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# Drug-induced Fatal Arrhythmias: Acquired long QT and Brugada Syndromes

**Isik Turker[a], Tomohiko Ai[a,b], Hideki Itoh[c], Minoru Horie[c]**

[a] Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, IN, USA

[b] Department of Clinical Laboratory Medicine, Juntendo University School of Medicine, Tokyo, Japan

[c] Department of Cardiovascular and Respiratory Medicine, Shiga University of Medical Science, Otsu, Shiga, Japan

Address for correspondence: Minoru Horie, MD PhD

Shiga University of Medical Science, Otsu, Japan

Phone: 81-77-548-2213; Fax: 543-5839; E-mail: horie@belle.shiga-med.ac.jp

**Abstract**

Since the early 1990s, the concept of primary "inherited" arrhythmia syndromes or ion channelopathies has evolved rapidly as a result of revolutionary progresses made in molecular genetics.  Alterations in genes coding for membrane proteins such as ion channels or their associated proteins responsible for the generation of cardiac action potentials (AP) have been shown to cause specific malfunctions which eventually lead to cardiac arrhythmias. These arrhythmic disorders include congenital long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, short QT syndrome, progressive cardiac conduction disease, *etc.*  Among these, long QT and Brugada syndromes are the most extensively studied, and drugs cause a phenocopy of these two diseases. To date, more than 10 different genes have been reported to be responsible for each syndrome. More recently, it was recognized that long QT syndrome can be latent, even in the presence of an unequivocally pathogenic mutation (silent mutation carrier). Co-existence of other pathological conditions in these silent mutation carriers may trigger a malignant form of ventricular arrhythmia, the so called *torsade de pointes* (TdP) that is most commonly brought about by drugs. In analogy to the drug-induced long QT syndrome, Brugada type 1 ECG can also be induced or unmasked by a wide variety of drugs and pathological conditions; so physicians may encounter patients with a latent form of Brugada syndrome. Of particular note, Brugada syndrome is frequently associated with atrial fibrillation whose therapeutic agents such as Vaughan Williams class IC drugs can unmask the dormant and asymptomatic Brugada syndrome. This review describes two types of drug-induced arrhythmias: the long QT and Brugada syndromes.

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**Abbreviations:**

AP, Action potential; BrS, Brugada syndrome; ERS, Early repolarization syndrome; ECG, Electrocardiogram; LQTS, Long QT syndrome; RVOT, Right ventricular outflow tract; SDR, Spatial dispersion of repolarization; SNP, Single nucleotide polymorphism; SCD, Sudden cardiac death; SIDS, Sudden infant death syndrome; TdP, Torsade de pointes; VF, Ventricular fibrillation; VT, Ventricular tachycardia

## 1. Introduction

For hundreds of years since the introduction of pharmacological therapeutics, drug-induced arrhythmias which may lead to fatal outcomes have been recognized to occur. One of the first recognized forms of drug-induced fatal arrhythmias was the so-called 'quinidine syncope' (Selzer and Wray, 1964). Later, Vaughan Williams class IA drugs like quinidine or disopyramide were found to block the rapid component of outward (repolarizing) potassium current (designated as $I_{Kr}$), thereby prolonging the action potential (AP) duration and leading to fatal ventricular arrhythmias (**Figure 1C**) (Dessertenne, 1966). Ironically, quinidine is now a widely accepted treatment and the most frequently used drug for Brugada syndrome (BrS) as well as early repolarization syndrome (ERS) owing to its inhibitory effect on transient outward currents ($I_{to}$) (Belhassen et al., 2015; Sacher et al., 2014). Similar to the drug-induced long QT syndrome (LQTS), numerous agents are reported to cause BrS (or Brugada type 1 ECG pattern) through blockage of the depolarizing (inward) sodium or calcium channels. Therefore, intrinsically, these two forms of drug-induced fatal arrhythmias are distinct in terms of arrhythmogenic circumstances created by the culprit drug. The former results from a blockade in outward currents, thereby enabling early afterdepolarizations; and the latter results from a blockade in inward currents and cardiac conduction delay (Priori et al., 2013).  In this review, we will describe drug-induced arrhythmias and their underlying mechanisms in the setting of ion channel diseases.

## 2. Current Concept of Long QT Syndromes

Since the clinical advent of electrocardiography (ECG) in the early 20th century, an abnormally prolonged QT interval was recognized to be associated with familial sudden death, and this syndrome was designated as congenital LQTS (Jervell and Lange-Nielsen, 1957; Romano et al., 1963; Ward, 1964). However, the novel concept of ion channel diseases has emerged and rapidly evolved only in the last two decades, and our understanding was deepened thanks to the detailed studies that were first done on LQTS (Curran et al., 1995; Priori et al., 2013; Sanguinetti et al., 1995; Wang et al., 1996; Wang et al., 1995a; Wang et al., 1995b). The LQTS, indeed, played the role of Rosetta Stone in the conceptualization of ion channel disorders as predicted by Dr. D. Zipes (Zipes, 1991).

In his 1991 review, Dr. Zipes predicted that LQTS could be the key disease that can serve to elucidate the pathologic mechanisms underlying sympathetic ventricular tachycardia (VT) as Wolff-Parkinson-White syndrome did serve to advance our understanding of reentry mechanisms. He hypothesized that the cause of the disease was an intrinsic abnormality of repolarization that lied within the heart itself: abnormal channel proteins reducing or blocking an outward (repolarizing) potassium currents or increasing inward (depolarizing) calcium or sodium currents. **Figure 1** presents this concept schematically (Horie and Itoh, 2007).

Congenital LQTS is now recognized as a heterogeneous disease entity characterized by prolonged ventricular repolarization associated with episodes of syncope and/or life-threatening cardiac arrhythmias, specifically TdP. In 1991, the same year of Dr. Zipes' review paper (Zipes, 1991), Keating and co-workers, using linkage

analyses, demonstrated that a DNA marker near the Harvey ras-1 locus (H-ras-1) on chromosome 11 was associated with LQTS (later classified as type 1: LQT1) (Keating et al., 1991). Four years later, in 1995, the same group found *hERG* (human ether-à-go-go-related gene), now referred to as *KCNH2*, to be responsible for LQT2 and *SCN5A* for LQT3 (Curran et al., 1995; Sanguinetti et al., 1995; Wang et al., 1995b). The *SCN5A* gene encodes the pore-forming α-subunit of the cardiac voltage-gated sodium channel (Na$_V$1.5), the channel responsible for the generation and subsequent propagation of cardiac AP through the heart. In the following 20 years, a multitude of variants in the genes encoding cardiac ion channels or their associated proteins have been shown to result in the malfunction of these proteins and thereby cause different types of inherited arrhythmias (Priori et al., 2013). On the basis of genetic testing, the prevalence of congenital LQTS is reported to be approximately 1/2,000 (Schwartz et al., 2009). Syncope is generally the first and most common manifestation of the disease, while sudden cardiac death (SCD) is rare (1–3%) (Zareba et al., 1998). Of the patients who eventually become symptomatic, 50% experience their first cardiac event by the age of 12, and 90% by the age of 40 (Moss et al., 1991). LQTS is also known to present itself as sudden infant death syndrome (SIDS) (Schwartz et al., 1998). A mutation in an LQTS-causing gene is found in approximately 10% of infants with SIDS (Arnestad et al., 2007).

At the very early stage of channelopathy research, the malfunction of ion channels was thought to be intrinsic (or congenital), but it was gradually recognized that extrinsic factors, especially drugs, can modulate cardiac ion channel function, and even result in their dysfunction. It is now widely accepted that there is a substantial number of

silent variant (or mutation) carriers (Itoh et al., 2016; Itoh et al., 2009; Priori et al., 1999). Even if the victims of drug-induced TdP show no other signs suggestive of congenital LQTS, there are still a substantial number of latent LQTS individuals amongst them carrying mildly dysfunctional variants of LQTS-related genes which would still be classified as congenital LQTS. These latent congenital LQTS forms should be strictly differentiated from "pure" drug-induced LQTS. With specific genotype knowledge in hand, a less restrictive "drugs to avoid" list can be created to avoid further impairment of the particular gene product that is dysfunctional, similar to the gene-specific therapies being investigated in congenital LQTS (Mazzanti et al., 2016). Therefore, genetic tests are of paramount clinical importance not only to the victims of drug-induced fatal arrhythmias, but also to their family members if they are suspected to be silent variant carriers.

In this connection, we very recently screened for the five major LQTS genes among 188 acquired LQTS probands, including drug-induced ones from Japan, France and Italy. In 53 subjects (28%), 47 disease-causing rare variants were identified with the majority of these being in *KCNH2,* which is at variance with previous reports of congenital LQTS (Itoh et al., 2016).  In this study, we also proposed a novel scoring system based on QT duration corrected for the heart rate, age and symptoms that can help physicians to identify individuals that are more likely to carry the LQTS variants. Again, it is of extreme importance to perform cascade screening in family members of drug-induced LQTS patients in order to identify silent mutation carriers who are at potential risk of drug-induced sudden cardiac death.

Only less than 1% of the genome is not identical between two unrelated

individuals and this tiny variability allows them to be distinguished by means of genetic analyses. When genetic variations at a given region are seen in more than 1% of the general population, this variant is defined as "polymorphism"; while when seen in less than 0.5% of the general population, the variant would be defined as "rare" polymorphism or mutation. Among genetic variations, single nucleotide polymorphisms (SNPs) are quite common and thought to specify the characteristics of each individual. When these SNPs are non-synonymous and cause substitution of amino acids, functions of the encoded proteins may be altered.

Up to date, several SNPs that are functionally normal in the absence of drugs have been found to be associated with drug-induced arrhythmias (Itoh et al., 2016; Itoh et al., 2009; Kaab et al., 2012; Nishio et al., 2009; Paulussen et al., 2004; Priori et al., 1999; Sesti et al., 2000). The fact that the Kv11.1 encoded by *KCNH2* is a major target of drugs, as will be described, may partially explain the unusually high frequency of *KCNH2* variants in acquired or drug-induced LQTS. For example, Sesti et al. (Sesti et al., 2000) identified a common polymorphism in *KCNE2*, which encodes MinK-related peptide 1 (MiRP1), the α -subunit of the Kv11.1 channel. The authors screened for variations in *KCNE2* in 98 patients with drug-induced LQTS and found the T8A polymorphism, which is also found in approximately 1.6% of the general population, in a patient with sulfamethoxazole-associated LQTS. In functional analysis, this SNP did not cause $K^+$ current reduction at baseline, but it significantly increased the sensitivity to inhibition $K^+$ currents by sulfamethoxazole.

Similarly, the SNP D85N in *KCNE1* which encodes the α-subunit of cardiac voltage-gated potassium channels was reported to be more prevalent in drug-induced

LQTS patients than in controls (Paulussen et al., 2004). This was also found to be the case in our cohort of LQTS probands where one homozygous and 23 heterozygous carriers were found (allele frequency 3.9%), which was significantly higher compared to the controls (0.81%) (Nishio et al., 2009). Recently, Kääb et al. conducted a study in drug-induced LQTS patients and they identified 1,386 SNPs tagging common haplotype blocks and 38 SNPs in 18 ion channel-associated genes. Again, *KCNE1-D85N* was found to predict drug-induced LQTS with an odds ratio of 9.0, with the variant allele being present in 8.6% of cases, 2.9% of drug-exposed control subjects, and 1.8% of population control subjects (Kaab et al., 2012).

More recently, *in silico* simulation programs were developed using mathematical models integrating the action of drugs on individual ion channels based on data obtained from ex-vivo studies (Mirams et al., 2011). Although this approach has been suggested to improve the cardiac safety assessment of newly-developed drugs, a one-size-fits-all approach without taking individual genetic differences into account would fall short of predicting drug safety in a given patient. Incorporating an individual's genetic data (such as SNPs that are shown to be associated with drug-induced changes in ion channel function) would mold these simulation programs into more robust and reliable risk prediction tools (Kubo et al., 2017).

## 3. Drug-induced Long QT Syndrome

While acquired forms of LQTS are also characterized by QT prolongation and TdP, these are provoked by the presence of extrinsic triggers such as QT-prolonging drugs, hypokalemia or hypomagnesemia, and bradycardia. The QT-prolonging drugs, which

are the most common culprit in acquired LQTS, include many of those in common use such as antihistamines, antibiotics, antidepressants, prokinetics. Therefore, drug-induced LQTS is of substantial concern to clinicians as they portend an unacceptable risk of arrhythmic sudden death in certain individuals. This concern have led to the withdrawal of many newly developing, otherwise useful agents following the observance of a small number of cases with QT prolongation and arrhythmias in phase 2 and 3 stages of drug development.

In 1995, *KCNH2* was first reported to be a causative gene for LQTS type 2 (LQT2) (Curran et al., 1995; Sanguinetti et al., 1995), and Kv11.1, the protein encoded by *KCNH2,* was later found to be a target of numerous agents that cause drug-induced LQTS (Mitcheson et al., 2005; Mitcheson et al., 2000; Smith et al., 2016). The hydrophobic central cavity of the Kv11.1 channels allows a large number of structurally-unrelated drugs to bind and render them inactive by plugging the ion conducting pore. Moreover, some of the culprit drugs interfere with trafficking of channel proteins from the endoplasmic reticulum to the cell membrane, thereby decreasing the channel membrane density (Cubeddu, 2009; 2016).

In addition to these inhibitory actions asserted directly by the QT-prolonging drugs, genetic variations in genes coding for the proteins metabolizing these drugs can also result in drug-induced QT prolongation by altering their serum levels (McBride et al., 2009). Moreover, as a result of drug-drug interactions, co-administered drugs can also alter the quantity or function of the proteins that are activating the QT-prolonging drug or clearing it from the body, resulting in an increase in the effective concentration of the

culprit drug, eventually causing prolongation of the QT interval and fatal arrhythmias (Dresser et al., 2000; Makita et al., 2002; Simard et al., 2001).

The list for QT-prolonging drugs is very long: antiarrhythmics (specifically Vaughan Williams class IA and III agents) (Goineau et al., 2012), prokinetics (cisapride) (Drici and Barhanin, 2000; Itoh et al., 2009; Makita et al., 2002; Rampe et al., 1997; Toga et al., 2007), antifungals (ketoconazole) (Cubeddu, 2016; Dumaine et al., 1998), antihistamines (terfenadine and astemizole) (Rampe et al., 1993; Salata et al., 1995; Wang et al., 2003; Woosley, 1996; Woosley et al., 1993), antiparkinsonian drugs (amantadine and budipine) (Scholz et al., 2003; Vernier et al., 1969), antibiotics (erythromycin) (Dumaine et al., 1998; Goineau et al., 2012; Itoh et al., 2009), antihyperlipidemics (probucol) (Guo et al., 2011; Guo et al., 2007; Hayashi et al., 2004), antipsychotics (haloperidol (Suessbrich et al., 1997) and phenothiazines (Drici et al., 1998; Katchman et al., 2006)).  Here, we do not touch on every culprit drug because a number of papers on drug-induced QT prolongation have been published. For a more comprehensive and updated list of QT-prolonging drugs, the reader is encouraged to access the frequently updated website at https://www.crediblemeds.org.

## 4. Current Concept of Brugada Syndrome

Brugada Syndrome (BrS) has been recognized as an important cause of SCD at a young age. In Southeast Asia, it is the most common cause of natural death in the young healthy population (Vatta et al., 2002). BrS is estimated to be responsible for

about 20% of sudden deaths in victims with structurally normal hearts and the mean age for SCD is around 40 years of age (Antzelevitch et al., 2005b).

BrS is recognized by the characteristic coved-type ST elevations (denoted as type 1) in right precordial leads in the absence of structural heart disease. **Figure 2** depicts typical ECG features induced by pilsicainide tolerance test. According to the J-Wave Syndromes Expert Consensus Report published in 2016 (Antzelevitch et al., 2016), BrS is diagnosed by the following criteria:

1.  In patients with spontaneous type 1 ST-segment elevation of 2 mm or more in at least one lead among leads V1-V3, positioned in the 2nd, 3rd or 4th intercostal space; or,

2.  In patients with drug-induced type 1 ST-segment elevation of 2 mm or more in at least one lead among leads V1-V3, positioned in the 2nd, 3rd or 4th intercostal space and at least one of the following: (i) unexplained SCD or documented VF/ polymorphic VT, (ii) nocturnal agonal respirations, (iii) syncope of probable arrhythmic cause, (iv) first or second degree relative with definite BrS.

In this consensus document, the team of experts also proposed a weighted scoring system that could enable clinicians to rule in probable BrS when above conditions are not fully met. For example, ECG abnormalities can wax and wane over short periods of time, sometimes resulting in diagnosis only after SCD occurs. With the scoring system, one could still rule in probable BrS with a combination of other ominous findings. Therefore, transientness of the ECG findings underscores the importance of genetic and/or drug provocation testing in cases suspicious for aborted SCD, documented

VT/VF or inducible VT/VF in cases suspicious for BrS, unexplained syncope, seizures, nocturnal agonal respirations, family history of unexplained sudden death before 45 years of age or spontaneous type 1 ECG pattern. Likewise, a comprehensive family screening should be performed after diagnosis of an index case is made. A negative cardiac test, however, should not be relied on to exclude BrS, rather the comprehensive clinical history should be taken into account while making diagnostic and therapeutic decisions (Ackerman et al., 2011).

In 1992, BrS was presented as a genetic disorder showing familial aggregation that was associated with a characteristic ECG pattern and sudden cardiac death secondary to polymorphic VT or VF (Brugada and Brugada, 1992). Only 6 years later, within a time frame that can be considered quite short for finding the molecular culprit for a newly described syndrome, the cardiac sodium channel encoding gene, *SCN5A*, was found to be associated with BrS (Chen et al., 1998). To date, more than 300 exonic mutations were identified in *SCN5A* resulting in BrS. Moreover, promoter region polymorphisms, intronic mutations, epigenetic and posttranslational modifications modulating the functional expression of *SCN5A* were also found to be implicated in the syndrome (Beltran-Alvarez et al., 2011; Bezzina et al., 2006; Fernández-Falgueras et al., 2016; Hong et al., 2005; Park et al., 2012). However, BrS is genetically very heterogeneous. While most common gene disorder resulting in BrS involve the gene *SCN5A* (accounting for 20-30% of the cases), there are more than 20 other genes found to be associated with BrS (Juang and Horie, 2016; Kapplinger et al., 2010; Watanabe and Minamino, 2016).

As new genes are being added to the list of culprit genes, new mutations in already known genes are also being discovered with newly diagnosed and reported cases (Turker et al., 2016). Apart from mutations, there are also common variants in cardiac ion channel genes that are not likely to cause harm on their own, but can predispose the carriers to drug-induced arrhythmias such as the polymorphism in *MiRP1* gene mentioned above in relation to drug-induced TdP (Abbott et al., 1999). A common variant allele of *SCN5A* (Y1102), which is present in 13-19% of African Americans, was found to strongly predispose harboring individuals to drug-induced arrhythmias (Splawski et al., 2002). Similarly, the common *SCN5A* promoter haplotype seen in 22% of the Asian population was found to account for 48% of variability in response to Na channel blocking agents, causing individuals carrying this haplotype to be more prone to developing diagnostic BrS ECG and arrhythmia susceptibility (Bezzina et al., 2006).

The vast majority of these polymorphisms predisposing the carriers to full BrS phenotype are yet to be discovered, but with genome-wide association studies, more are being found (Bezzina et al., 2013). In the future, results from these studies will shed light on drug-induced arrhythmias that occur in people who have been tested to be negative for the already known variants. Unfortunately, all of the genetic mechanisms identified thus far can only explain up to 30-35% of the BrS cases (Sarquella-Brugada et al., 2016). Moreover, even though 20 years ago BrS was described in structurally normal hearts, with today's technology, structural abnormalities are being identified in patients diagnosed with BrS making the assessment of genetic contribution more complicated (Catalano et al., 2009; Rudic et al., 2016; van Hoorn et al., 2012).

Mechanisms behind creation of macroscopic arrhythmias by cellular current changes remain controversial. Mainly two hypotheses, based on repolarization or depolarization changes, have been proposed and might be acting alone or in conjunction. The first hypothesis proposes amplification of the inherent differences in repolarization patterns of the different layers of myocardium which is commonly referred to as *the spatial dispersion of repolarization* (SDR) (Antzelevitch, 2001). $I_{to}$ is the most important current ascribed to SDR. It is present in the epicardial cells and M cells, but not in the innermost of the three myocardial layers, the endocardium **(Figure 3A)** (Antzelevitch, 2001). Moreover, in the right ventricle, $I_{to}$ is of nearly threefold magnitude compared to the left ventricle which is behind the arrhythmogenesis of right ventricular origin in BrS (Di Diego et al., 1996).

Transmural voltage difference in phase 1 repolarization caused by heterogeneous expression of $I_{to}$ between endocardium and epicardium explains the abnormal J point elevation seen in BrS **(Figure 3B)** (Antzelevitch, 2001). $I_{to}$ prominence subjects cells to all-or-none repolarization once the nadir of AP phase 1 reaches below the activation threshold of L-type calcium channels resulting in loss of AP dome and shortening of the AP duration **(Figure 3C)** (Yan and Antzelevitch, 1999). This is contributed by certain pathophysiologic conditions and drug interventions that decrease depolarizing currents (ischemia, sodium or calcium channel blockers, potassium channel openers *etc.*) (Antzelevitch, 2005). Heterogeneous loss of the AP dome in the epicardium results in epicardial dispersion of repolarization and contributes more to the inherent transmural heterogeneity. When the dome of AP is lost in epicardial cells, but not in endocardial cells, a transmural voltage gradient between endocardium and

epicardium occurs, showing itself as the characteristic ST segment elevations inscribed on the ECG (Yan and Antzelevitch, 1999).

Progression of currents, within the epicardium or transmurally, from areas where phase 2 is preserved to those where it is lost, cause short coupled re-excitations named phase 2 re-entry which provides the trigger for VT and VF seen in BrS **(Figure 3D)** (Wilde et al., 2002). This hypothesis is also supported by the ECG response of BrS patients to autonomic changes; *i.e.* parasympathetic activation induced increase in $I_{to}$ and/or decrease in $I_{Ca}$ attenuate the spike and dome pattern of the AP increasing the dispersion of repolarization and accentuating the ST elevation seen on ECG (Litovsky and Antzelevitch, 1990; Miyazaki et al., 1996; Mizumaki et al., 2004; Noda et al., 2002). Furthermore, $I_{to}$ blockers quinidine and 4-aminopyridine abolish phase 2 re-entry and resultant polymorphic VT that is provoked with pinacidil in canine wedge preparations (Yan and Antzelevitch, 1999). The importance of $I_{to}$ in development of arrhythmias through dispersion of repolarization was further demonstrated by comparison of two class 1 antiarrhythmic agents, ajmaline and flecainide. In a study by Wolpert et al., while ajmaline induced Brugada type ECG in 22 of 22 patients with suspected BrS, flecainide induced it in only 15 of the 22 patients. This was attributed to the greater $I_{to}$ blocking properties of flecainide but not of ajmaline. It is thought that with more $I_{to}$ blockage, flecainide better counteracts the loss of inward currents asserted by similar $I_{Na}$ blocking effects of these drugs, thereby causes less shortening of the AP duration in the RVOT and less dispersion of repolarization (Wolpert et al., 2005). Recently, Antzelevitch et al., on a canine wedge BrS model created with NS5806-induced increase in $I_{to}$ and verapamil induced decrease in $I_{Ca}$, observed late potentials and fractionated activities

on electrograms from epicardium but not from endocardium that is attributed to the

heterogeneousness of phase 2 of the AP (Szel and Antzelevitch, 2014). This finding fits

with fractionated electrograms observed in BrS patients (Nademanee et al., 2011). Also,

in support of the major role played by $I_{to}$ are the prevalence studies that show an 8-10

fold more occurrence of BrS in males (Priori et al., 2013). This is thought to be due to

the presence of a more prominent transient outward current ($I_{to}$) in males (Di Diego et

al., 2002). Supporting this, Matsuo et al. (Matsuo et al., 2003) reported disappearance

of BrS ECG pattern in two males after castration. In addition to being more prevalent,

male BrS presents with a more serious initial risk profile and worse outcomes. Males

show greater VF inducibility in electrophysiologic studies and 4-5 times more SCD than

women (Benito et al., 2008). In a cohort of 30 children, no male predisposition for BrS

was found, supporting the effect of androgens, which are absent in children (Probst et

al., 2007).

A second hypothesis for development of arrhythmias in BrS proposes slowing of

depolarization and conduction by fibrosis and decreased $I_{Na}$ in RVOT as the primary

mechanism. Relatively delayed depolarization in RVOT with respect to other sites of RV

creates regional potential differences that ascribe itself as the ST-segment elevation

seen on the right precordial leads (Coronel et al., 2005) (Meregalli et al., 2005) (**Figure

4**). This hypothesis is also supported by less drug-induced ST segment elevation

provoked by weaker $I_{Na}$ blockers, disopyramide and procainamide, compared to

stronger ones such as ajmaline (Shimizu et al., 2000). Similarly, class 1B agents have

no role in provocation because of less $I_{Na}$ blocking properties in slow or moderate heart

rates (Miyazaki et al., 1996; Shimizu et al., 2000). This hypothesis is also supported by

Postema et al.'s cardiac mapping study that showed delayed depolarization over the RVOT of BrS patients (Postema et al., 2008). Recently, Nadamanee et al. showed that BrS patients exhibited fractionated electrograms over the RVOT epicardium and ablation of areas with slow conduction eliminated the BrS ECG pattern in 8 of 9 cases (Nademanee et al., 2011). Further supporting this hypothesis is the presence of differentially conducting myocytes in the RVOT which initially develops as a slow conducting tissue and subsequently gains rapid conduction properties during development. Heterogeneity of the conduction caused by remnants of the embryonic tissue creates regional potential differences, triggering arrhythmias (Boukens et al., 2009).

Other mechanisms of BrS phenotype and development of arrhythmias involve abnormal neural crest cell migration, dysfunctional gap junction communication and connexome abnormalities. A discussion on these can be found in a recent review article by Dr. Brugada and colleagues (Sieira et al., 2016).

## 5. Drug-induced Brugada Syndrome

In biologically predisposed patients, environmental factors could modulate the observed phenotype. These individuals may have latent ion channel dysfunction that increases the susceptibility to acquired forms of BrS similar to drug-induced LQTS. Autonomic changes, hormonal changes, alcohol, fever, and medications can turn a normal ECG to a BrS ECG. Several studies reported that exercise (Kasanuki et al., 1997; Nademanee et al., 1997), atropine (Kasanuki et al., 1997) and isoproterenol

infusion (Kasanuki et al., 1997; Miyazaki et al., 1996) could normalize a BrS ECG, whereas muscarinic (Kasanuki et al., 1997; Miyazaki et al., 1996) and selective α-adrenoceptor stimulation (Miyazaki et al., 1996), through reflex vagal activation, could augment the ST elevation. This also explains the propensity of VT/VF episodes during night time in BrS. Similarly, while targeting sympathetic activity via left cardiac sympathetic denervation is a widely accepted therapy for intractable LQTS (Turker and Ai, 2014), it may increase arrhythmias in BrS. In a prospective cohort study of 17 LQTS patients who underwent sympathetic denervation, a patient with BrS-LQTS overlap syndrome was the only one to continue having arrhythmias after other causes were excluded (Olde Nordkamp et al., 2014). Several studies reported successful prevention of intractable episodes of VF in BrS using phosphodiesterase inhibitors, milrinone (Szel et al., 2013) and cilostazol (Shinohara et al., 2014; Szel et al., 2013; Tsuchiya et al., 2002). These drugs elevate cyclic AMP levels in the cell and increase L-type calcium current ($I_{Ca}$), thereby restoring the epicardial AP dome.

Recently, a cohort of suspected BrS patients who had a negative response to ajmaline challenge were re-challenged after they reached puberty (age 16) and 23% of them were found to have converted to a positive response which underscores the influence of hormonal and autonomic changes of puberty on BrS phenotype (Conte et al., 2014).

Fever has long been recognized as a risk factor for arrhythmias seen in BrS. Some *SCN5A* mutations cause alteration in sodium channel kinetics only at high temperatures (Dumaine et al., 1999; Samani et al., 2009). Other studies have suggested that sensibility to fever may not be due to mutations, but due to temperature-

dependent properties of the wild-type *SCN5A* or $I_{to}$, as well as fever induced facilitation of spontaneous activity in RVOT and Purkinje fibers (Keller et al., 2005; Pasquie et al., 2004). Although the exact mechanisms of fever-induced arrhythmias remain controversial, many reports of fever-provoked BrS phenotype underscore the importance of antipyretic management in patients with BrS (Barra et al., 2013; Kum et al., 2002; Morita et al., 2002; Porres et al., 2002; Saura et al., 2002). On the other extreme, cold exposure can also result in unmasking of the BrS phenotype by increasing $I_{to}$ (Nishida et al., 2004; Noda et al., 2003).

Ischemia involving the RVOT depresses L-type $I_{Ca}$ and activates $I_{KATP}$, unmasking BrS ECG (Kataoka, 2000). It can then be inferred, agents resulting in vasospasm and ischemia could increase the chance of arrhythmias in predisposed subjects (Chinushi et al., 2001; Noda et al., 2002). This also makes treatment of spontaneous vasospasm challenging in BrS as both nitrates and calcium channel blockers commonly used to treat coronary vasospasm could also induce the BrS phenotype (Antzelevitch et al., 2005b).

As can be summarized from above discussions, any drug that would decrease $I_{Na}$ or $I_{Ca}$ or increase $I_{to}$ would be arrhythmogenic in BrS. According to their mechanism of action, these drugs can be classified into three major groups:

**5-1. Sodium Channel Blockers**

The amplitude of $I_{Na}$ underlies the maximum positive membrane potential reached at the end of AP phase 0. If $I_{Na}$ is diminished, then AP phase 1 starts at lower membrane potential and ends at more negative potentials. The balance of inward and

outward currents at the end of phase 1 determines whether or not $I_{Ca}$ can overcome the outward currents and induce formation of the AP dome. Since endocardium and epicardium have different responses to $I_{Na}$ blocking agents (Krishnan and Antzelevitch, 1991), they cause transmural heterogeneity in the formation of the AP dome. Class IA and IC antiarrhythmic agents are therefore utilized in unmasking the BrS phenotype. **Figure 2** shows pilsicainide-induced ECG changes in a patient with drug-induced BrS who received the drug for treatment of atrial fibrillation. Generally class IC agents with the exception of flecainide have stronger $I_{Na}$ blocking effects than IA agents due to a faster dissociation of the latter class from the sodium channels. Class IB agents, on the other hand, are not as effective because of their small effect on $I_{Na}$ at normal heart rates.

Tricyclic antidepressants (amitriptyline (Bolognesi et al., 1997; Rouleau et al., 2001), desimipramine (Babaliaros and Hurst, 2002), nortriptyline (Bigwood et al., 2005; Tada et al., 2001), clomipramine (Goldgran-Toledano et al., 2002), imipramine (Ogata and Narahashi, 1989), *etc.*) and tetracyclic antidepressants (maprotiline (Bolognesi et al., 1997)), via their sodium channel blocking effects, are known to precipitate Brugada type ECG by diminishing the net inward current at the end of phase 1 AP. Among tricyclic antidepressants, amitriptyline and imipramine are also shown to reduce $I_{to}$ activation. (Casis and Sanchez-Chapula, 1998; Delpon et al., 1992) Moreover, amitriptyline also blocks $I_{Kr}$ (Jo et al., 2000). $I_{to}$ and $I_{Kr}$ blockage can compensate for the decrease in $I_{Na}$ and explain why amitriptyline fails to induce BrS phenotype when used alone (Minoura et al., 2012).

Neuroleptic drug class phenothiazines (chlorpromazine (Ogata and Narahashi, 1989), trifluoperazine (Klockner and Isenberg, 1987; Rouleau et al., 2001), cyamemazine (Crumb et al., 2006; Rouleau et al., 2001), perphenazine (Bolognesi et al., 1997)), haloperidol (Ogata and Narahashi, 1989) and loxapine (Rouleau et al., 2001) can induce BrS type ECG via sodium channel blocking properties.

SSRIs, particularly fluoxetine, have sodium and calcium channel blocking properties in mammalian ventricular myocytes and have been shown to induce BrS type ECG (Pacher et al., 2000b; Rouleau et al., 2001). Another SSRI, citalopram, has been found to inhibit activation of $I_{Na}$ as well (Pacher et al., 2000a). Other SSRIs, fluvoxamine (Stirnimann et al., 2010) and paroxetine (Bigwood et al., 2005) are also reported to unmask BrS ECG. Antihistaminic agents terfenadine (Di Diego et al., 2002), dimenhydrinate (Pastor et al., 2001) and diphenhydramine, (Lopez-Barbeito et al., 2005) through sodium channel blocking properties, precipitate BrS. It should be noted that tricyclic antidepressants, phenothiazines and antihistaminics have anticholinergic properties as well and would be expected to neutralize the Brugada phenotype; however, it is thought that the phenotype shows itself because of more predominant blockage of sodium channels than of muscarinic receptors with these drugs.

Antihistaminic drug, terfenadine, which has both $I_{Na}$ and $I_{Ca}$ blocking properties was shown to be more effective in provoking VT than $I_{Na}$ blockers alone in canine models of ventricular wedge preparations (Fish and Antzelevitch, 2004). Among sodium channel blocking agents those with potent $I_{to}$ blocking effects (flecainide and disopyramide) (Virag et al., 1998; Wolpert et al., 2005) are less likely or even not likely (quinidine) (Alings et al., 2001) to induce arrhythmogenesis. Lithium (Darbar et al.,

2005), cocaine (Bebarta and Summers, 2007; Littmann et al., 2000; Ortega-Carnicer et al., 2001), cannabis (Romero-Puche et al., 2012), alcohol (Habuchi et al., 1995; Rouleau et al., 2001) and anesthetic agents (propofol (Vernooy et al., 2006a), bupivacaine (Vernooy et al., 2006b), ketamine (Hara et al., 1998)) also unmask BrS phenotype by decreasing $I_{Na}$. Even though methadone is better known for its association with drug-induced long QT Syndrome, it has also been reported to induce BrS ECG (Junttila et al., 2008). Another synthetic opioid tramadol which blocks neuronal sodium channels is also reported to unmask BrS type ECG (Cole et al., 2012). Many antiepileptic medications assert their affect via blockage of the neuronal sodium channels. Some of these have also been shown to alter cardiac sodium channel kinetics (Xu et al., 1991), while some are yet to be shown to do so. A word of caution on the subject of sodium channel blockers and BrS should be made in the treatment of patients presenting with seizures.

Patients who develop a syncopal episode and found in a "post-ictal state" could have had an arrhythmic episode and found in a state of confusion due to cerebral hypoperfusion which could be mistaken for post-ictal status. In these patients well-intended therapeutic maneuvers with sodium channel blocking antiepileptic medications (phenytoin, carbamazepine, primidone, lamotrigine, and topiramate *etc.*) could induce BrS and have deleterious consequences. Therefore, diagnosis of seizure disorder should only be made after careful exclusion of the possibility of BrS.

## 5-2. Potassium Channel Openers

The balance of inward and outward currents at the end of AP phase 1 determines whether or not repolarization will occur in an all-or-none fashion; therefore, any increase in outward currents ($I_{KATP}$, $I_{to}$, and $I_{Kr}$) can cause loss of the AP dome and result in a vulnerable window in voltage gradients between areas where these currents are differentially expressed. $I_{KATP}$ activators, pinacidil (Di Diego et al., 2002) and nicorandil (Robert et al., 1999), have been shown to cause loss of the AP dome in areas where $I_{to}$ is prominent with resultant phase-2 reentry in experimental models. Glucose and insulin could unmask the BrS phenotype by decreasing serum potassium concentrations and accentuating $I_{to}$ (Nishizaki et al., 2003). Nogami et al. were able to provoke Brugada phenotype with insulin and glucose in 7 out of 7 men who had aborted SCD (Nogami et al., 2003). Diuretics and distal renal tubular acidosis can act in a similar manner by decreasing serum potassium levels (Mok et al., 2008; Nimmannit et al., 1991).

### 5-3. Calcium Channel Blockers

$I_{Ca}$ is the main current to form the AP dome. If it is diminished and cannot overcome the outward balance of currents at the end of phase 1 AP, the dome disappears. It has been shown that $I_{to}$ which is the main current responsible for formation of phase 1 is heterogeneously expressed in between different layers of the myocardium (Litovsky and Antzelevitch, 1988), therefore a strong $I_{Ca}$ acts as the rescuer of the AP dome where $I_{to}$ is increased. The basis of provocation of BrS phenotype with calcium channel blockers, in part, is due to failing to reach the potential threshold needed to rescue the AP dome in areas where $I_{to}$ is strong (RVOT). Calcium channel blockers (Chinushi et al., 2006; Fish and Antzelevitch, 2008) and β-blockers (Grace and

Camm, 2000; Kasanuki et al., 1997) unmask BrS by decreasing L-type calcium currents. Litovsky et al. showed that acetylcholine, by inhibition of $I_{Ca}$, can result in loss of the AP dome and trigger arrhythmias (Litovsky and Antzelevitch, 1990). Nitrates, similarly, have L-type Ca channel blocking properties and could induce BrS phenotype (Matsuo et al., 1998). Of the $I_{Na}$ blockers listed above, trifluoperazine (Klockner and Isenberg, 1987), cyamemazine (Crumb et al., 2006), fluoxetine (Pacher et al., 2000b), terfenadine (Fish and Antzelevitch, 2004), ketamine (Hara et al., 1998), alcohol (Habuchi et al., 1995) *etc.* also block $I_{Ca}$ increasing the effects of these drugs in uncovering the BrS phenotype.

## 5-4. Treatment and Prevention of Drug-induced BrS

Drug-induced BrS phenotype is not benign. In a recent series of 47 patients with drug-induced BrS ECG, 51% developed malignant arrhythmias (Junttila et al., 2008). Interestingly, however, not all the cases share similar prognosis. For example, when tricyclic antidepressants are the culprit for Brugada type ECG, malignant arrhythmias are far less common (Behr and Camm, 2008). In a recent review of 74 cases of drug-induced BrS, it was found that 31% of patients developed arrhythmias with a mortality rate of 14%. The only characteristics that differentiated patients who developed arrhythmias from those who did not were younger age and non-oral route of administration for the culprit drugs. Both in those with and without arrhythmias, duration of exposure to the drug before the BrS ECG developed was weeks to years, making ECG screening at the time of drug initiation impractical (Konigstein et al., 2016). Immediate withdrawal of the offending drug is effective in most BrS cases. If additional treatment is needed, agents that restore the inward and outward current balance can be

used. Isoproterenol has been shown to decrease the ST elevation inscribed by the dispersion of repolarization and suppress electrical storm in BrS patients (Miyazaki et al., 1996; Watanabe et al., 2006) (Ohgo et al., 2007). Cilostazol (Shinohara et al., 2014; Szel et al., 2013; Tsuchiya et al., 2002), bepridil (Ohgo et al., 2007), and milrinone (Szel et al., 2013) have also been shown to suppress VF in BrS patients. According to the J-Wave Syndromes Expert Consensus Report published in 2016, a drug-induced type 1 ST segment elevation in one of the right precordial leads is sufficient for the diagnosis of BrS when combined with various other clinical features (Antzelevitch et al., 2016). Therefore, in those with induced BrS, the offending agent or condition should be immediately withdrawn or treated and these individuals should be counseled on: (a) avoidance of drugs that may induce or aggravate ST-segment elevation in right precordial leads (for a dynamic list visit: http://www.brugadadrugs.org/) (Postema et al., 2009), (b) avoidance of excessive alcohol intake, and (c) immediate treatment of fever with antipyretic drugs.

Postema et al. initiated a dynamic website in 2009 as a repository of potentially arrhythmogenic drugs (Postema et al., 2009). This website is frequently updated as new drugs are added to or deleted from the implicated drugs list. In addition to being a professional resource of information for caregivers, it also serves as a resource for patients themselves in case they want to check the drugs they should avoid. The drugs on the website are listed in four categories: 1) drugs to be avoided by BrS patients; 2) drugs preferably avoided by BrS patients; 3) potential antiarrhythmic drugs in BrS patients; 4) diagnostic drugs in BrS. The recommendations follow the familiar AHA/ACC/ESC guidelines format and should be of help to physicians caring for

individuals with suspected BrS and to patients diagnosed with BrS (Postema et al.,

2009). A tabular form of the drugs discussed in this article can be viewed in **Table 1**.

6. Future Perspectives

     Drug-induced fatal arrhythmias are not uncommon. Substantial genetic

background has been shown to underlie the predisposition to drug-induced arrhythmic

events especially in the absence of structural heart disease. Not only medical

professionals, but also patients themselves should know the potential culprit drugs that

trigger LQTS or BrS phenocopy, and websites are very useful for the promotion of this

type of tailored medicine: https://www.crediblemeds.org and

http://www.brugadadrugs.org.

Conflict of Interest Statement:

The authors declare that there are no conflicts of interest.

**Table 1**

| Sodium Channel Blockers | |
|---|---|
| Class 1A antiarrhythmics | Ajmaline (Brugada et al., 2000; Wolpert et al., 2005), procainamide (Brugada et al., 2000), disopyramide (Shimizu et al., 2000), cibenzoline (Tada et al., 2000) |
| Class 1C antiarrhythmics | Pilsicainide (Fujiki et al., 1999; Turker et al., 2016), flecainide (Brugada et al., 2000; Fujiki et al., 1999; Krishnan and Josephson, 1998; Wolpert et al., 2005), propafenone (Matana et al., 2000) |
| Antidepressants | Tricyclics (amitriptyline (Bolognesi et al., 1997; Rouleau et al., 2001), nortriptyline (Bigwood et al., 2005; Tada et al., 2001), desipramine (Babaliaros and Hurst, 2002), clomipramine (Goldgran-Toledano et al., 2002)), tetracyclics (maprotiline (Bolognesi et al., 1997)), SSRIs (fluoxetine (Rouleau et al., 2001), paroxetine (Bigwood et al., 2005), fluvoxamine (Stirnimann et al., 2010)) |
| Neuroleptics | Phenothiazines (chlorpromazine) (Ogata and Narahashi, 1989), trifluoperazine (Rouleau et al., 2001), cyomemazine (Rouleau et al., 2001), perphenazine (Bolognesi et al., 1997)), haloperidol (Ogata and Narahashi, 1989), lithium (Darbar et al., 2005), loxapine (Rouleau et al., 2001) |
| Antiepileptics | Lamotrigine (Strimel et al., 2010), oxcarbazepine (El-Menyar et al., 2011), phenytoin (Swe et al., 2016) |
| Anesthetics | Propofol (Vernooy et al., 2006a), bupivacaine (Vernooy et al., 2006b), ketamine (Hara et al., 1998) |
| Analgesics | Methadone (Junttila et al., 2008), tramadol (Cole et al., 2012) |
| Antihistaminics | Terfenadine (Di Diego et al., 2002; Fish and Antzelevitch, 2004), dimenhydrinate (Pastor et al., 2001), diphenhydramine (Lopez-Barbeito et al., 2005) |
| Recreational drugs | Cocaine (Bebarta and Summers, 2007; Littmann et al., 2000; Ortega-Carnicer et al., 2001), cannabis (Romero-Puche et al., 2012), alcohol (Rouleau et al., 2001) |
| **Calcium Channel Blockers** | |
| Verapamil (Chinushi et al., 2006; Fish and Antzelevitch, 2008), diltiazem (Itoh et al., 1999), nifedipine (Antzelevitch et al., 2005a) | |

**Autonomic Regulators**

Acetylcholine (Miyazaki et al., 1996), edrophonium (Kasanuki et al., 1997; Miyazaki et al., 1996), neostigmine (Miyazaki et al., 1996), alpha agonists (Miyazaki et al., 1996)

**Beta Blockers**

Propranolol (Aouate et al., 2005; Kasanuki et al., 1997; Tada et al., 2000)

**Potassium Channel Openers**

Pinacidil (Di Diego et al., 2002), nicorandil (Robert et al., 1999)

**Potentially Therapeutic Drugs**

Isoproterenol (Miyazaki et al., 1996; Ohgo et al., 2007; Watanabe et al., 2006), cilostazol (Shinohara et al., 2014; Szel et al., 2013; Tsuchiya et al., 2002), bepridil (Ohgo et al., 2007), milrinone (Szel et al., 2013)

**Figure 1. Action potential and QT interval: A)** Schematic presentation of ion currents contributing to the phases of action potential (AP) in the ventricle. **B)** AP duration is determined by the balance of inward $Na^+$ and $Ca^{2+}$ currents (blue and yellow arrows) and outward $K^+$ current (red arrow) (left panel). An increase in the inward currents or a decrease in the outward currents prolongs the AP duration (middle panel) causing long QT syndrome (right panel). Abbreviations: $I_{Na}$: sodium current; $I_{to}$: transient outward potassium current; $I_{Ca,L}$: L-type calcium current; $I_{Kr}$: rapid component of delayed rectifier potassium current; $I_{Ks}$: slow component of delayed rectifier potassium current ; GOF: gain of function; LOF: loss of function. Reproduced from *Circ J.* 71, Suppl A:A50-53 (Horie and Itoh, 2007) with permission. **C)** ECG tracing showing the typical onset of drug-induced TdP (courtesy of Dr S. Matsuoka, Yamanasi University).

**Figure 2. Pilsicainide-induced Brugada pattern ECG changes:** Left panels show baseline precordial leads and the right panels show the same after intravenous injection of pilsicainide (0.8 mg/kg). Reproduced from *PLoS ONE* 11(8):e0161872 (Turker et al., 2016) with permission.

**Figure 3. Dispersion of repolarization and phase 2 reentry hypothesis in Brugada Syndrome: A)** $I_{to}$ is the main current responsible for the phase 1 of the AP and is absent in endocardial cells. **B)** Transmural voltage difference in phase 1 repolarization caused by heterogeneous expression of $I_{to}$ between endocardium and epicardium explains the abnormal J point elevation seen in J wave syndromes. **C)** $I_{to}$ prominence and/or decrease in inward sodium or calcium currents in BrS subject cells to all-or-none repolarization once the nadir of AP phase 1 reaches below the activation threshold of L-type calcium channels thereby resulting in loss of the AP dome and shortening of the AP duration. **D)** Progression of currents, within the epicardium or transmurally, from areas where phase 2 is preserved to those where it is lost cause short coupled re-excitations named phase 2 re-entry which provides the trigger for VT and VF seen in BrS. Modified from *J. Cardiovasc. Electrophysiol.* 12, 268-272 (Antzelevitch, 2001) with permission from John Wiley and Sons.

**Figure 4. Depolarization (conduction delay) hypothesis in Brugada Syndrome: A and B)** RVOT action potential is delayed with respect to the rest of the RV. **C)** The current travels from the more positive RV to the still undepolarized RVOT **(a)** and loops

back towards the RV **(b and c)**. **D)** The action potential traveling from the RV to RVOT

and then back to the RV creates the positive and negative inscriptions of the ST

segment seen in lead V2. **E and F)** In the next phase of the cardiac cycle, the potential

gradients between RVOT and RV are reversed due to AP delay in the RVOT and this

time, the current travels from the RVOT to the RV, resulting in the negative T wave seen

in **Figure 4F.** Modified from *Cardiovasc Res.* 67, 367-378 (Meregalli et. al., 2005) with

permission.

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Figure 1.



A.

Phase 1
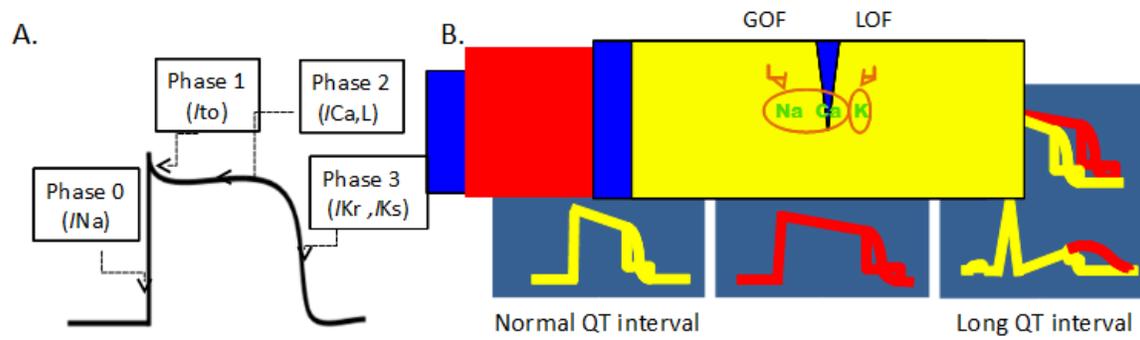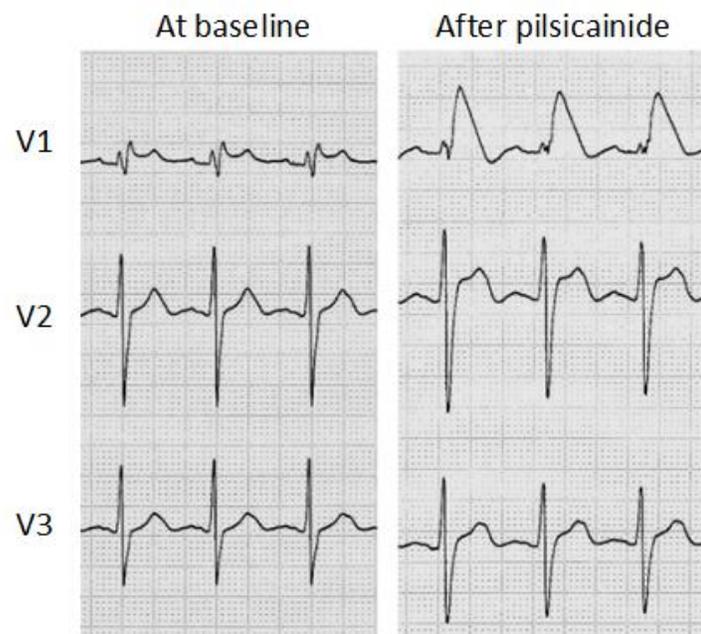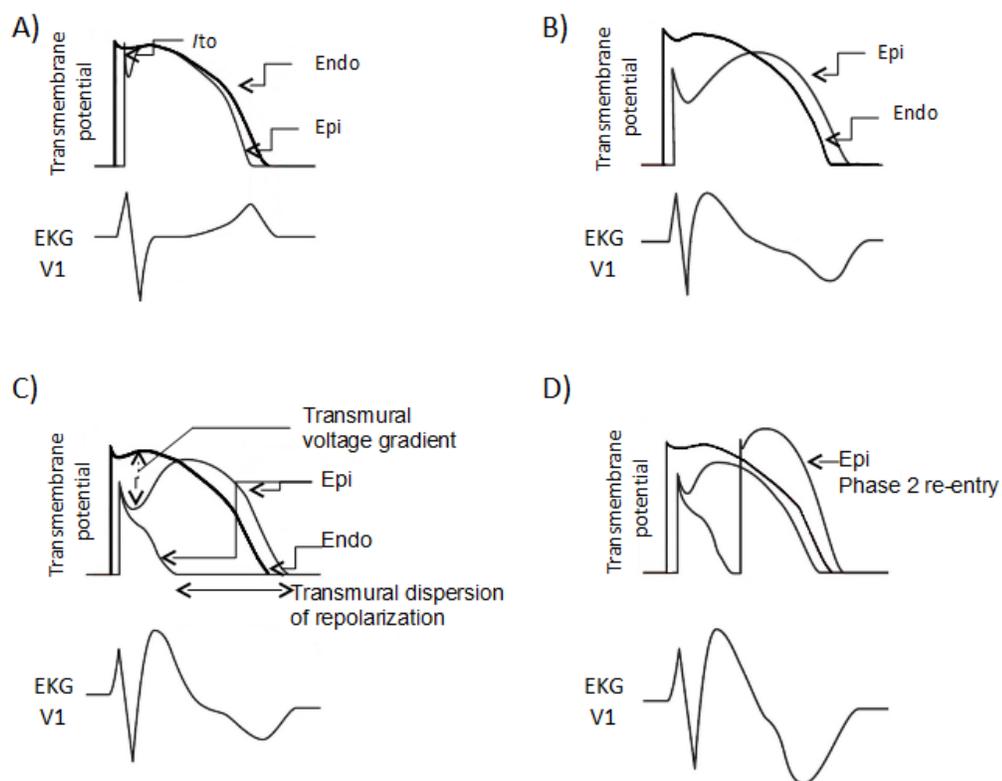(*I*to)

Phase 2
(*I*Ca,L)

Phase 0
(*I*Na)

Phase 3
(*I*Kr ,*I*Ks)

B.

GOF        LOF

Na  Ca  K

Normal QT interval

Long QT interval

Figure 2

Figure 3.

Figure 4.