

Figure 4 Kaplan-Meier estimates of the cumulative probability of aborted cardiac arrest or sudden cardiac death in (A) women with LQT1 and (B) men with LQT1, by QTc duration. ACA = aborted cardiac arrest; C-loop mutations = cytoplasmic-loop mutations; LQT1 = long QT syndrome type 1; QTc = corrected QT interval; SCD = sudden cardiac death.

However, because of a small sample of patients with >1 mutation, the current results should be interpreted with caution in the risk assessment of this subset.

Conclusions and clinical implications

Our data extend prior knowledge regarding genotype-specific risk assessment in LQTS.^{16,17} The present results suggest that the functional effects of mutations in the *KCNQ1*-encoded channel subunit may explain differences in the risk for life-threatening cardiac events between men and women with LQT1. Here, both men and women with LQT1-causative mutations localizing to the C loops (S2–S3 and S4–S5 linkers), the intracellular domains that connect the MS domains of the *KCNQ1*-encoded protein, have increased risk for not only LQT1-triggered syncope but also LQT1-triggered life-threatening cardiac events of ACA and SCD, possibly due to the increased sensitivity of these functional domains to adrenergic stimulation. In contrast, men with

LQT1 were shown to have an increased risk for ACA or SCD even in the presence of mutations localizing elsewhere predicted at the molecular/cellular level to be associated with lower risk. These findings suggest that a genotype-specific approach, incorporating clinical and mutation location/functional data, might further improve the risk assessment and management of patients with the most common genetic subtype of LQTS.

Appendix

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.hrthm.2012.01.020.

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Brugada Phenocopy: New Terminology and Proposed Classification

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Brugada syndrome is a channelopathy characterized on ECG by coved ST-segment elevation (≥ 2 mm) in the right precordial leads and is associated with an increased risk of malignant ventricular arrhythmias. The term Brugada phenocopy is proposed to describe conditions that induce Brugada-like ECG manifestations in patients without true Brugada syndrome. An extensive review of the literature identified case reports that were classified according to their suspected etiological mechanism. Future directions to learn more about these intriguing cases is discussed.

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Brugada syndrome; Brugada-like ECG pattern; Brugada-like ECG findings; Brugada syndrome mimicry

Brugada syndrome is a putative channelopathy characterized on ECG by a coved ST-segment elevation (≥ 2 mm) and subsequent inverted T wave in a minimum of two right precordial leads (Brugada Type-1 ECG pattern). It is associated with a propensity for malignant ventricular arrhythmias leading to sudden cardiac death in the absence of structural heart disease. The syndrome has been linked to over 80 mutations in the *SCN5A* gene and demonstrates an autosomal dominant mode of transmission.¹

The distinct Brugada Type-1 ECG pattern is dynamic and can often be concealed. Unmasking of the ECG signature can be accomplished by sodium channel blockers and febrile states.¹ In addition,

some drugs and conditions can induce a Brugada Type-1 ECG pattern in the absence of true congenital Brugada syndrome, representing a discrete clinical entity with a different pathophysiology.¹

Presently, the terminology used in the literature to describe Brugada Type-1 ECG patterns induced in patients without Brugada syndrome is diverse and variable, including acquired forms of Brugada syndrome, Brugada-like ECG patterns, Brugada-like ECG findings, Brugada-like ECG ST-segment abnormalities, and Brugada syndrome mimicry. The lack of consensus throughout the literature is confusing and creates uncertainty when differentiating between congenital Brugada syndrome, unmasked Brugada syndrome, and an

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induced Brugada Type-1 ECG pattern in the absence of the true condition. It would be advantageous to unify the nomenclature under a single, reasonable descriptor. Riera et al. introduced the term "Brugada phenocopy" to describe an acquired Brugada-like ECG pattern in the setting of propofol infusion syndrome.² As discussed by Riera, the term phenocopy describes "an environmental condition that imitates one produced by a gene" and serves as a reasonable, succinct description of acquired Brugada-like manifestations.³

Although there has been advancement in our understanding of true Brugada syndrome, there is currently limited discussion in the literature of the underlying mechanisms by which Brugada phenocopies develop.

The objective of this study is to review all published cases of Brugada phenocopies and classify them according to their pathogenesis. To understand how different mechanisms can produce a Brugada pattern in the absence of the genetic mutation, we will briefly discuss the current theories that explain the ECG manifestations and arrhythmogenesis of true Brugada syndrome.

CURRENT THEORIES EXPLAINING TRUE BRUGADA ECG MANIFESTATIONS

Depolarization Theory

The depolarization theory hypothesizes that the ST-segment elevation is caused by the conduction delay in the right ventricular outflow tract (RVOT), and the ventricular arrhythmia associated with the Brugada syndrome is induced by the abnormal current created by the delayed depolarization of the RVOT.⁴⁻⁶ This model is based on the mechanism explaining ST-segment elevation in regional transmural ischemia, where large potential difference between ischemic and nonischemic regions create current that reflects as ST-segment elevation.⁷ The delayed depolarization of the RVOT with respect to the other RV action potentials creates a potential difference between the right ventricle and the RVOT. The membrane potential of the RVOT is more negative than that of the RV during the hatch phase action potential. Hence, the intercellular current flows toward the RVOT, and the extracellular current travels away from the RVOT, forming a closed circuit. At the RVOT, the current conducts from the RVOT intercellular space to the extracellular space, traveling toward the ECG electrode po-

sitioned over the RVOT (V₂_{IC3}). The current is reflected as the elevated ST segment on V₂_{IC3}. Similarly, another current traveling between the RVOT and the RV is formed at the end of the action potential given that now the RVOT becomes more positive than the RV; the later current travels in the opposite direction of earlier current and is reflected as the negative T wave seen on V₂_{IC3}. Similar to regional transmural ischemia, ventricular tachyarrhythmias seen in Brugada syndrome patients is believed to originate from the border zone between early and delayed depolarizations.⁷ Delayed conduction is presumably caused by discrete structural abnormalities in the RV wall, preferentially in the RVOT. Strong evidence for this substrate is provided by recent epicardial mapping studies in 10 severely symptomatic patients, demonstrating fractionated potentials during 200–300 ms after the QRS complex. Substrate ablation resulted in resolution of the ST-segment elevation and associated arrhythmias.⁸ Further evidence from body surface maps (BSM) indicating heterogeneity of depolarization activity in the RVOT supports the depolarization theory.⁵ Epicardial electrograms recorded at the conus branch of the right coronary artery also indicated abnormality in the RVOT in some of the patients with Brugada syndrome, providing support for the depolarization theory.⁶

Repolarization Theory

The repolarization theory was founded on experimental data from studies using canine coronary-perfused right ventricular wedge preparations. According to this theory, a reduced inward sodium current and prominent outward current leads to the accentuation of the action potential notch in the right ventricular epicardium relative to the endocardium.⁴ This produces a transmural voltage gradient, which manifests electrocardiographically as the characteristic ST-segment elevation seen in Brugada syndrome. At the end of phase 1, certain epicardial sites undergo all-or-none repolarization, losing their action potential dome and resulting in the development of a local epicardial dispersion of repolarization. This heterogeneous repolarization environment leads to phase 2 reentry and coupled extrasystoles when action potential domes migrate from sites where they are present to sites where they were lost. A transmural dispersion of repolarization and extended refractory period are also generated, which presents the opportunity for

the phase 2 reentry extrasystoles to trigger polymorphic ventricular tachycardia.⁴

Cardiac Neural Crest Cell Theory

Elizari et al.⁹ proposed that the Brugada syndrome phenotype may be explained by abnormal expression of neural crest cells in the development of myocardial structures, primarily the RVOT. They hypothesize that the RVOT and its nearby structures have different embryologic origins than the rest of the heart and consequently possess different physiological, anatomical, and clinical characteristics. As well, the RVOT is identified as a vulnerable region of the heart based on the observation that conditions and drugs, which typically exhibit diffuse and uniform depolarization and/or repolarization changes have the greatest effect in the RVOT. The neural crest cell theory is built upon the idea that the Brugada syndrome manifestations are due to two underlying electrophysiologic mechanisms: heterogeneity of ventricular repolarization, which follows the concepts of the repolarization theory outlined earlier, and abnormal conduction slowing in the RVOT.⁹

The cardiac neural crest is vital in the morphogenesis of the RVOT and its neighboring structures. An essential molecule in the regulation of neural crest development is connexin 43 (Cx43), which is a gap junction protein that contributes to neural crest cell migration and the propagation properties of the cardiac impulse. Gap junctional communication facilitated by Cx43 has been linked to the differentiation of neural crest cells into cardiac myocytes. Consequently, improper gap junctional communication in the RVOT leads to errors in cardiac neural crest cell expression, which may result in tissue remodeling and altered gap junctional channel configuration. These abnormal changes in the myocardium provide a possible explanation for the repolarization heterogeneities contributing to the Brugada syndrome phenotype. In addition, the transmural and regional heterogenic Cx43 distribution resulting from tissue remodeling can cause the conduction slowing and late action of the RVOT that underlies Brugada syndrome manifestations.⁹

THE BRUGADA PHENOCOPY CONCEPT

Of importance in understanding the concept of Brugada phenocopies, is distinguishing between

these entities and cases of unmasked congenital Brugada syndrome. In the latter case, concealed or latent ECG manifestations are unmasked by certain agents and conditions in the presence of true Brugada syndrome. The defining feature of a Brugada phenocopy is the absence of true Brugada syndrome despite the presence of characteristic Brugada Type-1 ECG findings.

In accordance with the previously discussed repolarization theory, the characteristic ST-segment elevation seen in Brugada phenocopies can be explained by a transmural gradient that arises from an accentuated I_{to} -mediated action potential notch and a loss of the AP dome in the epicardium but not the endocardium. The loss of the AP dome can result from a disruption in the homeostasis of active inward and outward currents at the end of phase 1 of the AP.¹⁰ Specifically, any mechanism that increases outward currents (i.e., I_{to} , adenosine triphosphate-sensitive potassium current [I_{K-ATP}], delayed rectifier potassium current [I_{Ks}, I_{Kr}]) or decreases outwards currents (i.e., I_{Ca-L} , fast I_{Na}) will result in the characteristic ST-segment elevation seen in the Brugada Type-1 ECG.¹⁰ This provides a possible explanation of the general, underlying pathogenesis of the diverse forms of Brugada phenocopies.

UNMASKING TRUE BRUGADA SYNDROME BY FEVER IS DIFFERENT FROM BRUGADA PHENOCOPY

The relationship between febrile states and the Brugada syndrome is a particularly interesting phenomenon that deserves elaboration. There are numerous published cases of fever unmasking or accentuating the ECG manifestations of Brugada syndrome which are occasionally accompanied by ventricular arrhythmias.¹¹⁻³⁰

Upon review, all these cases demonstrated the normalization of Brugada ECG findings with resolution of the fever and no family history of sudden death. In only one case did the patient report a history of syncope, which involved several episodes associated with a past febrile episode. The results of drug provocation testing upon defervescence were mixed: some cases reports elicited a Brugada ECG pattern^{12,13,19,23} whereas the remainder described negative findings or did not indicate whether the test was completed.

A possible mechanism by which fever un-masks true Brugada syndrome can be explained

by temperature-sensitive *SCN5A* mutations. Using mammalian cell lines, Dumaine et al. demonstrated that Thr1620Met missense mutations on the *SCN5A* gene are temperature dependent, resulting in dysfunction at elevated temperatures due to the accelerated decay of inward sodium currents (I_{Na}).²⁹ Consequently, febrile states may exacerbate the mutant sodium channels, leading to an accentuation or unmasking of ECG manifestations and an increased risk of malignant arrhythmias in patients with Brugada syndrome. In addition, Keller et al. discovered a novel *SCN5A* mutation (F1344S) in a patient with Brugada syndrome and fever-induced ventricular fibrillation.³⁰ The authors presented evidence that sodium channel dysfunction coupled with a febrile state can lead to a shift in activation that is sufficient to produce Brugada ECG manifestations.³⁰

The positive and negative predictive values of the sodium channel blockage test using flecainide among *SCN5A*-positive patients and their family members were 96% and 36% respectively.³¹ Given such a low negative predictive value, negative sodium blocker test results for fever-induced Brugada syndrome patients may not be sufficient to classify these cases as Brugada phenocopies.

The unmasking of concealed Brugada syndrome during febrile states may increase the risk of life-threatening cardiac arrhythmias.²⁷

Juntilla et al. reported that the induction of a Brugada ECG pattern during acute events, including fever, can lead to the development of malignant arrhythmias even in the absence of a *SCN5A* mutation.³² Prompt recognition and treatment with antiarrhythmics is indicated and may be lifesaving.

UNMASKING TRUE BRUGADA SYNDROME BY SODIUM CHANNEL BLOCKERS IS DIFFERENT FROM BRUGADA PHENOCOPY

Of the three types of Brugada ECG patterns, only the Type-1 manifestations are considered to be a positive diagnostic sign of Brugada syndrome. Type-2 and 3 ECG are not considered diagnostic on their own, however, conversion of either of these ECG patterns to a Type-1 ECG via the administration of a sodium channel blocker is considered to be diagnostic for Brugada syndrome.¹ Currently, there are four sodium channel blockers used to unmask a Brugada Type-1 ECG in a patient suspected to have Brugada syndrome: two class 1A

antiarrhythmic agents, ajmaline and procainamide, and two class 1C antiarrhythmic agents, flecainide and pilsicainide.^{1,33} In addition, propafenone is another class 1C antiarrhythmic agent that can unmask Type-1 ECG manifestations through sodium channel blocking effects but is not used for diagnostic purposes. All five of these antiarrhythmic agents have been associated with malignant arrhythmias.³³

Following the organizational scheme outlined by Postema et al. (www.brugadadrugs.org),³³ there are two broad categories of agents that can unmask a Brugada Type-1 ECG: (1) agents that have a clear association with malignant arrhythmias, and (2) agents without a clear risk of inducing arrhythmias.³³ These categories will arbitrarily be referred to as Group 1 and 2 drugs, respectively.

Group 1 is composed of tricyclic antidepressants (amitriptyline, clomipramine, desipramine, and nortriptyline), antipsychotic agents (loxapine and trifluoperazine), lithium, bupivacaine, propofol, acetylcholine, alcohol, cocaine, and ergonovine.³³ Akin to the antiarrhythmic agents previously described, nearly all these substances induce a Type-1 ECG by augmenting ST-segment elevation in leads V1-V3 via sodium channel blockade.³³⁻⁵⁸ Given the mechanistic similarity to the diagnostic agents that unmask true Brugada syndrome, it would suggest that Group 1 drugs also function to unmask rather than mimic Brugada syndrome. Consequently, the Group 1 drugs for the most part cannot be considered Brugada phenocopies.

There are a few exceptions. Acetylcholine, ergonovine, and alcohol act on sites other than sodium channels to induce a Brugada Type-1 ECG pattern.^{34,35} Acetylcholine and ergonovine have been reported to decrease inward calcium channels, accentuating the action potential notch and leading to ST-segment elevation and ventricular fibrillation in patients with Brugada syndrome.³⁴ Similarly, alcohol has been shown to inhibit calcium channels as well.³⁵ There are at least two documented cases of alcohol associated with Brugada ECG manifestations. The first case involved a patient diagnosed with Brugada syndrome who developed a sustained monomorphic ventricular tachycardia from alcohol provocation.³⁶ It is uncertain whether or not the alcohol had a role in unmasking or accentuating ST-segment elevation, so this case may be outside the scope of our current discussion. The other case was of a patient who

presented with both alcohol and fluoxetine intoxication. Fluoxetine has been shown to induce a Type-1 ECG as well, so it is difficult to determine whether the ECG changes were due to alcohol or fluoxetine in this case.⁴⁴ Noda et al. report that acetylcholine and ergonovine are capable of augmenting ST-segment elevation in patients with Brugada syndrome, however, there is yet to be reports of either substance acting as a Brugada phenocopy.³⁴ It is evident that additional investigation is required to discern exactly how acetylcholine, ergonovine, and alcohol relate to Brugada syndrome and/or Brugada phenocopies.

The Group 2 drugs include antiarrhythmic drugs (amiodarone, cibenzoline, disopyramide, lidocaine, verapamil, and propranolol), psychotropic drugs (carbamazepine, cyamemazine, dosulepine, doxepin, fluoxetine, fluvoxamine, imipramine, maprotiline, paroxetine, perphenazine, phenytoin, and thioridazine), analgesics/ anesthetics (ketamine and tramadol), dimenhydrinate, diphenhydramine, edrophonium, indapamide, metoclopramide, and terfenadine.³³ All Group 2 drugs are all either confirmed or believed to possess sodium channel blocking effects.^{33,59-70} There are also a number of antianginal drugs that may be associated with a Type-1 ECG,^{1,33} however, given the current lack of evidence on the existence and nature of this relationship, the issue was not explored in this article. As well, not yet included on the "Brugada drugs" Website is a case of cannabis intoxication eliciting a Brugada-like ECG pattern. Not unlike the majority of agents associated with the Type-1 ECG, Daccarett et al. speculate that the manifestations are due to the sodium channel blocking effects of cannabis.⁷¹ As a result, a Brugada Type-1 ECG associated with the Group 2 drugs and cannabis suggests that they are cases of unmasked Brugada syndrome rather than Brugada phenocopy.

NEW PROPOSAL FOR A CLASSIFICATION OF BRUGADA PHENOCOPIES

Methods

Search Strategy

A literature review was performed on the following databases: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) from 1947 to January Week 4 2011, EMBASE from 1980 to February Week 1 2011 and PubMed (March Week 1, 2011).

On all of the databases, the "Brugada Syndrome" MeSH heading search results were combined with key word search results for "Brugada-like," "mimicking Brugada," "induced Brugada syndrome," "Brugada type," "Brugada sign," "Brugada-pattern," and "acquired Brugada." The combined search results were initially reviewed by two reviewers (MR, TN). Case reports were selected according to the inclusion criteria described below and ambiguous cases were reviewed by an expert electrophysiologist (AB) until consensus was reached.

In addition, the references of the included papers were reviewed for any outstanding case reports that were missed in the initial search.

Inclusion Criteria

- (1) The case report is published.
- (2) The case describes a patient with a Brugada ECG pattern (Type-1, 2, or 3) that is confirmed by an ECG tracing included in the article.
- (3) The patient described in the case does not have true Brugada syndrome, which is determined by an assessment of low clinical probability (symptoms, past medical history, family history), genetic testing, and/or provocative testing with flecainide, ajmaline, or procainamide or other sodium channel blockers.

Exclusion Criteria

- (1) The case is an example of the unmasking of an underlying true (or possible) Brugada syndrome.
- (2) The Brugada ECG pattern is likely due to the administration of flecainide, ajmaline or procainamide. These drugs are commonly used in provocative testing as a means of diagnosing true Brugada syndrome. Cases associated with other drugs, which their mechanism of action is blocking sodium channels are listed separately in section "unmasking Brugada syndrome."

RESULTS

Thirty-one cases were identified as meeting our inclusion criteria.⁷²⁻¹⁰² To confirm these cases as manifestations of Brugada phenocopies, we first sought to assess the clinical probability that the

Table 1. Summary of Brugada Phenocopies

Category	Number of Individuals (Number of Case Reports)	Mean Age (Range)	Male: Female	ECG Type	Presence of Structural Heart Disease	Case Report References
Metabolic conditions	14(14)	51.9 ± 17.8 (28–89)	13:1	13 Type-I 5 Type-II 4 Variable	0 Y 14 N	72–85
Mechanical compression	6(5)	45.7 ± 18.5 (19–66)	3:3	6 Type-I 0 Type-II 0 Variable	3 Y 3 N	86–90
Ischemia	4(4)	60.0 ± 6.7 (55–68)	2:2	4 Type-I 1 Type-II 1 Variable	1 Y 3 N	91–94
Myocardial & pericardial disease	8(6)	46.2 ± 13.9 (28–72)	5:3	5 Type-I 4 Type-II 2 Variable	2 Y 6 N	95–100
Miscellaneous	2(2)	22.5 ± 0.7 (22–23)	1:1	2 Type-I 1 Type-II 1 Variable	1 Y 1 N	101–102

Mean age is reported with ± standard deviation. ECG Type = presence of more than one type of Brugada ECG pattern.

patients had true Brugada syndrome. A patient was thought to have a low clinical probability of having true Brugada syndrome if they had a negative sodium channel blocker challenge test result, a lack of family history of syncope or sudden death, no previous history of syncope or cardiac arrhythmia, and was afebrile. Some cases fell under multiple categories and in those instances we assigned classification based on the most probable or dominant mechanism thought to induce the Brugada ECG pattern.

Five general categories were devised based on the underlying mechanism and are as follows: metabolic conditions, mechanical compression, ischemia, myocardial/pericardial diseases, and miscellaneous (Table 1).

Fourteen cases were included in the metabolic condition category.^{72–85} Thirteen patients showed Brugada Type-1 ECG and five showed Type-2 ECG. Four of the patients' ECG switched between a Brugada Type-1 and a Type-2 ECG pattern (i.e., had both). No case reported the presence of structural heart disease. The male to female ratio in this category was 13:1. The mean age was 51.9 ± 17.8 with a range of 28–89 years old. Fourteen cases were further categorized into three sub-categories: hypothermia, electrolyte disturbance, and hypothyroidism (Table 2).

We identified five publications of Brugada phenocopies induced by mechanical compression^{86–90}

(Table 3). Six patients were described in the five publications and all patients developed a Brugada Type-1 ECG pattern. The cases were further categorized into the subcategory extracardiac mechanical compression. The male to female ratio was 1:1. Two Japanese patients had pectus excavatum,⁸⁶ and one Japanese patient had right ventricular hypertrophy.⁸⁷ Other publications did not report any structural heart disease. The mean age of this category was 45.7 ± 18.5 with the age range of 19–66 years old.

Four cases were identified as ischemia-induced Brugada phenocopies.^{91–94} All four patients had Brugada Type-1 ECG, and one patient had an ECG that varied between Brugada Type-1 and 2 ECG pattern. The male to female ratio was 1:1. The mean age was 60.0 ± 6.7 with the age range of 55–68 years old. One patient described by Eggebrecht et al. had left ventricular hypertrophy with reduced RV function and was resuscitated from ventricular fibrillation.⁹¹ The cases were further categorized into two subcategories: right coronary and left coronary artery involvement (Table 4).

The last category is Brugada phenocopies induced by myocardial and/or pericardial disease. This category includes six publications, describing nine patients.^{95–100} Six patients showed Brugada Type-1 ECG pattern whereas four had Type-2. Two patients had the ECG pattern switch

Table 2. Classification Table for Metabolic Condition Induced Brugada Phenocopies

Categories	First Author (Publish year)	Descriptor	Age/ Gender	EKG type	Structural Heart Disease	Note	Outcome
Electrolyte disturbance	Irani (2010) ⁷⁴	Hyperkalemia	46/M	Type-1	Nonreported	Cocaine use	ECG normalization after resolution of hyperkalemia
	Kovacic (2004) ⁷⁶	Acidosis, Hyponatremia Hyperkalemia	38/M	Type-1	Nonreported	Polyuria, polydipsia	Normalization of ECG after treatment
	Kurisu (2009) ⁷⁷	Hyperkalemia	89/M	Type-1 & 2	Nonreported	Pancreatitis treatment with mesilate	Normalization of ECG after treatment
	Kutsuzawa (2001) ⁷⁸	Hypokalemia	53/M	Type-1	Nonreported	Hypokalemia	Normalization of ECG after treatment, ICD implants
	Mehta (2009) ⁷⁹	Hypercalcemia	62/M	Type-1	Nonreported	Rhabdomyolysis caused hypercalcemia	Normalization of ECG after treatment
	Mok (2008) ⁸⁰	Hypokalemia Hyponatremia	64/M	Type-1	Nonreported	Indapamide	Normalization of ECG after treatment
	Ortega-Carnicer (2002) ⁸¹	Hyperkalemia	34/M	Type-1	Nonreported	Diazepam and phenytoin administered	Normalization of ECG after hemodialysis
	Tamene (2010) ⁸³	Hyponatremia	63/M	Type-1	Nonreported	Metoprolol, hydrochlorothiazide, lisinopril, valproic acid and oral hypoglycemic	Normalization of ECG after serum sodium correction
	Tanawuttiwat (2010) ⁸⁴	Hyperkalemia	47/F	Type-1	Nonreported	Jaundice, leukocytosis, hepatitis with cirrhosis, thiamine and empiric antibiotics, renal failure, respiratory distress	Died during treatment, no ventricular fibrillation or polymorphic ventricular tachycardia was noted
Electrolyte disturbance	Tsai (2010) ⁸⁵	Thyrotoxic periodic paralysis with hypokalemia	51/M	Type-1	Nonreported	Low potassium, hypothyroidism,	Brugada ECG resolved after resolution of hypokalemia and hyper glycemia.
Hypothermia	Ansari (2003) ⁷²	Hypothermia	29/M	Type-1	Nonreported	Diabetes mellitus.	Normalization of ECG after regaining of temperature
	Bonnemeier (2008) ⁷⁵	Hypothermia	28/M	Type-2	Nonreported	Severe hypothermia,	Normalization of ECG after regaining of temperature
	Ortega-Carnicer (2008) ⁸²	Hypothermia	78/M	Type-1	Nonreported	COPD	Normalization of ECG after regaining of temperature, patient died four weeks later from multiorganic failure
Hypo-thyroidism	Khalil (2010) ⁷⁵	Adrenal insufficiency	47/M	Type-1 & 2	Nonreported	Primary adrenal insufficiency, hyperkalemic	Normalization of ECG after steroid supplementation

Descriptor = the primary condition that is believed to cause Brugada ECG pattern; M = male; F = female; Note = any medication taken or clinical condition that the patient presented; Outcome = resolution of Brugada ECG and patient mortality and morbidity, if available.

Table 3. Classification for Mechanical Compression Induced Brugada Phenocopies

	First Author (Publish Year)	Descriptor	Age/Gender	EKG type	Structural Heart Disease	Note	Outcome
Extracardiac mechanical compression	Kataoka (2002) ⁸⁶	Pectus excavatum	19/M 30/M	Type-1 Type-1	–	A patient (30/M) showed confirmed reduced RV motion	Not reported
	Nakazato (2003) ⁸⁷	Anterior mediastinal mass lesion	52/F	Type-1	Right ventricular hypertrophy	Fever/compression of RVOT	Gradual normalization of ECG after improvement of inflammatory markers
	Sasaki (2010) ⁸⁸	Reconstructive operation for esophageal cancer	63/M	Type-1	Nonreported	Compression of Anterior RV	Gradual normalization of ECG after treatment.
	Tarin (1999) ⁸⁹	Mediastinal tumor	66/F	Type-1	Nonreported	Amiodarone, Confirmed tumor displaced RVOT	6 month follow-up showed ECG without Brugada ECG
	Tomcsanyi (2002) ⁹⁰	Hemopericardium	44/F	Type-1	Nonreported	Tumor (organized hemopericardium) compressing the RV	Normal ECG after the removal of tumor

Descriptor = primary condition that is believed to cause BRUGADA ECG pattern; M = male; F = female; Note = any medication taken or clinical condition that the patient presented; Outcome = resolution of Brugada ECG and patient mortality and morbidity, if available.

between Type-1 and 2. Bramos et al. described a patient that had concentric hypertrophy.⁹⁵ Nayyar et al. described a patient with biventricular severe global systolic dysfunction.⁹⁷ The myocardial and pericardial cases were further categorized into the following four subcategories: acute myocarditis, chronic myocarditis, acute pericarditis, and myotonic dystrophy. The male to female ratio was 2:1. The mean age of this category was 46.2 ± 13.9 with the age range of 28–72 years old (Table 5).

The last two publications, we identified as Brugada phenocopies, do not belong in any of the categories described above and so were classified as miscellaneous. One case presented Ebstein's anomaly.¹⁰¹ This patient was a 23-year-old female who developed a Brugada Type-1 ECG. The second case was a presentation of a Brugada phenocopy related to external electrocution.¹⁰² The patient was a 22-year-old male who showed both Brugada Type-1 and 2 ECG patterns (Table 6).

DISCUSSION

Metabolic Conditions

Of the fourteen cases categorized as Brugada phenocopies induced by a metabolic condition,

eleven cases were suspected to be a result of an electrolyte disturbance. The patients described in these cases had underlying conditions, such as hypokalemia,^{78,80,85} hyperkalemia,^{74–77,81,84} hyponatremia,^{76,80,83} and hypercalcemia.⁷⁹ It has been speculated that electrolyte disturbances, such as hyperkalemia, hypokalemia, hyponatremia, and hypocalcemia, can amplify the transient outward current (I_{to}) mediated action potential notch and lead to the subsequent loss of the AP dome in the epicardium of the RVOT, which gives rise to a transmural voltage gradient and consequently produces the Brugada ECG pattern.¹⁰³

Hyperkalemia is thought to reproduce the Brugada sign by decreasing the resting membrane potential, which inactivates the cardiac sodium channels.^{103,104} The level of the inactivation varies across the cardiac tissue, showing more pronounced inactivation in the anteroseptal region.¹⁰³ The inactivation of sodium channels leads to an imbalance between inward sodium current and outward potassium current, resulting in a predominantly outward potassium current. This outward current is most pronounced in the right ventricle and is more active in the epicardial cells than in the endocardium and M cells.¹⁰⁴ Based on the ionic mechanisms underlying Brugada syndrome

Table 4. Classification of Ischemia Induced Brugada Phenocopies

Categories	First Author (Publish Year)	Descriptor	Age/Gender	EKG type	Structural Heart Disease	Note	Outcome
Right coronary	Eggebrecht (2009) ⁹¹	Isolated right ventricular infarction	55/F	Type-1	Left ventricular hypertrophy with reduced RV function	Resuscitated from ventricular fibrillation	Not reported
	Nakazato (2000) ⁹²	Inferior myocardial infarction	58/M	Type-1	Nonreported	Stenosis in the proximal segment of the right coronary artery	Not reported
Left coronary artery	Itoh (1999) ⁹³	Vasospastic angina	68/M	Type-1	Nonreported	Intercostals neuralgia, orthostatic hypotension, ST-segment exaggeration after procainamide administration	No syncope, dizziness, chest pain recurred during a follow-up period of 13 months
	Tomcsanyi (2003) ⁹⁴	Acute myocardial infarction	59/F	Type-1 & 2	Nonreported	Raised cardiac marker	Not reported

Descriptor = the primary condition that is believed to cause Brugada ECG pattern; M = male; F = female; Note = any medication taken or clinical condition that the patient presented; Outcome = resolution of Brugada ECG and patient mortality and morbidity, if available.

proposed by Antzelevitch,¹⁰⁵ dominance of I_{to} may lead to the loss of the action potential dome in the right ventricular epicardium resulting in the Brugada Type-1 ECG pattern. Hyperkalemia, a common electrolyte disturbance in adrenal insufficiency, is believed to have induced the Brugada syndrome phenocopy.⁷⁶ It is worth noting that Littmann et al. showed a significant difference in the ECG manifestation between the hyperkalemic-induced Brugada ECG pattern and the true Brugada ECG pattern.¹⁰³ The differences include wide complex rhythm or wide complex tachycardia without visible P waves and abnormal axis deviation notably seen in hyperkalemic-induced Brugada phenocopy patients.¹⁰³ Whether this difference is also seen in other Brugada phenocopies induced by electrolyte disturbances is worth investigating.

Hypokalemia is also known to accentuate the Brugada ECG pattern by enhancing the I_{to} .¹⁰⁶ Whether hypocalcemia can also augment the I_{to} is

unknown. Our review found only one case report of hypercalcemia-induced Brugada phenocopy,⁷⁹ in which the authors did not speculate on the mechanism underlying the Brugada ECG manifestations. Hyponatremia is believed to reduce I_{Na} current due to a diminished ionic gradient, leaving the I_{to} unopposed which may cause a loss of the action potential dome in the right ventricular epicardium.⁸⁰ It is worth to note that individual case reports may favor the depolarization or the repolarization theory, however; we may prefer to leave both hypotheses open.

The remaining three cases were hypothermia-induced Brugada phenocopies.^{72-73,82} In all these cases, the Brugada ECG pattern resolved after normalization of body temperature. Ortega-Carnicer et al. hypothesized that hypothermia causes a total loss of the epicardial action potential dome leading to coved ST-segment elevation.⁸² It has been previously demonstrated in vivo canine model that

Table 5. Classification of Myocardial, Pericardial Disease Induced Brugada Phenocopies

Categories	First Author (Publish Year)	Descriptor of Condition	Age/Gender	EKG type	Structural Heart Disease	Note	Outcome
Acute myocarditis	Bramos (2009) ⁹⁵	Cardiac amyloidosis	72/F	Type-1	Concentric hypertrophy	Narrow complex tachycardia was present	Normalization of ECG after 1 day
	Kim (2008) ⁹⁶	Hematologic disease leading to acute myocarditis	42/M 46/M	Type-1 Type-1 & 2	Nonreported	Increase WBC count	Patient 1, ECG normalized after 2 months Patient 2 eventually died
	Nayyar (2009) ⁹⁷	Myocarditis	56/F	Type-1	Biventricular severe global systolic dysfunctions	Aluminum Phosphide Poisoning	Died on third day of admission from acute renal shutdown.
Chronic myocarditis	Brito (2010) ⁹⁸	Chagas disease cardiomyopathy	56/F	Type-1 & 2	Nonreported	Syncope, palpitation, apical left ventricular aneurysm	Not reported
Acute pericarditis	Ozeke (2006) ⁹⁹	Pericarditis	28/M 36/M	Type-2	Nonreported	Both patients were afebrile, no prescription drug noted.	ECG normalized after treatment ibuprofen
Myotonic dystrophy	Rudnik-Schoneborn (2010) ¹⁰⁰	Myotonic dystrophy	49/M	Type-2	Nonreported	Metformin, myotonic dystrophy confirmed by genetic testing	Not reported

Descriptor = the primary condition that is believed to cause Brugada ECG pattern; M = male; F = female; Note = any medication taken or clinical condition that the patient presented; Outcome = resolution of Brugada ECG and patient mortality and morbidity, if available.

cooling the epicardium of the RVOT resulted in a reproducible generation of a Brugada-like ECG pattern.¹⁰⁶ Furthermore, increased transmural dispersion and increased ventricular arrhythmogenesis were observed in canine models, raising the question that perhaps the high fatality rate in hypothermic patients can be, in part, attributed to cardiac arrhythmia linked to sodium channel dysfunction. This is only speculative, giving the fact that hypothermia induces repolarization changes that could be considered proarrhythmogenic by itself.

Ischemia

There is a limited number of Brugada phenocopy cases associated with ischemia currently in the literature, and the current understanding of the association between the two conditions is poor. We identified four case reports as ischemia-related Brugada phenocopies.⁹¹⁻⁹⁴ Two of the cases were associated with right coronary artery as the culprit vessel, and the other two were linked to the left coronary artery. Out of the four cases, one case reported left ventricular hypertrophy with reduced

Table 6. Miscellaneous Cases of Brugada Phenocopies

Categories	First Author (Publish Year)	Descriptor	Age/Gender	EKG type	Structural Heart Disease	Note	Outcome
Tricuspid valve defect	Kaiser (2010) ¹⁰¹	Ebstein's anomaly	23/F	Type-1	Tricuspid valve defect	Left posterior fascicular block, right branch block	Not reported
External electrocution	Rangaraj (2009) ¹⁰²	Accidental electric burn	22/M	Type-1 & 2	Nonreported	Persistent early repolarization, RBBB	ECG normalized over time

Descriptor = the primary condition that is believed to cause Brugada ECG pattern; M = male; F = female; Note = any medication taken or clinical condition that the patient presented; Outcome = resolution of Brugada ECG and patient mortality and morbidity, if available.

RV function,⁹¹ whereas the other three showed no structural heart disease. No family history of sudden cardiac death was reported and the clinical presentation suggested that the cases were true Brugada syndrome. Itoh et al. reported a case of coronary spasm accompanied by Brugada ECG pattern but suspected that the case was coincidental.⁹³ The other three cases were related to myocardial infarction, but there were no explanations offered as to how ischemia and Brugada ECG pattern may be related.^{91-92,94}

Mechanical Compression

Several cases reported mechanical compression as the main inducer of a Brugada phenocopy. A general trend is that the Brugada ECG normalizes after the source of mechanical compression is relieved. Tarin et al. reported the first case of compression-induced Brugada phenocopy⁸⁹ in which the compression of the RVOT by a mediastinal tumor led to the Brugada-like ECG pattern. The normalization of the ECG abnormalities after the removal of the tumor suggests that the mechanical compression was the cause. Nakazato et al. reported a similar case of a mass lesion compressing the RVOT and inducing the Brugada ECG. Once again the ECG normalized after the compression was relieved by antibiotic treatment. However, inflammation could have also played a role.⁸⁷ In addition, Kataoka et al. reported cases of Brugada ECG pattern related to pectus excavatum and suspected that long term mechanical injury to the right ven-

tricular free led to the development of the Brugada phenocopy.⁸⁶

Myocardial and Pericardial Disease

Chagas' disease is acquired from a parasitic infection by the protozoan *Trypanosoma cruzi* that can result in a form of chronic myocarditis. The majority of cases in North America have arisen from individuals who contracted the infection whereas in endemic areas outside the continent.¹⁰⁷ A historical paper from the Rosenbaum's team in the early '80s reported up to 7% of ST-segment changes after the administration of ajmaline.¹⁰⁸ Some of these changes resemble the Brugada Type-1 ECG pattern. Since then, several reports suggested that in some patients with Chagas' disease, a Brugada Type-1 ECG can be found.³ Brito et al. reported a case of a woman with a long-time diagnosis of Chagas' disease presenting with syncopal episodes and was found to have a Brugada Type-1 ECG pattern upon further investigation.⁹⁸ The authors speculate the ECG findings are due to the pathological changes associated with Chagas' disease, particularly in the right ventricle (dromotropic disorders). The previously discussed depolarization theory attributes the Brugada ECG manifestations to conduction delays and depolarization abnormalities in the RVOT. In addition, although the Brugada syndrome has been defined as a condition without structural cardiac defects, there has been increasing evidence that these patients may have concealed structural abnormalities particularly in the region of the right

ventricle.^{98,109} Specifically, Takagi et al. found abnormalities in the right ventricle using electron beam computed tomography in patients with Brugada syndrome.¹⁰⁹

Myotonic dystrophy Type-2 is a genetic condition that exhibits an autosomal dominant mode of inheritance and affects multiple organ systems, frequently including the heart.¹⁰⁰ A recent paper by Rudnik-Schoneborn et al. describes two cases of myotonic dystrophy Type-2 associated with a Brugada-like ECG pattern.¹⁰⁰ The first involves a recent presentation of myotonic dystrophy in a patient that also had several near syncopal episodes. Genetic testing showed a missense mutation in the *SCN5A* gene and the patient's uncle died suddenly at 61 years old. The second is a chronic case of myotonic dystrophy in which the patient had two episodes of near syncope and induction of a Brugada Type-2 ECG pattern upon ajmaline provocation, but was negative for *SCN5A* gene mutations and reported no family history for sudden cardiac death. Although Rudnik-Schoneborn et al. addressed that these cases could represent a rare association of myotonic dystrophy and Brugada syndrome (particularly in the second case), they also proposed that myotonic dystrophy Type-2 may behave as a Brugada phenocopy. This idea is supported by a French study that examined 500 cases of myotonic dystrophy Type-1 and found that the incidence of Brugada-like ECG pattern in this study sample was 80 times the incidence in the normal population.¹¹⁰ The mechanism by which myotonic dystrophy may present as a Brugada phenocopy is still unclear and requires further investigation.

In addition, two cases of acute myocarditis leading to Brugada phenocopy were reported by Kim et al.⁹⁶ The first case presented with myocarditis due to hypereosinophilic syndrome, whereas the second was due to acute lymphoblastic leukemia with myocardial involvement. The authors speculated that the ECG manifestations may be due to isolated myocardial injury or infiltrative malignant cells leading to ischemia, localized conduction delay or spatial heterogeneity of refractoriness.⁹⁶

Bramos et al. documented the first case of a cardiac amyloidosis inducing an intermittent Brugada Type-1 ECG pattern.⁹⁵ Cardiac amyloidosis is an infiltrative disease that involves the deposition of protein fibrils in the myocardium, which can result in abnormalities in cardiac structure and conduction. In this case, the patient had experienced short episodes of presyncope in the past but no

episodes of syncope and no family history of sudden cardiac death. Further investigations were denied by the patient so neither genetic testing or provocation testing were completed. The structural abnormalities that can result from cardiac amyloidosis include ventricular wall thickening, atrial enlargement, diastolic dysfunction, wall echogenicity and strain of myocardial contractile function. Defects can also arise with the conduction system and include prolongation of the infra-His conduction times and H-V interval, which have been shown to be predictors of sudden cardiac death.⁹⁵ Although it is not completely clear how cardiac amyloidosis may precipitate a Brugada phenocopy, it would appear that the ECG changes can be attributed to the conduction and structural (particularly in the right ventricle) abnormalities of the disease.

There is also evidence of pericardial disease presenting as a Brugada phenocopy. Ozeke et al. reported on two separate cases of acute pericarditis presenting with an associated Brugada Type-2 ECG pattern.⁹⁹ Currently, there is insufficient information in the literature to discern the mechanism by which acute pericarditis might induce Brugada phenocopies.

Miscellaneous

In our review of the literature, we encountered two cases of Brugada phenocopies that did not fit into the mechanistic categorization scheme outlined above, leading to the creation of a miscellaneous section.

The first case is a nonoperated Ebstein's anomaly inducing a Brugada ECG pattern. Also noted on the patient's ECG were signs of left posterior fascicular block (LPFB) associated with right bundle branch block (RBBB). The ECG manifestations are attributed to the activation of the left ventricular anterolateral wall and delayed activation of the left ventricular posteroinferior wall due to the LPFB.¹⁰¹

In the second case, a young man presented with trauma sustained from an electrical burn injury associated with an ECG exhibiting a Brugada Type-1 ECG pattern in lead V₁ and a Type-2 in lead V₂.¹⁰² His past medical history was unremarkable and there was no family history of syncope or sudden death. Because the ECG manifestations resolved spontaneously after 24 hours and his family members were found to have normal ECG recordings, no provocative testing or further

Table 7. Terminology of the Brugada Syndrome and its Associated Manifestations

	Manifested Brugada Syndrome	Concealed Brugada Syndrome	Brugada Phenocopy
ECG	Spontaneous ST-segment elevation in one or more precordial leads, V ₁₋₃ .	Normal ECG, ST-segment elevation in precordial lead, V ₁₋₃ only when exposed to unmasking agents.	Normal ECG, Brugada Type-1 or 2 ECG pattern induced by exposure to pathological conditions or drugs that are not known to be unmasking agent.
Resolution of ECG	Spontaneous Brugada ECG persists	Brugada Type-1 or 2 ECG pattern resolves once unmasking agent is withdrawn.	Brugada Type-1 or 2 ECG pattern resolves once underlying condition is treated.
Family history	Often associated with a family history of syncope and/or sudden death	Often associated with a family history of syncope and/or sudden death	Unlikely to have a family history of syncope or sudden death
Patient outcome	Increased risk of cardiac arrhythmia and sudden death	Increased risk of Cardiac arrhythmia and sudden death	Unknown

investigations were pursued. Rangaraj et al. speculated that the Brugada phenocopy may have been caused by electrical injury to the myocardium resulting in spatial dispersion of repolarization.¹⁰²

RECOMMENDATIONS FOR FUTURE BRUGADA PHENOCOPY CASE REPORT PUBLICATION

Having reviewed the case reports currently published on Brugada phenocopies, we would like to propose a few recommendations to ensure future case reports present a clear clinical picture that is distinct from the true Brugada syndrome (Table 7). Firstly, it is essential to include a 12-lead ECG tracing with emphasis on the right precordial leads V₁-V₃. The ECG manifestations are a defining feature of the Brugada syndrome and Brugada phenocopies and thus a clear ECG tracing of reasonable quality is required. The inclusion of additional leads is desirable and highly recommendable.¹¹¹ Secondly, it is paramount to comment on the presence of a past medical history of syncope and a family history of sudden death or syncope, which can be of help in differentiating between true Brugada syndrome and Brugada phenocopies. Including whether or not provocative testing, genetic testing, and ECG tracings of immediate family

members were recorded is also important in helping to rule out true Brugada syndrome. Finally, it would be beneficial to report whether the Brugada ECG pattern resolved after the treatment of the underlying cause; otherwise it is difficult to classify them as a Brugada phenocopy, because we cannot know whether the underlying condition was truly behind the Brugada ECG manifestation. It is important to document the resolution of the Brugada ECG to infer a direct association between the "environmental factor" and the Brugada ECG pattern.

In addition, it would be good practice for authors to comment on patient outcomes to further the investigation on whether there is a correlation between Brugada phenocopies and malignant cardiac arrhythmia.

CONCLUSIONS

Given the extensive and variable terminology currently in use to describe a Brugada-like ECG pattern in the absence of true Brugada syndrome, our first objective was to propose the adoption of the term Brugada phenocopy, coined by Riera et al., to prevent confusion.

Given the growing collection of Brugada phenocopy cases, we believe our classification scheme based on etiological mechanism will provide much

needed organization to current and future reports alike. From our examination, it would appear that most Brugada phenocopies may occur in relation to cardiac sodium channel blocking effects or cardiac structural abnormalities, particularly those affecting the right ventricle. We acknowledge that there is a need for further investigation on this topic to better understand each mechanism, but we hope to have provided an adequate starting framework for further discussion.

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Mutations in Cytoplasmic Loops of the KCNQ1 Channel and the Risk of Life-Threatening Events

Implications for Mutation-Specific Response to β -Blocker Therapy in Type 1 Long-QT Syndrome

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Background— β -Adrenergic stimulation is the main trigger for cardiac events in type 1 long-QT syndrome (LQT1). We evaluated a possible association between ion channel response to β -adrenergic stimulation and clinical response to β -blocker therapy according to mutation location.

Methods and Results—The study sample comprised 860 patients with genetically confirmed mutations in the *KCNQ1* channel. Patients were categorized into carriers of missense mutations located in the cytoplasmic loops (C loops), membrane-spanning domain, C/N terminus, and nonmissense mutations. There were 27 aborted cardiac arrest and 78 sudden cardiac death events from birth through 40 years of age. After multivariable adjustment for clinical factors, the presence of C-loop mutations was associated with the highest risk for aborted cardiac arrest or sudden cardiac death (hazard ratio versus nonmissense mutations=2.75; 95% confidence interval, 1.29–5.86; $P=0.009$). β -Blocker therapy was associated with a significantly greater reduction in the risk of aborted cardiac arrest or sudden cardiac death among patients with C-loop mutations than among all other patients (hazard ratio=0.12; 95% confidence interval, 0.02–0.73; $P=0.02$; and hazard ratio=0.82; 95% confidence interval, 0.31–2.13; $P=0.68$, respectively; P for interaction=0.04). Cellular expression studies showed that membrane spanning and C-loop mutations produced a similar decrease in current, but only C-loop mutations showed a pronounced reduction in channel activation in response to β -adrenergic stimulation.

Conclusions—Patients with C-loop missense mutations in the *KCNQ1* channel exhibit a high risk for life-threatening events and derive a pronounced benefit from treatment with β -blockers. Reduced channel activation after sympathetic activation can explain the increased clinical risk and response to therapy in patients with C-loop mutations. (*Circulation*. 2012;125:1988-1996.)

Key Words: adrenergic beta-antagonists ■ ion channels ■ long QT syndrome ■ mutation

Long-QT syndrome type 1 (LQT1) is the most common type of inherited long-QT syndrome (LQTS), accounting for $\approx 35\%$ of all patients and $>50\%$ of genotyped patients.¹ LQT1 arises from a decrease in repolarizing potassium

current resulting from mutations in the *KCNQ1* gene. Four *KCNQ1*-derived α -subunits assemble to form the I_{Ks} channel along with obligatory auxiliary subunits derived from *KCNE1*. Exercise is the main trigger for cardiac arrhythmic

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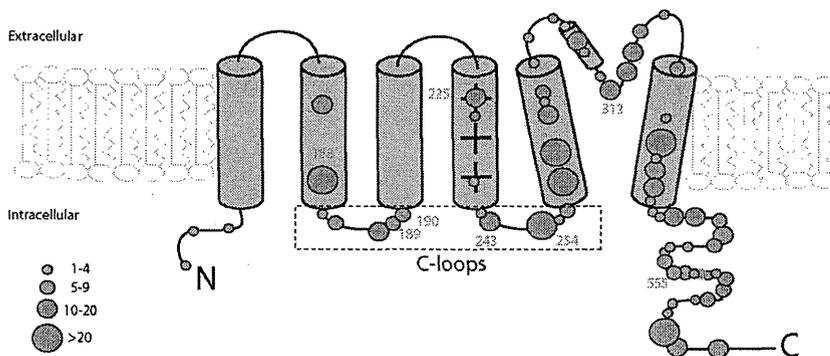


Figure 1. Frequency and location of mutations in the KCNQ1 potassium channel. Diagrammatic location of 99 different mutations in the KCNQ1 potassium channel involving 860 subjects. The α -subunit involves the N-terminus (N), 6 membrane-spanning segments, 2 cytoplasmic loops (S2-S3 and S4-S5), and the C-terminus portion (C). The size of the circles reflects the number of subjects with mutations at the respective locations.

events in patients with LQT1.² Activation of β 1-adrenergic receptors is the major signaling pathway contributing to the increase in heart rate and cardiac output during exercise. β 1-Adrenergic receptor activation leads to activation of protein kinase A (PKA), which directly phosphorylates the KCNQ1 subunit, increasing I_{Ks} function.^{3,4} The increase in I_{Ks} is thought to suppress the premature beats and afterdepolarization induced by increased L-type Ca^{2+} currents during β -adrenergic stimulation.⁵ Accordingly, β -blockers have been considered the first-line therapy in LQT1 patients without a history of aborted cardiac arrest (ACA). Data from several prior LQTS studies^{1,6} demonstrate that despite the reduction in the risk of cardiac events with β -blocker therapy among LQT1 patients, there is a considerable cardiac residual event rate among patients who are being treated with this mode of medical therapy (\approx 10 cardiac events per 100 person-years),⁶ suggesting that β -blockers may be less effective in certain subgroups of LQT1 patients.

Editorial see p 1961
Clinical Perspective on p 1996

The KCNQ1 protein consists of 676 amino acid residues with an intracellular N-terminus region, 6 membrane-spanning segments with 2 connecting cytoplasmic loops (C loops), and an intracellular C-terminus region.⁷ Prior genotype-phenotype studies have provided important information on the effect of location and coding type of the channel mutations on the phenotypic manifestations and clinical course of LQT1 patients. These studies have shown that missense mutations and mutations located at the transmembrane region (including the C loops) were associated with greater risk for cardiac events.⁸ However, the mechanism related to the increased risk associated with transmembrane mutations has not been studied. C loops, part of the transmembrane region, were suggested to affect adrenergic channel regulation by PKA.⁹ We therefore hypothesized that the previously reported finding about the risk associated with transmembrane mutations⁸ is related to the effect of C-loop mutations within this region. Accordingly, the present study was carried out in a large cohort of subjects having a spectrum of KCNQ1 mutations from the International LQTS Registry and was designed to investigate the clinical outcomes among KCNQ1 mutation carriers by further dividing the transmembrane region into membrane-spanning and C-loop domains, to determine a possible differential response to β -blocker therapy depending on mutation location and

function related to PKA regulation, and to relate the clinical data to functional studies of changes in I_{Ks} function and β -adrenergic receptor regulation in mammalian cells.

Methods

Study Sample

The study comprised 860 patients with genetically confirmed KCNQ1 mutations derived from 170 proband-identified families. The proband in each family had QTc prolongation not resulting from a known secondary cause. The subjects were drawn from the Rochester (n=637), the Netherlands (n=94), the Japanese (n=82), the Danish (n=43), and the Swedish (n=4) portions of the Multi-center Mutation Registry. All subjects or their guardians provided informed consent for the genetic and clinical studies. Patients with congenital deafness and patients with multiple LQTS-associated mutations were excluded from the study.

Phenotype Characterization

On enrollment, routine clinical and ECG information was obtained from birth to the participants' enrolled age, and ongoing clinical information was obtained at yearly intervals thereafter. For each patient, data on personal and family histories, cardiac events, and therapy were systematically recorded at enrollment and at each visit or medical contact. Clinical data, recorded on prospectively designed forms, included patient and family histories and demographic, ECG, therapeutic, and cardiac event information. Data on β -blocker therapy included the starting date and discontinuation date if appropriate. Information on the end point of ACA or sudden cardiac death (SCD) was also verified through requested medical records. Every effort was made to confirm an underlying life-threatening arrhythmia when observed or documented by medical staff.

Genotype Characterization

The KCNQ1 mutations were identified with the use of standard genetic tests performed in academic molecular genetics laboratories. Genetic alterations of the amino acid sequence were characterized by location and by the specific type of mutation (missense, splice site, in-frame insertions/deletions, nonsense, stop codon, and frameshift).

We evaluated the risk associated with 4 main prespecified subgroups: C- or N-terminus missense, membrane-spanning missense, C-loop missense, and nonmissense (ie, splice sites, in-frame insertions, in-frame deletions, stop codons, and frameshift). The membrane-spanning region of the KCNQ1-encoded channel was defined as the coding sequence involving amino acid residues between 124 and 170 (S1-S2), 196 and 241 (S3-S4), and 263 and 355 (S5-S6), with the C-loop region between residues 171 to 195 (S2-S3) and 242 to 262 (S4-S5; Figure 1). The N-terminus region was defined before residue 124 and the C-terminus region after residue 355.

To minimize survival bias, we included patients who died before they were genotyped (n=64). They were assumed to have the mutation that their first-degree relatives had. All other patients were confirmed through genotyping.

Cellular Expression Studies

To study the mechanism underlying the risk for cardiac events in patients with missense C-loop mutations, we measured channel function and regulation for channels formed with wild-type (WT) subunits coexpressed with 4 mutant subunits present in C loops (G189R, R190Q, R243C, and V254M) and 4 mutant subunits present in the non-C-loop domains: 3 in the membrane-spanning domain (T312I, G168R, and S225L) and 1 in the C terminus (R555C). The mutations chosen included the most common mutations in the LQT1 registry. WT and mutant KCNQ1 subunit cDNA and KCNE1 subunit cDNA were transfected into HEK293T cells.¹⁰ Mutant KCNQ1 cDNA was transfected in combination with WT-KCNQ1 to mimic the heterozygous nature of the disease (WT-KCNQ1:mutant KCNQ1:KCNE1=0.5:0.5:1). Fluorescence-conjugated and -tagged constructs were used to evaluate the efficiency of the cotransfection of WT and mutant subunits¹¹ (see the online-only Data Supplement). Of the HEK293T cells cotransfected with both WT and mutant subunits, 85% to 90% showed fluorescence of at least 1 subunit transfected, and 85% to 95% of transfected cells expressed all the subunits transfected (Figure I in the online-only Data Supplement). All electrophysiology determinations were performed with the untagged subunit. Expression of WT and mutant subunits was confirmed by Western blot (Figure II in the online-only Data Supplement). Expression levels were not significantly decreased for the mutant subunits compared with WT. We measured ion channel currents after channel depolarization to 20 mV for 4 seconds from -80-mV holding potential before and after application of forskolin, a PKA activator (10 μ mol/mL), with standard electrophysiological techniques and physiological solutions. Current was normalized for all voltages to cell capacitance, and further normalization was performed between WT and mutant. The normalization to WT currents was accomplished by use of WT cell currents transfected and measured on the same day as the currents measured from mutant channel.¹⁰ Pipettes used had resistances ranging from 2 to 6 MOhm. Series resistance compensation of >70% was used to compensate for voltage drops in the pipette. All experiments were performed at room temperature. Details of the molecular biology and electrophysiological methods are given in the Materials and Methods section of the online-only Data Supplement.

End Point

The primary end point of the study was the occurrence of a first life-threatening cardiac event, comprising ACA requiring external defibrillation as part of the resuscitation or LQTS-related SCD (abrupt in onset without evident cause if witnessed or death that was not explained by any other cause if it occurred in an unwitnessed setting) from birth through 40 years of age. Follow-up after 40 years of age was not included to minimize the influence of coronary disease on cardiac events. The consistency of the results among patients who received an implantable cardioverter-defibrillator during follow-up was evaluated in a secondary analysis that included the occurrence of a first appropriate implantable cardioverter-defibrillator shock in the composite ACA or SCD end point.

Statistical Analysis

Characteristics of the 4 subgroups of patients categorized by mutation location and type were compared by use of a 1-way ANOVA test or χ^2 and Fisher exact tests as appropriate. The probability of a first life-threatening cardiac event by the mutation location and type subgroup was graphically displayed according to the Kaplan-Meier method, with comparison of instantaneous risk by the log-rank test. The Cox proportional-hazards survivorship model was used to evaluate the independent contribution of clinical and genetic factors to the first occurrence of a life-threatening cardiac event from birth through 40 years of age. The Cox regression models, stratified by decade of birth year and allowing for time-dependent covariates, were fit to estimate the adjusted hazard ratio function of age. Therefore, to fulfill the assumption of proportional hazards for sex over the entire age range, a time-dependent covariate for sex (via an interaction with time) was incorporated, allowing for different

hazard ratios by sex before and after 13 years of age. This was justified by the known higher risk of cardiac events or life-threatening cardiac events among male subjects before adolescence and a similar or higher female risk after the onset of adolescence.¹²⁻¹⁶ Patients who did not have an ECG for QTc measurement (n=127) were identified in the Cox models as QTc missing, and all Cox models were adjusted for this QTc-missing parameter. The influence of time-dependent β -blocker therapy (the age at which β -blocker therapy was initiated) on outcome in the subgroups of patients with and without C-loop missense mutations was determined by adding a time-dependent β -blocker-by-mutation category interaction term to the multivariable Cox model. We have adjusted for the effect of potential lack of independence between subjects using the robust sandwich estimator for family membership.^{17,18} This robust sandwich covariance estimator is used with correlated data. Correlations among data points in the Cox model lead to underestimation of the SE used in significance testing, whereas the robust estimator uses an inflated variance estimate, taking family membership or other clustering connection into account. All significant predictors of life-threatening event risk remained significant with or without the use of this robust measure of variance. It should be noted that there is seldom more than a single observed outcome (ACA/SCD) per family (only 7% of families had >1 event); thus, the standard model-based SEs, confidence intervals, *P* values, and likelihood ratio tests are valid.¹⁶

We have carried out the following additional secondary analyses: (1) including the biophysical function of the mutations (categorized as dominant negative, haploinsufficiency, and unknown) as a covariate in the model, (2) excluding the large subgroup of patients with V254M mutations, and (3) including appropriate implantable cardioverter-defibrillator shocks in the composite end point. In addition, to assess whether fuller adjustment for family membership was important, regression models that included shared frailty terms (ie, random effects) for family were fit.

The statistical software used for the analyses was SAS version 9.20 (SAS Institute Inc, Cary, NC). For the fitting of models with frailty terms, the software used was Splus 7.0.0 for Sun SPARC. For electrophysiology and biochemistry experiments, 1-way ANOVA followed by the Tukey post hoc test was applied to assess statistical significance for multiple-group comparisons by use of SPSS Statistics (IBM). An unpaired Student *t* test was used for 2-group comparisons. A 2-sided significance level of 0.05 was used for hypothesis testing.

Results

Study Sample

The spectrum of mutations as categorized by location and type and their respective number of carriers are presented in Table I-A in the online-only Data Supplement. The location and frequency of missense mutations are presented diagrammatically in Figure 1. Of the 99 total different KCNQ1 mutations identified, 77 were missense mutations and 22 were nonmissense mutations. Missense mutations were further categorized according to their location: 28 different mutations in C-terminus or N-terminus regions (26 in C terminus), 34 mutations in membrane-spanning regions, and 15 mutations in the C-loop regions (8 in S2-S3 loop and 7 in S4-S5 loop). The clinical characteristics of patients in the 4 mutation location/type subgroups are presented in Table 1. Of the 860 study subjects, 20% had C/N terminal missense mutations, 44% had membrane-spanning missense mutations, 15% had C-loop missense mutations, and 22% had nonmissense mutations. Patients with C-loop missense mutations exhibited the longest QTc interval at enrollment, were treated with β -blockers more frequently during follow-up, and had a higher frequency of cardiac events of any type, including