A Tale of 2 Diseases
The History of Long-QT Syndrome and Brugada Syndrome

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ABSTRACT

The Brugada syndrome (BrS) and long-QT syndrome (LQTS) present as congenital or acquired disorders with diagnostic electrocardiograms (ST-segment elevation and prolonged QT interval, respectively) and increased risk for malignant arrhythmias. Our understanding of the 2 disease forms (congenital vs. acquired) differs. A female patient on quinidine for atrial fibrillation who develops torsades de pointes (TdP) and ventricular fibrillation (VF) requiring resuscitation is diagnosed with "acquired LQTS" and is discharged with no therapy other than instructions to avoid QT-prolonging medications. In contrast, an asymptomatic male patient who develops a Brugada electrocardiogram on flecainide is diagnosed with "asymptomatic BrS" and could be referred for an electrophysiological evaluation that could result in defibrillator implantation. The typical patient undergoing defibrillator implantation for BrS is asymptomatic but has a Brugada electrocardiogram provoked by a drug. The authors describe how the histories of LQTS and BrS went through the same stages, but in different sequences, leading to different conclusions. (J Am Coll Cardiol 2016;67:100–8) © 2016 by the American College of Cardiology Foundation.

“History is nothing whatever but a record of what living persons have done in the past.”

~Rose Wilder Lane (1)

This observation is exemplified by the nonparallel pathways that led to different approaches for the management of 2 common arrhythmic syndromes: long-QT syndrome (LQTS) and Brugada syndrome (BrS).

The 2013 Heart Rhythm Society, European Heart Rhythm Association, and Asia Pacific Heart Rhythm Society consensus report states that congenital LQTS (cLQTS) is diagnosed “in the presence of [corrected] QT interval >500 ms...when a secondary cause for QT-prolongation is absent.” In contrast, BrS is diagnosed “in patients with ST-segment elevation with type 1 morphology...either spontaneously or after provocative drug test with a Class I antiarrhythmic drug” (2).

This fundamental discrepancy in diagnostic approach is intriguing. After all, both LQTS and BrS share important characteristics: both present as congenital or acquired (mainly drug-induced) arrhythmogenic disorders; both have diagnostic electrocardiograms (ECGs), with a prolonged QT interval in the former (Figure 1) and coved ST-segment elevation >2 mm in the latter (Figure 2); and both may lead to polymorphic ventricular tachyarrhythmias (Figures 1 and 2). However, our understanding of the interplay between these 2 forms (congenital and acquired) of disease differs.

Take, for example, the following patients: 1) a woman on quinidine for atrial fibrillation who develops torsades de pointes (TdP) and ventricular fibrillation (VF) requiring resuscitation; and 2) an asymptomatic man who develops a type 1 Brugada ECG after receiving intravenous flecainide. After cardiac arrest from quinidine, the female patient is likely to receive a diagnosis of drug-induced LQTS (diLQTS) and will be discharged with no therapy, other than instructions to avoid QT-prolonging medications. In contrast, the asymptomatic male patient with flecainide-induced ST-segment elevation is likely to be diagnosed with asymptomatic BrS and could be
referred for an electrophysiological study (EPS) that, if the findings are positive, will result in the implantation of an implantable cardioverter-defibrillator (ICD).

We explore the possibility that the divergent course of events during the description of these 2 diseases led to the paradigms behind their different modes of treatment. In other words, the histories of LQTS and BrS went through the same stages, including: 1) description of the congenital and acquired forms of each disease; 2) understanding of the pathophysiology of each disease type; and 3) understanding of the interaction between the 2 disease variants, with the eventual development of diagnostic tests. However, the sequence of these stages differed for LQTS and BrS (Central Illustration).

ACT I: HISTORY OF LQTS

RECOGNITION OF THE CONGENITAL FORM OF LQTS. The recognition that QT prolongation might be responsible for sudden death emerged in the late 1950s, as Jervell and Lange-Nielsen (3) and Levine and Woodworth (4) described sudden deaths in children with congenital deafness. In the affected children, ECGs showing prolonged QT intervals were documented, although no malignant tachyarrhythmias were captured (3,4). Shortly thereafter, Romano et al. (5) and Ward (6) reported additional families with long QT intervals and sudden death but without deafness. None of the original publications included recordings of the arrhythmias’ onset, although some investigators had them (Figure 1). Consequently, the cause-and-effect association between QT prolongation and the risk for sudden death remained unexplained for years. Although Levine and Woodworth’s (4) contribution was never acknowledged, the Jervell-Lange-Nielsen and Romano-Ward syndromes became recognized as cLQTS with and without deafness, respectively. It would take 40 years to explain the deafness component of the syndrome (7). More important, the story of an acquired form of LQTS was developing in parallel, and it would take the same amount of time before physicians grasped the interplay between the congenital and the acquired forms of the disease.

diLQTS. In 1964, Selzer and Wray (8) documented polymorphic ventricular tachyarrhythmia as the cause of “quinidine syncope.” Tales of patients treated with quinidine suddenly collapsing, sometimes even dying suddenly, had been around since the early 1920s (9,10), but the connection between quinidine and long QT intervals had not been recognized. Instead, “systemic embolism” or “quinidine shock” from toxic effects on the nervous system (11) were the prevailing explanations. Dessertenne (12) not only described in detail the same arrhythmia in patients with atrioventricular block but also coined the term eventually used to denote the unique arrhythmia of LQTS: torsades de pointes.

Strange as it may sound today, neither Dessertenne (12) nor Selzer and Wray (8) considered QT prolongation as the cause of TdP, instead blaming the arrhythmia on widening of the QRS complex. The lack of understanding of the interplay between the drug effects, the QT prolongation, and the arrhythmia is best illustrated by the use of quinidine at that time to treat the arrhythmias caused by congenital (3) and atrioventricular block-related (13) LQTS. Only during the following years was QT prolongation by quinidine linked to arrhythmia causation (14-16).

Other drugs were soon found to display comparable effects on the QT segment, with similar consequences, making diLQTS a recognized entity. This phenomenon became even more intriguing as medications with noncardiac indications (naturally assumed to have no cardiac effects) were recognized to display proarhythmic effects. The first was the antipsychotic drug thioridazine (17). Ironically, as described earlier, quinidine was used at some point to treat this new form of diLQTS (17). The medical community would have to wait until the 1990s before the mechanism of QT prolongation by noncardiac drugs would finally be understood.

UNDERSTANDING QT PROLONGATION. The mechanism responsible for QT prolongation remained elusive for decades. The observation that syncope and cardiac arrest in patients with cLQTS are often triggered by stress (18) led researchers to believe that sympathetic imbalance is responsible for the disease. Animal experiments showing that stimulation of the left sympathetic ganglion produced QT prolongation (19) provided credible proof for the “sympathetic imbalance” theory, to the point that in 1971, Moss and McDonald (20) performed left sympathectomy in a woman with severe cLQTS, demonstrating not only dramatic shortening of her QT interval but antiarrhythmic effects as well. We now understand that inhibition of sympathetic tone prevents arrhythmia triggers in patients with the arrhythmogenic substrate of LQTS. It turned out that left cardiac sympathetic denervation, a procedure conceived for the wrong reasons, proved an effective therapeutic measure for LQTS patients refractory or intolerant to
beta-blockers (21). Nevertheless, in those days, the therapeutic effects of sympathectomy reinforced the misconception of “unbalanced sympathetic innervations.”

As with other familial diseases, the assumption that a genetic etiology lies at the heart of LQTS was held for years (22), although proper technological methods were unavailable. Genetic research at the end of the 1980s focused on the candidate gene approach, which relies on physiology-based mechanistic hypotheses. In 1988, calcium-channel dysfunction was proposed as possible etiology for LQTS but was also ruled out (23). Then, in 1991, after years of meticulous research on 3 large families with LQTS residing in Utah, Keating et al. (24) published a probable link between LQTS and a region in chromosome 11, ultimately pointing to the Harvey-ras 1 gene. Ironically, this proved to be “the wrong gene” (25), as Harvey-ras 1 simply happened to be near the true culprit gene, KCNQ1, which encodes the main component of the IKS potassium channel. Nevertheless, this formidable work shifted the attention of scientists to genes encoding cardiomyocyte membrane ion channels. Four years later, 2 reports, appearing only a few pages apart in the same issue of Cell, established HERG (26) and SCN5A (27) (encoding a potassium and a sodium channel, respectively) as the causes of the second and third recognized forms of cLQTS. This finally clarified that patients with LQTS have arrhythmogenic prolongation of their action potential (and thus their QT intervals) because of faulty repolarizing currents caused by mutations in genes encoding specific ion channels located at the myocyte.

![Figure 1: Initial Reports of the Congenital Long-QT Syndrome](image-url)
membrane. Research on dILQTS was also influenced dramatically by these great leaps forward.

**UNDERSTANDING dILQTS.** During the first decades after its recognition, dILQTS was considered “idiosyncratic,” simply unpredictable, although high-risk characteristics (older women, patients with heart failure) had been recognized (28). In 1981 (11 years before the discovery of the genes responsible for cLQTS), Colatsky (29) demonstrated, in an animal model, that quinidine prolongs the action potential, even suggesting that suppression of the potassium delayed-rectifier current (IKr) was the probable etiology. In 1988, Roden et al. (30) proved this hypothesis correct, showing that action potential prolongation by quinidine was due to blockade of the IKr channel. The same year, Jackman et al. (31) demonstrated that patients with drug-induced TdP were at higher risk for recurrence when exposed to a second offending drug and that their QT intervals tended to be at the upper end of the normal range, even before drug exposure. This led them to propose an “inborn predisposition” as the etiology for dILQTS (31). The unraveled mechanism of cLQTS (as described earlier) now served to establish IKr blockade as the cause of dILQTS (32). Yet the question of who is prone to dILQTS remained unanswered.

In 1998, Roden (33) wrote a brief editorial, “Taking the ‘Idio’ out of ‘Idiosyncratic’: Predicting Torsades..."
de Pointes,” as a comment on a paper describing electrocardiographic predictors of TdP after almokalant treatment for atrial fibrillation (34). That original report on almokalant is no longer remembered, but a term coined in Roden’s accompanying editorial, “reduced repolarization reserve,” was soon to be quoted in practically all future publications on diLQTS. According to the principle of reduced repolarization reserve, some patients were more prone to drug-induced TdP than others because of additional factors (including genetic background) that impair the repolarization current. Genetic support for this model came from studies showing incomplete penetrance of long-QT genes among members of families.
carrying the mutant gene, resulting in seemingly normal QT intervals that were unmasked only after exposure to a repolarization challenge (35,36). The overlap between congenital and acquired LQTS was finally understood to some extent.

**EVOLUTION OF DIAGNOSTIC PRINCIPLES AND INTERPRETATIONS OF CHALLENGE TESTS.** A direct result of the identification of genes causing cLQTS was the realization that some carriers of genetic mutations had QT intervals within the normal range (37), such that a significant overlap exists between the QT intervals of the healthy and the affected populations. Consequently, diagnostic tests to distinguish the former from the latter group became imperative. In 1998, Yan and Antzelevitch (38) reproduced T-wave patterns similar to the prototypic LQT1, LQT2, and LQT3 in a laboratory model of canine myocardium subjected to Iks, Ikir, and sodium-channel blockers, respectively. Yet the administration of potassium-channel blockers as a diagnostic test for cLQTS was scarcely used in clinical practice, because other tests, including the use of epinephrine (39,40) and, less commonly, adenosine (41), to expose the abnormal response of the QT interval to drug-induced changes in heart rate were used. Together with the use of exercise (42) and “quick standing” (43) tests, this achieved excellent diagnostic accuracy, limiting the need for drug challenge tests directly interfering with repolarization. Use of Ikir blockers to challenge repolarization was used primarily to identify patients prone to developing diLQTS. For example, Kääb et al. (44) demonstrated that patients with histories of drug-induced TdP had excessive QT prolongation when challenged with intravenous sotalol. Similarly, Kannankeril et al. (45) showed that relatives of patients with diLQTS had excessive QT prolongation after exposure to quinidine. It was only in 2008 that erythromycin was used to unmask genetically positive long-QT patients with normal QT intervals, marking the first use of an Ikir blocker to diagnose cLQTS (46). The use of Ikir blockers never became common practice for diagnosing cLQTS. This aspect of history was very different from the sequence of events leading to the use of sodium-channel blockers to diagnose congenital BrS.

**EVOLUTION OF THERAPEUTIC APPROACHES.** It was mainly through the multicenter cooperation generated by the International Long QT Syndrome Registry (22,47), initiated by Schwartz and Moss, that adequate data could be generated for better understanding of the clinical and electrocardiographic (and ultimately genetic) risk factors for malignant arrhythmias in cLQTS. Treatment of cLQTS was never on the basis of randomized studies. Instead, as early as 1975, Schwartz et al. (18) reviewed all published cases of cLQTS reported by then, including the empirical treatment they had received. In contrast to digoxin (proposed for its QT-shortening effect), phenobarbital, or hydantoin, beta-blockers effectively prevented recurrent arrhythmias (18). By the time the ICD became clinically available, the medical community knew that the vast majority of patients with cLQTS do well on beta-blockers. It so happened that ICD implantation became indicated only for patients with LQTS with recurrent arrhythmias while on beta-blockers, or for a small minority of asymptomatic patients with identifiable high-risk characteristics (2). Here, too, the evolution of therapeutic approaches in BrS was different.

**ACT II: HISTORY OF BrS**

**BrS: DISCOVERY OF THE INHERITED FORM.** In 1992, Pedro and Josep Brugada (48) described “a distinct clinical and electrocardiographic syndrome of right bundle branch block, persistent ST-elevation and sudden cardiac death” (Figure 2). Similar electrocardiographic patterns had been reported decades earlier but considered benign (Figure 2A) (49). In 1989, Martini et al. (50) described comparable ECGs in patients with otherwise “idiopathic VF” (Figure 2B) and concluded that these patients probably had some form of right ventricular cardiomyopathy.

Yan and Antzelevitch (51) coined the eponym “Brugada syndrome” in a report describing the cellular basis of the J waves on the ECG. That the Brugada brothers were the only authors of the original report, combined with the interesting phonetics of “Brugada” and the long title of this newly described entity, probably contributed to its quick adoption. In contrast to LQTS, for which it took >30 years from its first description to identification of the responsible gene, this process took only 6 years for BrS. In 1998, Chen et al. (52) identified 3 mutations in the SCN5A gene, encoding the alpha subunit of the cardiac sodium channel, pointing out sodium-channel mutations as the underlying cause of the disease.

**DRUG CHALLENGE TO UNRAVEL BrS.** Soon after the initial description of BrS, it became clear that the distinctive coved ST-segment elevation was not present in affected patients at all times, obviating the need for a diagnostic test to expose “concealed BrS” (53,54). A fascinating sequence of events set the background for the use of sodium-channel blockers for unraveling congenital BrS. One year before the first
report of BrS (48), Krishnan and Antzelevitch (55) demonstrated that sodium-channel blockers applied on canine myocardium produced ST-segment elevation by abbreviating action potentials in the epicardium more than in the endocardium, thus increasing the dispersion of ventricular repolarization. Miyazaki et al. (56) astutely noticed that 1 patient with BrS demonstrated augmented ST-segment elevation when treated with disopyramide (a sodium-channel blocker) for atrial fibrillation. After discussing this observation with Antzelevitch (T. Miyazaki, personal communication, May 2015), Miyazaki challenged 3 patients with BrS and intermittent ST-segment elevation with disopyramide or procainamide (another sodium-channel blocker). Aggravation of the Brugada electrocardiographic pattern immediately occurred in all 3 patients, and the observations were published as “Antiarhythmic Drug Modulation of ST-Segment Elevation in Patients With Brugada Syndrome” (56). Thus, when Chen et al. (52) described that SCN5A mutations were behind the congenital BrS, the stage was set to test sodium-channel blockers as a means to unravel congenital BrS. In 2000, Brugada et al. (57), by now using ajmaline to block the sodium channel, found 100% concordance between positive results on an ajmaline test and the presence of SCN5A mutations in family members with BrS. Consensus papers embraced the sodium-channel-blocker drug challenge as a diagnostic criterion for congenital BrS in proper clinical context (58).

DRUG-INDUCED BrS. Sudden deaths in cocaine users had been reported for years, but the mechanism was poorly understood (59,60) given the drug’s myriad effects, including vasoactive effects, in addition to sodium-channel-blocking activity. The first reports connecting cocaine use with BrS arrived in the mid-1990s, describing coved ST-segment elevation in young patients with normal coronary arteries, now interpreted as “unmasked BrS” (61). Other cardiac and noncardiac drugs were soon found to display a similar drug-induced BrS (62).

THERAPEUTIC APPROACH FOR BrS. The first reports on BrS portrayed an alarming picture for asymptomatic patients recognized because of their ECGs. Young, ostensibly healthy men with this peculiar electrocardiographic pattern were considered at risk for impending doom, as cardiac arrest rates for initially asymptomatic patients appeared to be as high as 10% per year (63). Given the contemporary availability of ICDs, it seemed logical to advise such asymptomatic patients (if they had inducible VF during EPS) to undergo ICD implantation (64,65). As discussed in detail (66), these recommendations were also applied to asymptomatic patients who had their BrS “unraveled” by sodium-channel-blocker tests. The DEBUT (Defibrillator Versus β-Blocker for Unexplained Death in Thailand) randomized study, conducted in the 1990s, comparing drug therapy with ICD therapy for BrS with cardiac arrest or malignant syncpe (65), was prematurely stopped because of the unacceptably high mortality rate in the medication arm. Regrettably, the medication used in the “drug arm” of this trial (propranolol) was the wrong drug to test. In fact, this beta-blocker with sodium-channel-blocker properties is now listed among the “drugs to preferably avoid” in BrS (62). By the time the DEBUT trial was designed, quinidine had already been successfully used to prevent recurrent arrhythmias in idiopathic VF (67,68), and shortly after publication of the DEBUT trial, quinidine was also found to be effective in BrS (69,70). By now, however, the ICD was already “the only acceptable therapy” for BrS (58). As the years passed, accumulating data showed that the rates of sudden deaths in patients with BrS were much lower for the subgroup that was asymptomatic at the time of diagnosis (71), and the therapeutic approach was challenged. Nevertheless, these patients were (and still are) referred for EPS and may undergo ICD implantation (72).

ACT III: LOOKING BACK TO UNDERSTAND HOW WE GOT HERE

“History never looks like history when you are living through it.”
—John W. Gardner (73)

The therapeutic approach to asymptomatic patients radically differs between BrS and LQTS. This is due in part to the less forgiving course of BrS; only a minority of patients with BrS will develop arrhythmias, but for those who do, cardiac arrest is often the presenting symptom (74). In contrast, in LQTS, patients with cardiac arrest often have warning symptoms in the form of syncope, or identifiable high-risk characteristics, such as a very long QT interval (75). Also, the safety profile in terms of adverse events is better for beta-blockers than for quinidine.

However, history also appears to have influenced the way these patients are treated. By 2006, one-half of the ICD implantations performed in Europe for BrS were in completely asymptomatic patients. Moreover, the most common indication for ICD implantation in the asymptomatic group was a “positive ajmaline test with positive EPS” (76). Sure enough, at 3 years of follow-up, only 1.6% of the initially asymptomatic patients who had type I Brugada ECGs
revealed by the ajmaline test had experienced spontaneous VF, whereas 31% had serious ICD-related complications (76). Publication of these numbers eventually led to a more conservative approach, and nowadays, the proportion of ICD implantations for asymptomatic BrS, particularly that “revealed by drugs,” is decreasing, at least in academic institutions (72). Prophylactic defibrillator implantation for asymptomatic patients who develop long QT intervals when challenged by medications would be unthinkable to most of us. To understand how we ended up with so many ICDs in asymptomatic patients with drug-exposed Brugada ECGs, we ought to look back at how the understanding of LQTS and BrS evolved over the years.

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