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

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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.

Keywords: drug-induced arrhythmias; ion channelopathy; long QT syndrome; Brugada syndrome; genetic variants; silent mutation carrier

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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 ($Na_V1.5$), 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.

References

Abbott GW, Sesti F, Splawski I, Buck ME, Lehmann MH, Timothy KW, Keating MT and Goldstein SA (1999) MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. *Cell* **97**:175-187.

Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP, Heart Rhythm S and European Heart Rhythm A (2011) HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology* **13**:1077-1109.

Alings M, Dekker L, Sadee A and Wilde A (2001) Quinidine induced electrocardiographic normalization in two patients with Brugada syndrome. *Pacing and clinical electrophysiology : PACE* **24**:1420-1422.

Antzelevitch C (2001) The Brugada syndrome: ionic basis and arrhythmia mechanisms. *Journal of cardiovascular electrophysiology* **12**:268-272.

Antzelevitch C (2005) In vivo human demonstration of phase 2 reentry. *Heart rhythm : the official journal of the Heart Rhythm Society* **2**:804-806.

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 and Wilde A (2005a) Brugada syndrome: report of the second consensus conference. *Heart rhythm : the official journal of the Heart Rhythm Society* **2**:429-440.

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 and Wilde A (2005b) Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* **111**:659-670.

Aouate P, Clerc J, Viard P and Seoud J (2005) Propranolol intoxication revealing a Brugada syndrome. *Journal of cardiovascular electrophysiology* **16**:348-351.

Arnestad M, Crotti L, Rognum TO, Insolia R, Pedrazzini M, Ferrandi C, Vege A, Wang DW, Rhodes TE, George AL, Jr. and Schwartz PJ (2007) Prevalence of long-QT syndrome gene variants in sudden infant death syndrome. *Circulation* **115**:361-367.

Babaliaros VC and Hurst JW (2002) Tricyclic antidepressants and the Brugada syndrome: an example of Brugada waves appearing after the administration of desipramine. *Clinical cardiology* **25**:395-398.

Barra S, Providencia R and Nascimento J (2013) Fever outperforms flecainide test in the unmasking of type 1 Brugada syndrome electrocardiogram. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology* **15**:394.

Bebarta VS and Summers S (2007) Brugada electrocardiographic pattern induced by cocaine toxicity. *Annals of emergency medicine* **49**:827-829.

Behr ER and Camm AJ (2008) Letter by Behr and Camm regarding article, "Induced Brugada-type electrocardiogram, a sign for imminent malignant arrhythmias". *Circulation* **118**:e701; author reply e702.

Belhassen B, Rahkovich M, Michowitz Y, Glick A and Viskin S (2015) Management of Brugada Syndrome: Thirty-Three-Year Experience Using Electrophysiologically Guided Therapy With Class 1A Antiarrhythmic Drugs. *Circulation Arrhythmia and electrophysiology* **8**:1393-1402.

Beltran-Alvarez P, Pagans S and Brugada R (2011) The cardiac sodium channel is post-translationally modified by arginine methylation. *Journal of proteome research* **10**:3712-3719.

Benito B, Sarkozy A, Mont L, Henkens S, Berruezo A, Tamborero D, Arzamendi D, Berne P, Brugada R, Brugada P and Brugada J (2008) Gender differences in clinical manifestations of Brugada syndrome. *Journal of the American College of Cardiology* **52**:1567-1573.

Bezzina CR, Barc J, Mizusawa Y, Remme CA, Gourraud JB, Simonet F, Verkerk AO, Schwartz PJ, Crotti L, Dagradi F, Guicheney P, Fressart V, Leenhardt A, Antzelevitch C, Bartkowiak S, Borggrefe M, Schimpf R, Schulze-Bahr E, Zumhagen S, Behr ER, Bastiaenen R, Tfelt-Hansen J, Olesen MS, Kaab S, Beckmann BM, Weeke P, Watanabe H, Endo N, Minamino T, Horie M, Ohno S, Hasegawa K, Makita N, Nogami A, Shimizu W, Aiba T, Froguel P, Balkau B, Lantieri O, Torchio M, Wiese C, Weber D, Wolswinkel R, Coronel R, Boukens BJ, Bezieau S, Charpentier E, Chatel S, Despres A, Gros F, Kyndt F, Lecointe S, Lindenbaum P,

Portero V, Violleau J, Gessler M, Tan HL, Roden DM, Christoffels VM, Le Marec H, Wilde AA, Probst V, Schott JJ, Dina C and Redon R (2013) Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. *Nature genetics* **45**:1044-1049.

Bezzina CR, Shimizu W, Yang P, Koopmann TT, Tanck MW, Miyamoto Y, Kamakura S, Roden DM and Wilde AA (2006) Common sodium channel promoter haplotype in asian subjects underlies variability in cardiac conduction. *Circulation* **113**:338-344.

Bigwood B, Galler D, Amir N and Smith W (2005) Brugada syndrome following tricyclic antidepressant overdose. *Anaesthesia and intensive care* **33**:266-270.

Bolognesi R, Tsialtas D, Vasini P, Conti M and Manca C (1997) Abnormal ventricular repolarization mimicking myocardial infarction after heterocyclic antidepressant overdose. *The American journal of cardiology* **79**:242-245.

Boukens BJ, Christoffels VM, Coronel R and Moorman AF (2009) Developmental basis for electrophysiological heterogeneity in the ventricular and outflow tract myocardium as a substrate for life-threatening ventricular arrhythmias. *Circulation research* **104**:19-31.

Brugada P and Brugada J (1992) Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *Journal of the American College of Cardiology* **20**:1391-1396.

Brugada R, Brugada J, Antzelevitch C, Kirsch GE, Potenza D, Towbin JA and Brugada P (2000) Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. *Circulation* **101**:510-515.

Casis O and Sanchez-Chapula JA (1998) Mechanism of block of cardiac transient outward K+ current (I(to)) by antidepressant drugs. *Journal of cardiovascular pharmacology* **32**:527-534.

Catalano O, Antonaci S, Moro G, Mussida M, Frascaroli M, Baldi M, Cobelli F, Baiardi P, Nastoli J, Bloise R, Monteforte N, Napolitano C and Priori SG (2009) Magnetic resonance investigations in Brugada syndrome reveal unexpectedly high rate of structural abnormalities. *European heart journal* **30**:2241-2248.

Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, Potenza D, Moya A, Borggrefe M, Breithardt G, Ortiz-Lopez R, Wang Z, Antzelevitch C, O'Brien RE, Schulze-Bahr E, Keating MT, Towbin JA and Wang Q (1998) Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* **392**:293-296.

Chinushi M, Kuroe Y, Ito E, Tagawa M and Aizawa Y (2001) Vasospastic angina accompanied by Brugada-type electrocardiographic abnormalities. *Journal of cardiovascular electrophysiology* **12**:108-111.

Chinushi M, Tagawa M, Nakamura Y and Aizawa Y (2006) Shortening of the ventricular fibrillatory intervals after administration of verapamil in a patient with Brugada syndrome and vasospastic angina. *Journal of electrocardiology* **39**:331-335.

Cole JB, Sattiraju S, Bilden EF, Asinger RW and Bertog SC (2012) Isolated tramadol overdose associated with Brugada ECG pattern. *Pacing and clinical electrophysiology : PACE* **35**:e219-221.

Conte G, de Asmundis C, Ciconte G, Julia J, Sieira J, Chierchia GB and Brugada P (2014) Follow-up from childhood to adulthood of individuals with family history of Brugada syndrome and normal electrocardiograms. *Jama* **312**:2039-2041.

Coronel R, Casini S, Koopmann TT, Wilms-Schopman FJ, Verkerk AO, de Groot JR, Bhuiyan Z, Bezzina CR, Veldkamp MW, Linnenbank AC, van der Wal AC, Tan HL, Brugada P, Wilde AA and de Bakker JM (2005) Right ventricular fibrosis and conduction delay in a patient with clinical signs of Brugada syndrome: a combined electrophysiological, genetic, histopathologic, and computational study. *Circulation* **112**:2769-2777.

Crumb W, Llorca PM, Lancon C, Thomas GP, Garay RP and Hameg A (2006) Effects of cyamemazine on hERG, INa, ICa, Ito, Isus and IK1 channel currents, and on the QTc interval in guinea pigs. *European journal of pharmacology* **532**:270-278.

Cubeddu LX (2009) Iatrogenic QT Abnormalities and Fatal Arrhythmias: Mechanisms and Clinical Significance. *Current cardiology reviews* **5**:166-176.

Cubeddu LX (2016) Drug-induced Inhibition and Trafficking Disruption of ion Channels: Pathogenesis of QT Abnormalities and Drug-induced Fatal Arrhythmias. *Current cardiology reviews* **12**:141-154.

Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED and Keating MT (1995) A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. *Cell* **80**:795-803.

Darbar D, Yang T, Churchwell K, Wilde AA and Roden DM (2005) Unmasking of brugada syndrome by lithium. *Circulation* **112**:1527-1531.

Delpon E, Tamargo J and Sanchez-Chapula J (1992) Effects of imipramine on the transient outward current in rabbit atrial single cells. *British journal of pharmacology* **106**:464-469.

Dessertenne F (1966) [Ventricular tachycardia with 2 variable opposing foci]. *Archives des maladies du coeur et des vaisseaux* **59**:263-272.

Di Diego JM, Cordeiro JM, Goodrow RJ, Fish JM, Zygmunt AC, Perez GJ, Scornik FS and Antzelevitch C (2002) Ionic and cellular basis for the predominance of the Brugada syndrome phenotype in males. *Circulation* **106**:2004-2011.

Di Diego JM, Sun ZQ and Antzelevitch C (1996) I(to) and action potential notch are smaller in left vs. right canine ventricular epicardium. *The American journal of physiology* **271**:H548-561.

Dresser GK, Spence JD and Bailey DG (2000) Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clinical pharmacokinetics* **38**:41-57.

Drici MD and Barhanin J (2000) Cardiac K+ channels and drug-acquired long QT syndrome. *Therapie* **55**:185-193.

Drici MD, Wang WX, Liu XK, Woosley RL and Flockhart DA (1998) Prolongation of QT interval in isolated feline hearts by antipsychotic drugs. *Journal of clinical psychopharmacology* **18**:477-481.

Dumaine R, Roy ML and Brown AM (1998) Blockade of HERG and Kv1.5 by ketoconazole. *The Journal of pharmacology and experimental therapeutics* **286**:727-735.

Dumaine R, Towbin JA, Brugada P, Vatta M, Nesterenko DV, Nesterenko VV, Brugada J, Brugada R and Antzelevitch C (1999) Ionic mechanisms responsible for the electrocardiographic phenotype of the Brugada syndrome are temperature dependent. *Circulation research* **85**:803-809.

El-Menyar A, Khan M, Al Suwaidi J, Eljerjawy E and Asaad N (2011) Oxcarbazepine-induced resistant ventricular fibrillation in an apparently healthy young man. *The American journal of emergency medicine* **29**:693 e691-693.

Fernández-Falgueras A, Campuzano O and Iglesias A (2016) Genetics of Brugada Syndrome.

Fish JM and Antzelevitch C (2004) Role of sodium and calcium channel block in unmasking the Brugada syndrome. *Heart rhythm : the official journal of the Heart Rhythm Society* **1**:210-217.

Fish JM and Antzelevitch C (2008) Cellular mechanism and arrhythmogenic potential of T-wave alternans in the Brugada syndrome. *Journal of cardiovascular electrophysiology* **19**:301-308.

Fujiki A, Usui M, Nagasawa H, Mizumaki K, Hayashi H and Inoue H (1999) ST segment elevation in the right precordial leads induced with class IC antiarrhythmic drugs: insight into the mechanism of Brugada syndrome. *Journal of cardiovascular electrophysiology* **10**:214-218.

Goineau S, Legrand C and Froget G (2012) Whole-cell configuration of the patch-clamp technique in the hERG channel assay to predict the ability of a compound to prolong QT interval. *Current protocols in pharmacology* **Chapter 10**:Unit 10 15.

Goldgran-Toledano D, Sideris G and Kevorkian JP (2002) Overdose of cyclic antidepressants and the Brugada syndrome. *The New England journal of medicine* **346**:1591-1592.

Grace AA and Camm AJ (2000) Voltage-gated calcium-channels and antiarrhythmic drug action. *Cardiovascular research* **45**:43-51.

Guo J, Li X, Shallow H, Xu J, Yang T, Massaeli H, Li W, Sun T, Pierce GN and Zhang S (2011) Involvement of caveolin in probucol-induced reduction in hERG plasma-membrane expression. *Molecular pharmacology* **79**:806-813.

Guo J, Massaeli H, Li W, Xu J, Luo T, Shaw J, Kirshenbaum LA and Zhang S (2007) Identification of IKr and its trafficking disruption induced by probucol in cultured neonatal rat cardiomyocytes. *The Journal of pharmacology and experimental therapeutics* **321**:911-920.

Habuchi Y, Furukawa T, Tanaka H, Lu LL, Morikawa J and Yoshimura M (1995) Ethanol inhibition of Ca2+ and Na+ currents in the guinea-pig heart. *European journal of pharmacology* **292**:143-149.

Hara Y, Chugun A, Nakaya H and Kondo H (1998) Tonic block of the sodium and calcium currents by ketamine in isolated guinea pig ventricular myocytes. *The Journal of veterinary medical science* **60**:479-483.

Hayashi K, Shimizu M, Ino H, Yamaguchi M, Terai H, Hoshi N, Higashida H, Terashima N, Uno Y, Kanaya H and Mabuchi H (2004) Probucol aggravates long QT syndrome associated with a novel missense mutation M124T in the N-terminus of HERG. *Clinical science* **107**:175-182.

Hong K, Guerchicoff A, Pollevick GD, Oliva A, Dumaine R, de Zutter M, Burashnikov E, Wu YS, Brugada J, Brugada P and Brugada R (2005) Cryptic 5' splice site activation in SCN5A associated with Brugada syndrome. *Journal of molecular and cellular cardiology* **38**:555-560.

Horie M and Itoh H (2007) Disorders of cardiac repolarization: long QT and short QT syndromes. *Circulation journal : official journal of the Japanese Circulation Society* **71 Suppl A**:A50-53.

Itoh E, Suzuki K and Tanabe Y (1999) A case of vasospastic angina presenting Brugada-type ECG abnormalities. *Japanese circulation journal* **63**:493-495.

Itoh H, Crotti L, Aiba T, Spazzolini C, Denjoy I, Fressart V, Hayashi K, Nakajima T, Ohno S, Makiyama T, Wu J, Hasegawa K, Mastantuono E, Dagradi F, Pedrazzini M, Yamagishi M, Berthet M, Murakami Y, Shimizu W, Guicheney P, Schwartz PJ and Horie M (2016) The genetics underlying acquired long QT syndrome: impact for genetic screening. *European heart journal* **37**:1456-1464.

Itoh H, Sakaguchi T, Ding WG, Watanabe E, Watanabe I, Nishio Y, Makiyama T, Ohno S, Akao M, Higashi Y, Zenda N, Kubota T, Mori C, Okajima K, Haruna T, Miyamoto A, Kawamura M, Ishida K, Nagaoka I, Oka Y, Nakazawa Y, Yao T, Jo H, Sugimoto Y, Ashihara T, Hayashi H, Ito M, Imoto K, Matsuura H and Horie M (2009) Latent genetic backgrounds and molecular pathogenesis in drug-induced long-QT syndrome. *Circulation Arrhythmia and electrophysiology* **2**:511-523.

Jervell A and Lange-Nielsen F (1957) Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death. *American heart journal* **54**:59-68.

Jo SH, Youm JB, Lee CO, Earm YE and Ho WK (2000) Blockade of the HERG human cardiac K(+) channel by the antidepressant drug amitriptyline. *British journal of pharmacology* **129**:1474-1480.

Juang J-MJ and Horie M (2016) Genetics of Brugada syndrome. *Journal of Arrhythmia*.

Junttila MJ, Gonzalez M, Lizotte E, Benito B, Vernooy K, Sarkozy A, Huikuri HV, Brugada P, Brugada J and Brugada R (2008) Induced Brugada-type electrocardiogram, a sign for imminent malignant arrhythmias. *Circulation* **117**:1890-1893.

Kaab S, Crawford DC, Sinner MF, Behr ER, Kannankeril PJ, Wilde AA, Bezzina CR, Schulze-Bahr E, Guicheney P, Bishopric NH, Myerburg RJ, Schott JJ, Pfeufer A, Beckmann BM, Martens E, Zhang T, Stallmeyer B, Zumhagen S, Denjoy I, Bardai A, Van Gelder IC, Jamshidi Y, Dalageorgou C, Marshall V, Jeffery S, Shakir S, Camm AJ, Steinbeck G, Perz S, Lichtner P, Meitinger T, Peters A, Wichmann HE, Ingram C, Bradford Y, Carter S, Norris K, Ritchie MD, George AL, Jr. and Roden DM (2012) A large candidate gene survey identifies the KCNE1 D85N polymorphism as a possible modulator of drug-induced torsades de pointes. *Circulation Cardiovascular genetics* **5**:91-99.

Kapplinger JD, Tester DJ, Alders M, Benito B, Berthet M, Brugada J, Brugada P, Fressart V, Guerchicoff A, Harris-Kerr C, Kamakura S, Kyndt F, Koopmann TT, Miyamoto Y, Pfeiffer R, Pollevick GD, Probst V, Zumhagen S, Vatta M, Towbin JA, Shimizu W, Schulze-Bahr E, Antzelevitch C, Salisbury BA, Guicheney P, Wilde AA, Brugada R, Schott JJ and Ackerman MJ (2010) An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. *Heart rhythm : the official journal of the Heart Rhythm Society* **7**:33-46.

Kasanuki H, Ohnishi S, Ohtuka M, Matsuda N, Nirei T, Isogai R, Shoda M, Toyoshima Y and Hosoda S (1997) Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. *Circulation* **95**:2277-2285.

Kataoka H (2000) Electrocardiographic patterns of the Brugada syndrome in right ventricular infarction/ischemia. *The American journal of cardiology* **86**:1056.

Katchman AN, Koerner J, Tosaka T, Woosley RL and Ebert SN (2006) Comparative evaluation of HERG currents and QT intervals following challenge with suspected torsadogenic and nontorsadogenic drugs. *The Journal of pharmacology and experimental therapeutics* **316**:1098-1106.

Keating M, Dunn C, Atkinson D, Timothy K, Vincent GM and Leppert M (1991) Consistent linkage of the long-QT syndrome to the Harvey ras-1 locus on chromosome 11. *American journal of human genetics* **49**:1335-1339.

Keller DI, Rougier JS, Kucera JP, Benammar N, Fressart V, Guicheney P, Madle A, Fromer M, Schlapfer J and Abriel H (2005) Brugada syndrome and fever: genetic and molecular characterization of patients carrying SCN5A mutations. *Cardiovascular research* **67**:510-519.

Klockner U and Isenberg G (1987) Calmodulin antagonists depress calcium and potassium currents in ventricular and vascular myocytes. *The American journal of physiology* **253**:H1601-1611.

Konigstein M, Rosso R, Topaz G, Postema PG, Friedensohn L, Heller K, Zeltser D, Belhassen B, Adler A and Viskin S (2016) Drug-induced Brugada syndrome: Clinical characteristics and

risk factors. *Heart rhythm : the official journal of the Heart Rhythm Society* **13**:1083-1087.

Krishnan SC and Antzelevitch C (1991) Sodium channel block produces opposite electrophysiological effects in canine ventricular epicardium and endocardium. *Circulation research* **69**:277-291.

Krishnan SC and Josephson ME (1998) ST segment elevation induced by class IC antiarrhythmic agents: underlying electrophysiologic mechanisms and insights into drug-induced proarrhythmia. *Journal of cardiovascular electrophysiology* **9**:1167-1172.

Kubo T, Ashihara T, Tsubouchi T and Horie M (2017) Significance of integrated in silico transmural ventricular wedge preparation models of human non-failing and failing hearts for safety evaluation of drug candidates. *Journal of pharmacological and toxicological methods* **83**:30-41.

Kum LC, Fung JW and Sanderson JE (2002) Brugada syndrome unmasked by febrile illness. *Pacing and clinical electrophysiology : PACE* **25**:1660-1661.

Litovsky SH and Antzelevitch C (1988) Transient outward current prominent in canine ventricular epicardium but not endocardium. *Circulation research* **62**:116-126.

Litovsky SH and Antzelevitch C (1990) Differences in the electrophysiological response of canine ventricular subendocardium and subepicardium to acetylcholine and isoproterenol. A direct effect of acetylcholine in ventricular myocardium. *Circulation research* **67**:615-627.

Littmann L, Monroe MH and Svenson RH (2000) Brugada-type electrocardiographic pattern induced by cocaine. *Mayo Clinic proceedings* **75**:845-849.

Lopez-Barbeito B, Lluis M, Delgado V, Jimenez S, Diaz-Infante E, Nogue-Xarau S and Brugada J (2005) Diphenhydramine overdose and Brugada sign. *Pacing and clinical electrophysiology : PACE* **28**:730-732.

Makita N, Horie M, Nakamura T, Ai T, Sasaki K, Yokoi H, Sakurai M, Sakuma I, Otani H, Sawa H and Kitabatake A (2002) Drug-induced long-QT syndrome associated with a subclinical SCN5A mutation. *Circulation* **106**:1269-1274.

Matana A, Goldner V, Stanic K, Mavric Z, Zaputovic L and Matana Z (2000) Unmasking effect of propafenone on the concealed form of the Brugada phenomenon. *Pacing and clinical electrophysiology : PACE* **23**:416-418.

Matsuo K, Akahoshi M, Seto S and Yano K (2003) Disappearance of the Brugada-type electrocardiogram after surgical castration: a role for testosterone and an explanation for the male preponderance. *Pacing and clinical electrophysiology : PACE* **26**:1551-1553.

Matsuo K, Shimizu W, Kurita T, Inagaki M, Aihara N and Kamakura S (1998) Dynamic changes of 12-lead electrocardiograms in a patient with Brugada syndrome. *Journal of cardiovascular electrophysiology* **9**:508-512.

Mazzanti A, Maragna R, Faragli A, Monteforte N, Bloise R, Memmi M, Novelli V, Baiardi P, Bagnardi V, Etheridge SP, Napolitano C and Priori SG (2016) Gene-Specific Therapy With Mexiletine Reduces Arrhythmic Events in Patients With Long QT Syndrome Type 3. *Journal of the American College of Cardiology* **67**:1053-1058.

McBride BF, Yang T and Roden DM (2009) Influence of the G2677T/C3435T haplotype of MDR1 on P-glycoprotein trafficking and ibutilide-induced block of HERG. *The pharmacogenomics journal* **9**:194-201.

Meregalli PG, Wilde AA and Tan HL (2005) Pathophysiological mechanisms of Brugada syndrome: depolarization disorder, repolarization disorder, or more? *Cardiovascular research* **67**:367-378.

Minoura Y, Di Diego JM, Barajas-Martinez H, Zygmunt AC, Hu D, Sicouri S and Antzelevitch C (2012) Ionic and cellular mechanisms underlying the development of acquired Brugada syndrome in patients treated with antidepressants. *Journal of cardiovascular electrophysiology* **23**:423-432.

Mirams GR, Cui Y, Sher A, Fink M, Cooper J, Heath BM, McMahon NC, Gavaghan DJ and Noble D (2011) Simulation of multiple ion channel block provides improved early prediction of compounds' clinical torsadogenic risk. *Cardiovascular research* **91**:53-61.

Mitcheson J, Perry M, Stansfeld P, Sanguinetti MC, Witchel H and Hancox J (2005) Structural determinants for high-affinity block of hERG potassium channels. *Novartis Foundation symposium* **266**:136-150; discussion 150-138.

Mitcheson JS, Chen J, Lin M, Culberson C and Sanguinetti MC (2000) A structural basis for drug-induced long QT syndrome. *Proceedings of the National Academy of Sciences of the United States of America* **97**:12329-12333.

Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y and Ogawa S (1996) Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. *Journal of the American College of Cardiology* **27**:1061-1070.

Mizumaki K, Fujiki A, Tsuneda T, Sakabe M, Nishida K, Sugao M and Inoue H (2004) Vagal activity modulates spontaneous augmentation of ST elevation in the daily life of patients with Brugada syndrome. *Journal of cardiovascular electrophysiology* **15**:667-673.

Mok NS, Tong CK and Yuen HC (2008) Concomitant-acquired Long QT and Brugada syndromes associated with indapamide-induced hypokalemia and hyponatremia. *Pacing and clinical electrophysiology : PACE* **31**:772-775.

Morita H, Nagase S, Kusano K and Ohe T (2002) Spontaneous T wave alternans and premature ventricular contractions during febrile illness in a patient with Brugada syndrome. *Journal of cardiovascular electrophysiology* **13**:816-818.

Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J, Hall WJ, Weitkamp L, Vincent GM, Garson A, Jr. and et al. (1991) The long QT syndrome. Prospective longitudinal study of 328 families. *Circulation* **84**:1136-1144.

Nademanee K, Veerakul G, Chandanamattha P, Chaothawee L, Ariyachaipanich A, Jirasirirojanakorn K, Likittanasombat K, Bhuripanyo K and Ngarmukos T (2011) Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. *Circulation* **123**:1270-1279.

Nademanee K, Veerakul G, Nimmannit S, Chaowakul V, Bhuripanyo K, Likittanasombat K, Tunsanga K, Kuasirikul S, Malasit P, Tansupasawadikul S and Tatsanavivat P (1997) Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. *Circulation* **96**:2595-2600.

Nimmannit S, Malasit P, Chaovakul V, Susaengrat W, Vasuvattakul S and Nilwarangkur S (1991) Pathogenesis of sudden unexplained nocturnal death (lai tai) and endemic distal renal tubular acidosis. *Lancet* **338**:930-932.

Nishida K, Fujiki A, Mizumaki K, Sakabe M, Sugao M, Tsuneda T and Inoue H (2004) Canine model of Brugada syndrome using regional epicardial cooling of the right ventricular outflow tract. *Journal of cardiovascular electrophysiology* **15**:936-941.

Nishio Y, Makiyama T, Itoh H, Sakaguchi T, Ohno S, Gong YZ, Yamamoto S, Ozawa T, Ding WG, Toyoda F, Kawamura M, Akao M, Matsuura H, Kimura T, Kita T and Horie M (2009) D85N, a KCNE1 polymorphism, is a disease-causing gene variant in long QT syndrome. *Journal of the American College of Cardiology* **54**:812-819.

Nishizaki M, Sakurada H, Ashikaga T, Yamawake N, Fujii H, Arita M, Isobe M and Hiraoka M (2003) Effects of glucose-induced insulin secretion on ST segment elevation in the Brugada syndrome. *Journal of cardiovascular electrophysiology* **14**:243-249.

Noda T, Shimizu W, Taguchi A, Satomi K, Suyama K, Kurita T, Aihara N and Kamakura S (2002) ST-segment elevation and ventricular fibrillation without coronary spasm by intracoronary injection of acetylcholine and/or ergonovine maleate in patients with Brugada syndrome. *Journal of the American College of Cardiology* **40**:1841-1847.

Noda T, Shimizu W, Tanaka K and Chayama K (2003) Prominent J wave and ST segment elevation: serial electrocardiographic changes in accidental hypothermia. *Journal of cardiovascular electrophysiology* **14**:223.

Nogami A, Nakao M, Kubota S, Sugiyasu A, Doi H, Yokoyama K, Yumoto K, Tamaki T, Kato K, Hosokawa N, Sagai H, Nakamura H, Nitta J, Yamauchi Y and Aonuma K (2003) Enhancement of J-ST-segment elevation by the glucose and insulin test in Brugada syndrome. *Pacing and clinical electrophysiology : PACE* **26**:332-337.

Ogata N and Narahashi T (1989) Block of sodium channels by psychotropic drugs in single guinea-pig cardiac myocytes. *British journal of pharmacology* **97**:905-913.

Ohgo T, Okamura H, Noda T, Satomi K, Suyama K, Kurita T, Aihara N, Kamakura S, Ohe T and Shimizu W (2007) Acute and chronic management in patients with Brugada syndrome associated with electrical storm of ventricular fibrillation. *Heart rhythm : the official journal of the Heart Rhythm Society* **4**:695-700.

Olde Nordkamp LR, Driessen AH, Odero A, Blom NA, Koolbergen DR, Schwartz PJ and Wilde AA (2014) Left cardiac sympathetic denervation in the Netherlands for the treatment of inherited arrhythmia syndromes. *Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation* **22**:160-166.

Ortega-Carnicer J, Bertos-Polo J and Gutierrez-Tirado C (2001) Aborted sudden death, transient Brugada pattern, and wide QRS dysrrhythmias after massive cocaine ingestion. *Journal of electrocardiology* **34**:345-349.

Pacher P, Bagi Z, Lako-Futo Z, Ungvari Z, Nanasi PP and Kecskemeti V (2000a) Cardiac electrophysiological effects of citalopram in guinea pig papillary muscle comparison with clomipramine. *General pharmacology* **34**:17-23.

Pacher P, Magyar J, Szigligeti P, Banyasz T, Pankucsi C, Korom Z, Ungvari Z, Kecskemeti V and Nanasi PP (2000b) Electrophysiological effects of fluoxetine in mammalian cardiac tissues. *Naunyn-Schmiedeberg's archives of pharmacology* **361**:67-73.

Park JK, Martin LJ, Zhang X, Jegga AG and Benson DW (2012) Genetic variants in SCN5A promoter are associated with arrhythmia phenotype severity in patients with

heterozygous loss-of-function mutation. *Heart rhythm : the official journal of the Heart Rhythm Society* **9**:1090-1096.

Pasquie JL, Sanders P, Hocini M, Hsu LF, Scavee C, Jais P, Takahashi Y, Rotter M, Sacher F, Victor J, Clementy J and Haissaguerre M (2004) Fever as a precipitant of idiopathic ventricular fibrillation in patients with normal hearts. *Journal of cardiovascular electrophysiology* **15**:1271-1276.

Pastor A, Nunez A, Cantale C and Cosio FG (2001) Asymptomatic brugada syndrome case unmasked during dimenhydrinate infusion. *Journal of cardiovascular electrophysiology* **12**:1192-1194.

Paulussen AD, Gilissen RA, Armstrong M, Doevendans PA, Verhasselt P, Smeets HJ, Schulze-Bahr E, Haverkamp W, Breithardt G, Cohen N and Aerssens J (2004) Genetic variations of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 in drug-induced long QT syndrome patients. *Journal of molecular medicine* **82**:182-188.

Porres JM, Brugada J, Urbistondo V, Garcia F, Reviejo K and Marco P (2002) Fever unmasking the Brugada syndrome. *Pacing and clinical electrophysiology : PACE* **25**:1646-1648.

Postema PG, van Dessel PF, de Bakker JM, Dekker LR, Linnenbank AC, Hoogendijk MG, Coronel R, Tijssen JG, Wilde AA and Tan HL (2008) Slow and discontinuous conduction conspire in Brugada syndrome: a right ventricular mapping and stimulation study. *Circulation Arrhythmia and electrophysiology* **1**:379-386.

Postema PG, Wolpert C, Amin AS, Probst V, Borggrefe M, Roden DM, Priori SG, Tan HL, Hiraoka M, Brugada J and Wilde AA (2009) Drugs and Brugada syndrome patients: review of the

literature, recommendations, and an up-to-date website (www.brugadadrugs.org). *Heart rhythm : the official journal of the Heart Rhythm Society* **6**:1335-1341.

Priori SG, Napolitano C and Schwartz PJ (1999) Low penetrance in the long-QT syndrome: clinical impact. *Circulation* **99**:529-533.

Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G and Tracy C (2013) HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart rhythm : the official journal of the Heart Rhythm Society* **10**:1932-1963.

Probst V, Denjoy I, Meregalli PG, Amirault JC, Sacher F, Mansourati J, Babuty D, Villain E, Victor J, Schott JJ, Lupoglazoff JM, Mabo P, Veltmann C, Jesel L, Chevalier P, Clur SA, Haissaguerre M, Wolpert C, Le Marec H and Wilde AA (2007) Clinical aspects and prognosis of Brugada syndrome in children. *Circulation* **115**:2042-2048.

Rampe D, Roy ML, Dennis A and Brown AM (1997) A mechanism for the proarrhythmic effects of cisapride (Propulsid): high affinity blockade of the human cardiac potassium channel HERG. *FEBS letters* **417**:28-32.

Rampe D, Wible B, Brown AM and Dage RC (1993) Effects of terfenadine and its metabolites on a delayed rectifier K+ channel cloned from human heart. *Molecular pharmacology* **44**:1240-1245.

Robert E, Aya AG, de la Coussaye JE, Peray P, Juan JM, Brugada J, Davy JM and Eledjam JJ (1999) Dispersion-based reentry: mechanism of initiation of ventricular tachycardia in isolated rabbit hearts. *The American journal of physiology* **276**:H413-423.

Romano C, Gemme G and Pongiglione R (1963) [Rare Cardiac Arrythmias of the Pediatric Age. Ii. Syncopal Attacks Due to Paroxysmal Ventricular Fibrillation. (Presentation of 1st Case in Italian Pediatric Literature)]. *La Clinica pediatrica* **45**:656-683.

Romero-Puche AJ, Trigueros-Ruiz N, Cerdan-Sanchez MC, Perez-Lorente F, Roldan D and Vicente-Vera T (2012) Brugada electrocardiogram pattern induced by cannabis. *Revista espanola de cardiologia* **65**:856-858.

Rouleau F, Asfar P, Boulet S, Dube L, Dupuis JM, Alquier P and Victor J (2001) Transient ST segment elevation in right precordial leads induced by psychotropic drugs: relationship to the Brugada syndrome. *Journal of cardiovascular electrophysiology* **12**:61-65.

Rudic B, Schimpf R, Veltmann C, Doesch C, Tulumen E, Schoenberg SO, Borggrefe M and Papavassiliu T (2016) Brugada syndrome: clinical presentation and genotype-correlation with magnetic resonance imaging parameters. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology* **18**:1411-1419.

Sacher F, Derval N, Horlitz M and Haissaguerre M (2014) J wave elevation to monitor quinidine efficacy in early repolarization syndrome. *Journal of electrocardiology* **47**:223-225.

Salata JJ, Jurkiewicz NK, Wallace AA, Stupienski RF, 3rd, Guinosso PJ, Jr. and Lynch JJ, Jr. (1995) Cardiac electrophysiological actions of the histamine H1-receptor antagonists

astemizole and terfenadine compared with chlorpheniramine and pyrilamine. *Circulation research* **76**:110-119.

Samani K, Wu G, Ai T, Shuraih M, Mathuria NS, Li Z, Sohma Y, Purevjav E, Xi Y, Towbin JA, Cheng J and Vatta M (2009) A novel SCN5A mutation V1340I in Brugada syndrome augmenting arrhythmias during febrile illness. *Heart rhythm : the official journal of the Heart Rhythm Society* **6**:1318-1326.

Sanguinetti MC, Jiang C, Curran ME and Keating MT (1995) A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the IKr potassium channel. *Cell* **81**:299-307.

Sarquella-Brugada G, Campuzano O, Arbelo E, Brugada J and Brugada R (2016) Brugada syndrome: clinical and genetic findings. *Genetics in medicine : official journal of the American College of Medical Genetics* **18**:3-12.

Saura D, Garcia-Alberola A, Carrillo P, Pascual D, Martinez-Sanchez J and Valdes M (2002) Brugada-like electrocardiographic pattern induced by fever. *Pacing and clinical electrophysiology : PACE* **25**:856-859.

Scholz EP, Zitron E, Kiesecker C, Lueck S, Kathofer S, Thomas D, Weretka S, Peth S, Kreye VA, Schoels W, Katus HA, Kiehn J and Karle CA (2003) Drug binding to aromatic residues in the HERG channel pore cavity as possible explanation for acquired Long QT syndrome by antiparkinsonian drug budipine. *Naunyn-Schmiedeberg's archives of pharmacology* **368**:404-414.

Schwartz PJ, Stramba-Badiale M, Crotti L, Pedrazzini M, Besana A, Bosi G, Gabbarini F, Goulene K, Insolia R, Mannarino S, Mosca F, Nespoli L, Rimini A, Rosati E, Salice P and Spazzolini C (2009) Prevalence of the congenital long-QT syndrome. *Circulation* **120**:1761-1767.

Schwartz PJ, Stramba-Badiale M, Segantini A, Austoni P, Bosi G, Giorgetti R, Grancini F, Marni ED, Perticone F, Rosti D and Salice P (1998) Prolongation of the QT interval and the sudden infant death syndrome. *The New England journal of medicine* **338**:1709-1714.

Selzer A and Wray HW (1964) Quinidine Syncope. Paroxysmal Ventricular Fibrillation Occurring during Treatment of Chronic Atrial Arrhythmias. *Circulation* **30**:17-26.

Sesti F, Abbott GW, Wei J, Murray KT, Saksena S, Schwartz PJ, Priori SG, Roden DM, George AL, Jr. and Goldstein SA (2000) A common polymorphism associated with antibiotic-induced cardiac arrhythmia. *Proceedings of the National Academy of Sciences of the United States of America* **97**:10613-10618.

Shimizu W, Antzelevitch C, Suyama K, Kurita T, Taguchi A, Aihara N, Takaki H, Sunagawa K and Kamakura S (2000) Effect of sodium channel blockers on ST segment, QRS duration, and corrected QT interval in patients with Brugada syndrome. *Journal of cardiovascular electrophysiology* **11**:1320-1329.

Shinohara T, Ebata Y, Ayabe R, Fukui A, Okada N, Yufu K, Nakagawa M and Takahashi N (2014) Combination therapy of cilostazol and bepridil suppresses recurrent ventricular fibrillation related to J-wave syndromes. *Heart rhythm : the official journal of the Heart Rhythm Society* **11**:1441-1445.

Sieira J, Dendramis G and Brugada P (2016) Pathogenesis and management of Brugada syndrome. *Nature reviews Cardiology*.

Simard C, O'Hara GE, Prevost J, Guilbaud R, Massee R and Turgeon J (2001) Study of the drug-drug interaction between simvastatin and cisapride in man. *European journal of clinical pharmacology* **57**:229-234.

Smith JL, Anderson CL, Burgess DE, Elayi CS, January CT and Delisle BP (2016) Molecular pathogenesis of long QT syndrome type 2. *J Arrhythm* **32**:373-380.

Splawski I, Timothy KW, Tateyama M, Clancy CE, Malhotra A, Beggs AH, Cappuccio FP, Sagnella GA, Kass RS and Keating MT (2002) Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. *Science* **297**:1333-1336.

Stirnimann G, Petitprez S, Abriel H and Schwick NG (2010) Brugada syndrome ECG provoked by the selective serotonin reuptake inhibitor fluvoxamine. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology* **12**:282-283.

Strimel WJ, Woodruff A, Cheung P, Kirmani BF and Stephen Huang SK (2010) Brugada-like electrocardiographic pattern induced by lamotrigine toxicity. *Clinical neuropharmacology* **33**:265-267.

Suessbrich H, Schonherr R, Heinemann SH, Attali B, Lang F and Busch AE (1997) The inhibitory effect of the antipsychotic drug haloperidol on HERG potassium channels expressed in Xenopus oocytes. *British journal of pharmacology* **120**:968-974.

Swe T, Bhattarai B and Dufresne A (2016) Type 1 Brugada pattern ECG due to supra-therapeutic phenytoin level. *BMJ case reports* **2016**.

Szel T and Antzelevitch C (2014) Abnormal repolarization as the basis for late potentials and fractionated electrograms recorded from epicardium in experimental models of Brugada syndrome. *Journal of the American College of Cardiology* **63**:2037-2045.

Szel T, Koncz I and Antzelevitch C (2013) Cellular mechanisms underlying the effects of milrinone and cilostazol to suppress arrhythmogenesis associated with Brugada syndrome. *Heart rhythm : the official journal of the Heart Rhythm Society* **10**:1720-1727.

Tada H, Nogami A, Shimizu W, Naito S, Nakatsugawa M, Oshima S and Taniguchi K (2000) ST segment and T wave alternans in a patient with Brugada syndrome. *Pacing and clinical electrophysiology : PACE* **23**:413-415.

Tada H, Sticherling C, Oral H and Morady F (2001) Brugada syndrome mimicked by tricyclic antidepressant overdose. *Journal of cardiovascular electrophysiology* **12**:275.

Toga T, Kohmura Y and Kawatsu R (2007) The 5-HT(4) agonists cisapride, mosapride, and CJ-033466, a Novel potent compound, exhibit different human ether-a-go-go-related gene (hERG)-blocking activities. *Journal of pharmacological sciences* **105**:207-210.

Tsuchiya T, Ashikaga K, Honda T and Arita M (2002) Prevention of ventricular fibrillation by cilostazol, an oral phosphodiesterase inhibitor, in a patient with Brugada syndrome. *Journal of cardiovascular electrophysiology* **13**:698-701.

Turker I and Ai T (2014) Bilateral cardiac sympathetic denervation: the last resort? *Heart rhythm : the official journal of the Heart Rhythm Society* **11**:367-368.

Turker I, Makiyama T, Vatta M, Itoh H, Ueyama T, Shimizu A, Ai T and Horie M (2016) A Novel SCN5A Mutation Associated with Drug Induced Brugada Type ECG. *PloS one* **11**:e0161872.

van Hoorn F, Campian ME, Spijkerboer A, Blom MT, Planken RN, van Rossum AC, de Bakker JM, Wilde AA, Groenink M and Tan HL (2012) SCN5A mutations in Brugada syndrome are associated with increased cardiac dimensions and reduced contractility. *PloS one* **7**:e42037.

Vatta M, Dumaine R, Varghese G, Richard TA, Shimizu W, Aihara N, Nademanee K, Brugada R, Brugada J, Veerakul G, Li H, Bowles NE, Brugada P, Antzelevitch C and Towbin JA (2002) Genetic and biophysical basis of sudden unexplained nocturnal death syndrome (SUNDS), a disease allelic to Brugada syndrome. *Human molecular genetics* **11**:337-345.

Vernier VG, Harmon JB, Stump JM, Lynes TE, Marvel JP and Smith DH (1969) The toxicologic and pharmacologic properties of amantadine hydrochloride. *Toxicology and applied pharmacology* **15**:642-665.

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 and Brugada R (2006a) Electrocardiographic changes predicting sudden death in propofol-related infusion syndrome. *Heart rhythm : the official journal of the Heart Rhythm Society* **3**:131-137.

Vernooy K, Sicouri S, Dumaine R, Hong K, Oliva A, Burashnikov E, Timmermans C, Delhaas T, Crijns HJ, Antzelevitch C, Rodriguez LM and Brugada R (2006b) Genetic and biophysical basis for bupivacaine-induced ST segment elevation and VT/VF. Anesthesia unmasked Brugada syndrome. *Heart rhythm : the official journal of the Heart Rhythm Society* **3**:1074-1078.

Virag L, Varro A and Papp JG (1998) Effect of disopyramide on potassium currents in rabbit ventricular myocytes. *Naunyn-Schmiedeberg's archives of pharmacology* **357**:268-275.

Wang J, Della Penna K, Wang H, Karczewski J, Connolly TM, Koblan KS, Bennett PB and Salata JJ (2003) Functional and pharmacological properties of canine ERG potassium channels. *American journal of physiology Heart and circulatory physiology* **284**:H256-267.

Wang Q, Curran ME, Splawski I, Burn TC, Millholland JM, VanRaay TJ, Shen J, Timothy KW, Vincent GM, de Jager T, Schwartz PJ, Toubin JA, Moss AJ, Atkinson DL, Landes GM, Connors TD and Keating MT (1996) Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. *Nature genetics* **12**:17-23.

Wang Q, Shen J, Li Z, Timothy K, Vincent GM, Priori SG, Schwartz PJ and Keating MT (1995a) Cardiac sodium channel mutations in patients with long QT syndrome, an inherited cardiac arrhythmia. *Human molecular genetics* **4**:1603-1607.

Wang Q, Shen J, Splawski I, Atkinson D, Li Z, Robinson JL, Moss AJ, Towbin JA and Keating MT (1995b) SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* **80**:805-811.

Ward OC (1964) A New Familial Cardiac Syndrome in Children. *Journal of the Irish Medical Association* **54**:103-106.

Watanabe A, Fukushima Kusano K, Morita H, Miura D, Sumida W, Hiramatsu S, Banba K, Nishii N, Nagase S, Nakamura K, Sakuragi S and Ohe T (2006) Low-dose isoproterenol for repetitive ventricular arrhythmia in patients with Brugada syndrome. *European heart journal* **27**:1579-1583.

Watanabe H and Minamino T (2016) Genetics of Brugada syndrome. *Journal of human genetics* **61**:57-60.

Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG, Towbin JA and Study Group on the Molecular Basis of Arrhythmias of the European Society of C (2002) Proposed diagnostic criteria for the Brugada syndrome. *European heart journal* **23**:1648-1654.

Wolpert C, Echternach C, Veltmann C, Antzelevitch C, Thomas GP, Spehl S, Streitner F, Kuschyk J, Schimpf R, Haase KK and Borggrefe M (2005) Intravenous drug challenge using flecainide and ajmaline in patients with Brugada syndrome. *Heart rhythm : the official journal of the Heart Rhythm Society* **2**:254-260.

Woosley RL (1996) Cardiac actions of antihistamines. *Annual review of pharmacology and toxicology* **36**:233-252.

Woosley RL, Chen Y, Freiman JP and Gillis RA (1993) Mechanism of the cardiotoxic actions of terfenadine. *Jama* **269**:1532-1536.

Xu YQ, Pickoff AS and Clarkson CW (1991) Evidence for developmental changes in sodium channel inactivation gating and sodium channel block by phenytoin in rat cardiac myocytes. *Circulation research* **69**:644-656.

Yan GX and Antzelevitch C (1999) Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. *Circulation* **100**:1660-1666.

Zareba W, Moss AJ, Schwartz PJ, Vincent GM, Robinson JL, Priori SG, Benhorin J, Locati EH, Towbin JA, Keating MT, Lehmann MH and Hall WJ (1998) Influence of genotype on the clinical course of the long-QT syndrome. International Long-QT Syndrome Registry Research Group. *The New England journal of medicine* **339**:960-965.

Zipes DP (1991) The long QT interval syndrome. A Rosetta stone for sympathetic related ventricular tachyarrhythmias. *Circulation* **84**:1414-1419.

Figure 1.

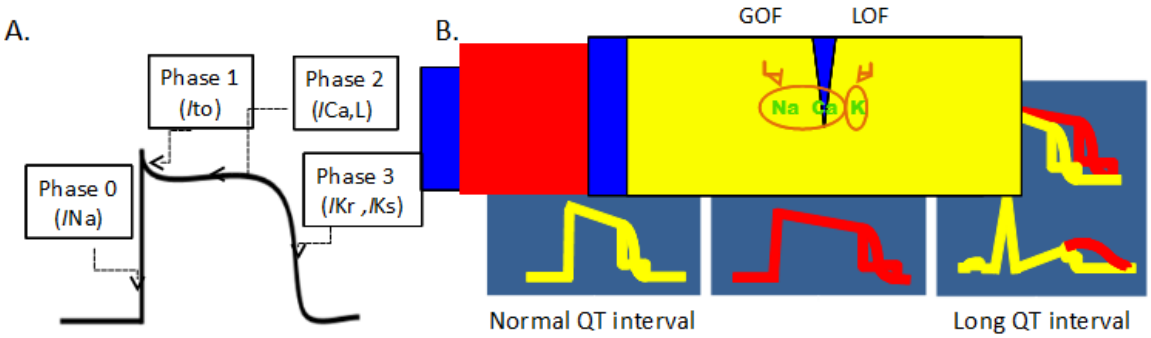

Figure 2

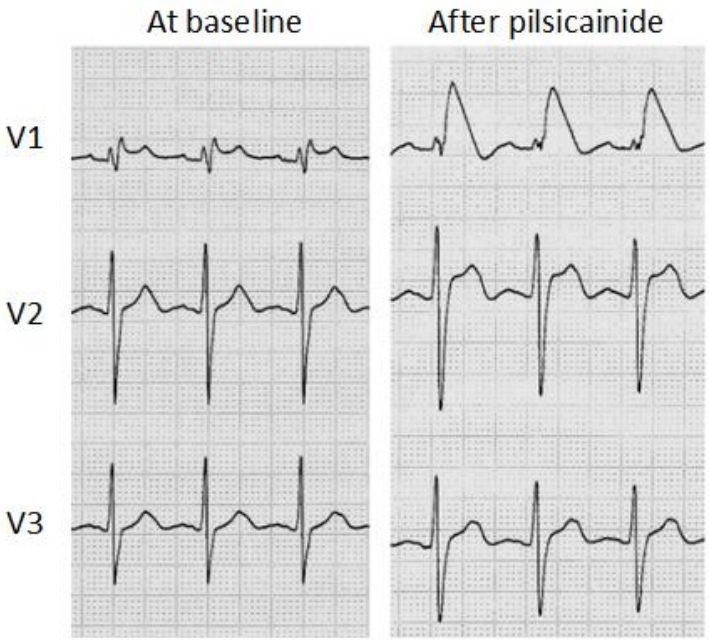

Figure 3.

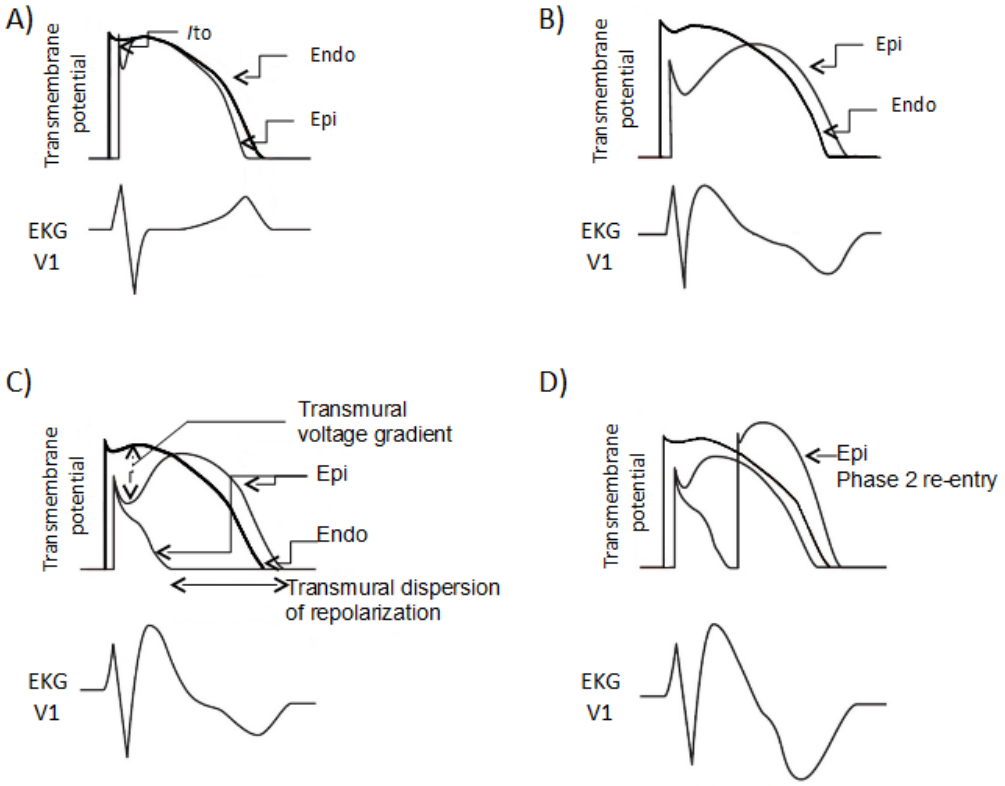

Figure 4.