissaguerre M, Gaita F. Short QT syndrome: clinical findings and diagnostic-therapeutic implications. *Eur Heart J* 2006; **27**: 2440-2447 [PMID: 16926178]

59 **Gollob MH**, Redpath CJ, Roberts JD. The short QT syndrome: proposed diagnostic criteria. *J Am Coll Cardiol* 2011; **57**: 802-812 [PMID: 21310316 DOI: 10.1016/j.jacc.2010.09.048]

60 **Antzelevitch C**, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, Guerchicoff A, Pfeiffer R, Oliva A, Wollnik B, Gelber P, Bonaros EP, Burashnikov E, Wu Y, Sargent JD, Schickel S, Oberheiden R, Bhatia A, Hsu LF, Haïssaguerre M, Schimpf R, Borggrefe M, Wolpert C. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. *Circulation* 2007; **115**: 442-449 [PMID: 17224476]

61 **Brugada R**, Hong K, Dumaine R, Cordeiro J, Gaita F, Borggrefe M, Menendez TM, Brugada J, Pollevick GD, Wolpert C, Burashnikov E, Matsuo K, Wu YS, Guerchicoff A, Bianchi F, Giustetto C, Schimpf R, Brugada P, Antzelevitch C. Sudden death associated with short-QT syndrome linked to mutations in HERG. *Circulation* 2004; **109**: 30-35 [PMID: 14676148 DOI: 10.1161/01.CIR.0000109482.92774.3A]

62 **Tseng GN**. I(Kr): the hERG channel. *J Mol Cell Cardiol* 2001; **33**: 835-849 [PMID: 11343409 DOI: 10.1006/jmcc.2000.1317]

63 **Bellocq C**, van Ginneken AC, Bezzina CR, Alders M, Escande D, Mannens MM, Baró I, Wilde AA. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. *Circulation* 2004; **109**: 2394-2397 [PMID: 15159330 DOI: 10.1161/01.CIR.0000130409.72142.FE]

64 **Barhanin J**, Lesage F, Guillemare E, Fink M, Lazdunski M, Romey G. K(V)LQT1 and lsK (minK) proteins associate to form the I(Ks) cardiac potassium current. *Nature* 1996; **384**: 78-80 [PMID: 8900282]

65 **Priori SG**, Pandit SV, Rivolta I, Berenfeld O, Ronchetti E, Dhamoon A, Napolitano C, Anumonwo J, di Barletta MR, Gudapakkam S, Bosi G, Stramba-Badiale M, Jalife J. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. *Circ Res* 2005; **96**: 800-807 [PMID: 15761194 DOI: 10.1161/01.RES.0000162101.76263.8c]

66 **Templin C**, Ghadri JR, Rougier JS, Baumer A, Kaplan V, Albesa M, Sticht H, Rauch A, Puleo C, Hu D, Barajas-Martinez H, Antzelevitch C, Lüscher TF, Abriel H, Duru F. Identification of a novel loss-of-function calcium channel gene mutation in short QT syndrome (SQTS6). *Eur Heart J* 2011; **32**: 1077-1088 [PMID: 21383000]

67 **Lu HR**, Vlaminckx E, Hermans AN, Rohrbacher J, Van Ammel K, Towart R, Pugsley M, Gallacher DJ. Predicting drug-induced changes in QT interval and arrhythmias: QT-shortening drugs point to gaps in the ICHS7B Guidelines. *Br J Pharmacol* 2008; **154**: 1427-1438 [PMID: 18493243]

68 **Holbrook M**, Malik M, Shah RR, Valentin JP. Drug induced shortening of the QT/QTc interval: an emerging safety issue warranting further modelling and evaluation in drug research and development? *J Pharmacol Toxicol Methods* 2009; **59**: 21-28 [PMID: 18834945]

69 **Shah RR**. Drug-induced QT interval shortening: potential harbinger of proarrhythmia and regulatory perspectives. *Br J Pharmacol* 2010; **159**: 58-69 [PMID: 19563537]

70 **Schimpf R**, Veltmann C, Papavassiliu T, Rudic B, Göksu T, Kuschyk J, Wolpert C, Antzelevitch C, Ebner A, Borggrefe M, Brandt C. Drug-induced QT-interval shortening following antiepileptic treatment with oral rufinamide. *Heart Rhythm* 2012; **9**: 776-781 [PMID: 22245794]

71 **Brugada P**, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 1992; **20**: 1391-1396 [PMID: 1309182]

72 **Wilde AA**, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG, Towbin JA. Proposed diagnostic criteria for the Brugada syndrome. *Eur Heart J* 2002; **23**: 1648-1654 [PMID: 12448445]

73 **Antzelevitch C**, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, LeMarec H, Nademanee K, Perez Riera AR, Shimizu W, Schulze-Bahr E, Tan H, Wilde A. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 2005; **111**: 659-670 [PMID: 15655131 DOI: 10.1161/01.CIR.0000152479.54298.51]

74 **Bayés de Luna A**, Brugada J, Baranchuk A, Borggrefe M, Breithardt G, Goldwasser D, Lambiase P, Riera AP, Garcia-Niebla J, Pastore C, Oreto G, McKenna W, Zareba W, Brugada R, Brugada P. Current electrocardiographic criteria for diagnosis of Brugada pattern: a consensus report. *J Electrocardiol* 2012; **45**: 433-442 [PMID: 22920782]

75 **Mizusawa Y**, Wilde AA. Brugada syndrome. *Circ Arrhythm Electrophysiol* 2012; **5**: 606-616 [PMID: 22715240]

76 **Hu D**, Barajas-Martinez H, Burashnikov E, Springer M, Wu Y, Varro A, Pfeiffer R, Koopmann TT, Cordeiro JM, Guerchicoff A, Pollevick GD, Antzelevitch C. A mutation in the beta 3 subunit of the cardiac sodium channel associated with Brugada ECG phenotype. *Circ Cardiovasc Genet* 2009; **2**: 270-278 [PMID: 20031595]

77 **London B**, Michalec M, Mehdi H, Zhu X, Kerchner L, Sanyal S, Viswanathan PC, Pfahnl AE, Shang LL, Madhusudanan M, Baty CJ, Lagana S, Aleong R, Gutmann R, Acker-

man MJ, McNamara DM, Weiss R, Dudley SC. Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na+ current and causes inherited arrhythmias. *Circulation* 2007; **116**: 2260-2268 [PMID: 17967977 DOI: 10.1161/CIRCULATIONAHA.107.703330]

78 **Delpón E**, Cordeiro JM, Núñez L, Thomsen PE, Guerchicoff A, Pollevick GD, Wu Y, Kanters JK, Larsen CT, Hofman-Bang J, Burashnikov E, Christiansen M, Antzelevitch C. Functional effects of KCNE3 mutation and its role in the development of Brugada syndrome. *Circ Arrhythm Electrophysiol* 2008; **1**: 209-218 [PMID: 19122847]

79 **Giudicessi JR**, Ye D, Tester DJ, Crotti L, Mugione A, Nesterenko VV, Albertson RM, Antzelevitch C, Schwartz PJ, Ackerman MJ. Transient outward current (I(to)) gain-of-function mutations in the KCND3-encoded Kv4.3 potassium channel and Brugada syndrome. *Heart Rhythm* 2011; **8**: 1024-1032 [PMID: 21349352]

80 **Ohno S**, Zankov DP, Ding WG, Itoh H, Makiyama T, Doi T, Shizuta S, Hattori T, Miyamoto A, Naiki N, Hancox JC, Matsuura H, Horie M. KCNE5 (KCNE1L) variants are novel modulators of Brugada syndrome and idiopathic ventricular fibrillation. *Circ Arrhythm Electrophysiol* 2011; **4**: 352-361 [PMID: 21493962]

81 **Meregalli PG**, Wilde AA, Tan HL. Pathophysiological mechanisms of Brugada syndrome: depolarization disorder, repolarization disorder, or more? *Cardiovasc Res* 2005; **67**: 367-378 [PMID: 15913579]

82 **Wilde AA**, Postema PG, Di Diego JM, Viskin S, Morita H, Fish JM, Antzelevitch C. The pathophysiological mechanism underlying Brugada syndrome: depolarization versus repolarization. *J Mol Cell Cardiol* 2010; **49**: 543-553 [PMID: 20659475]

83 **Nishii N**, Nagase S, Morita H, Kusano KF, Namba T, Miura D, Miyaji K, Hiramatsu S, Tada T, Murakami M, Watanabe A, Banba K, Sakai Y, Nakamura K, Oka T, Ohe T. Abnormal restitution property of action potential duration and conduction delay in Brugada syndrome: both repolarization and depolarization abnormalities. *Europace* 2010; **12**: 544-552 [PMID: 20083482]

84 **Yan GX**, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. *Circulation* 1999; **100**: 1660-1666 [PMID: 10517739 DOI: 10.1161/01.CIR.100.15.1660]

85 **Tukkie R**, Sogaard P, Vleugels J, de Groot IK, Wilde AA, Tan HL. Delay in right ventricular activation contributes to Brugada syndrome. *Circulation* 2004; **109**: 1272-1277 [PMID: 14993143 DOI: 10.1161/01.CIR.0000118467.53182.D1]

86 **Postema PG**, van Dessel PF, de Bakker JM, Dekker LR, Linnenbank AC, Hoogendijk MG, Coronel R, Tijssen JG, Wilde AA, Tan HL. Slow and discontinuous conduction conspire in Brugada syndrome: a right ventricular mapping and stimulation study. *Circ Arrhythm Electrophysiol* 2008; **1**: 379-386 [PMID: 19808433]

87 **Lambiase PD**, Ahmed AK, Ciaccio EJ, Brugada R, Lizotte E, Chaubey S, Ben-Simon R, Chow AW, Lowe MD, McKenna WJ. High-density substrate mapping in Brugada syndrome: combined role of conduction and repolarization heterogeneities in arrhythmogenesis. *Circulation* 2009; **120**: 106-117, 1-4 [PMID: 19564561]

88 **Postema PG**, van Dessel PF, Kors JA, Linnenbank AC, van Herpen G, Ritsema van Eck HJ, van Geloven N, de Bakker JM, Wilde AA, Tan HL. Local depolarization abnormalities are the dominant pathophysiologic mechanism for type 1 electrocardiogram in brugada syndrome a study of electrocardiograms, vectorcardiograms, and body surface potential maps during ajmaline provocation. *J Am Coll Cardiol* 2010; **55**: 789-797 [PMID: 20170818]

89 **Postema PG**, Wolpert C, Amin AS, Probst V, Borggrefe M, Roden DM, Priori SG, Tan HL, Hiraoka M, Brugada J, Wilde AA. Drugs and Brugada syndrome patients: review of the literature, recommendations, and an up-to-date website (www.brugadadrugs.org). *Heart Rhythm* 2009; **6**: 1335-1341 [PMID: 19716089]

90 **Ray WA**, Meredith S, Thapa PB, Hall K, Murray KT. Cyclic antidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther* 2004; **75**: 234-241 [PMID: 15001975 DOI: 10.1016/j.clpt.2003.09.019]

91 **Darbar D**, Yang T, Churchwell K, Wilde AA, Roden DM. Unmasking of brugada syndrome by lithium. *Circulation* 2005; **112**: 1527-1531 [PMID: 16144991]

92 **Sawhney V**, Thomas G, Webster P, Schilling R. Resolution of Brugada-pattern ECG after withdrawal of the selective serotonin reuptake inhibitor paroxetine. *Heart* 2010; **96**: 1165-1166 [PMID: 20478856]

93 **Stirnimann G**, Petitprez S, Abriel H, Schwick NG. Brugada syndrome ECG provoked by the selective serotonin reuptake inhibitor fluvoxamine. *Europace* 2010; **12**: 282-283 [PMID: 19875396]

94 **Yap YG**, Behr ER, Camm AJ. Drug-induced Brugada syndrome. *Europace* 2009; **11**: 989-994 [PMID: 19482855]

95 **Vernooy K**, Sicouri S, Dumaine R, Hong K, Oliva A, Burashnikov E, Timmermans C, Delhaas T, Crijns HJ, Antzelevitch C, Rodriguez LM, Brugada R. Genetic and biophysical basis for bupivacaine-induced ST segment elevation and VT/VF. Anesthesia unmasked Brugada syndrome. *Heart Rhythm* 2006; **3**: 1074-1078 [PMID: 16945804 DOI: 10.1016/j.hrthm.2006.05.030]

96 **Vernooy K**, Delhaas T, Cremer OL, Di Diego JM, Oliva A, Timmermans C, Volders PG, Prinzen FW, Crijns HJ, Antzelevitch C, Kalkman CJ, Rodriguez LM, Brugada R. Electrocardiographic changes predicting sudden death in propofol-related infusion syndrome. *Heart Rhythm* 2006; **3**: 131-137 [PMID: 16443524]

97 **Littmann L**, Monroe MH, Svenson RH. Brugada-type electrocardiographic pattern induced by cocaine. *Mayo Clin Proc* 2000; **75**: 845-849 [PMID: 10943241]

98 **Bebarta VS**, Summers S. Brugada electrocardiographic pattern induced by cocaine toxicity. *Ann Emerg Med* 2007; **49**: 827-829 [PMID: 17512876]

99 **Irani F**, Kasmani R, Kanjwal Y. Hyperkalemia and cocaine induced dynamic Brugada-type electrocardiogram. *Eur J Emerg Med* 2010; **17**: 113-115 [PMID: 19641464]

100 **Bauman JL**, Grawe JJ, Winecoff AP, Hariman RJ. Cocaine-related sudden cardiac death: a hypothesis correlating basic science and clinical observations. *J Clin Pharmacol* 1994; **34**: 902-911 [PMID: 7983233]

P- Reviewers Petix N, Tamargo JL **S- Editor** Wen LL
L- Editor A **E- Editor** Ma S